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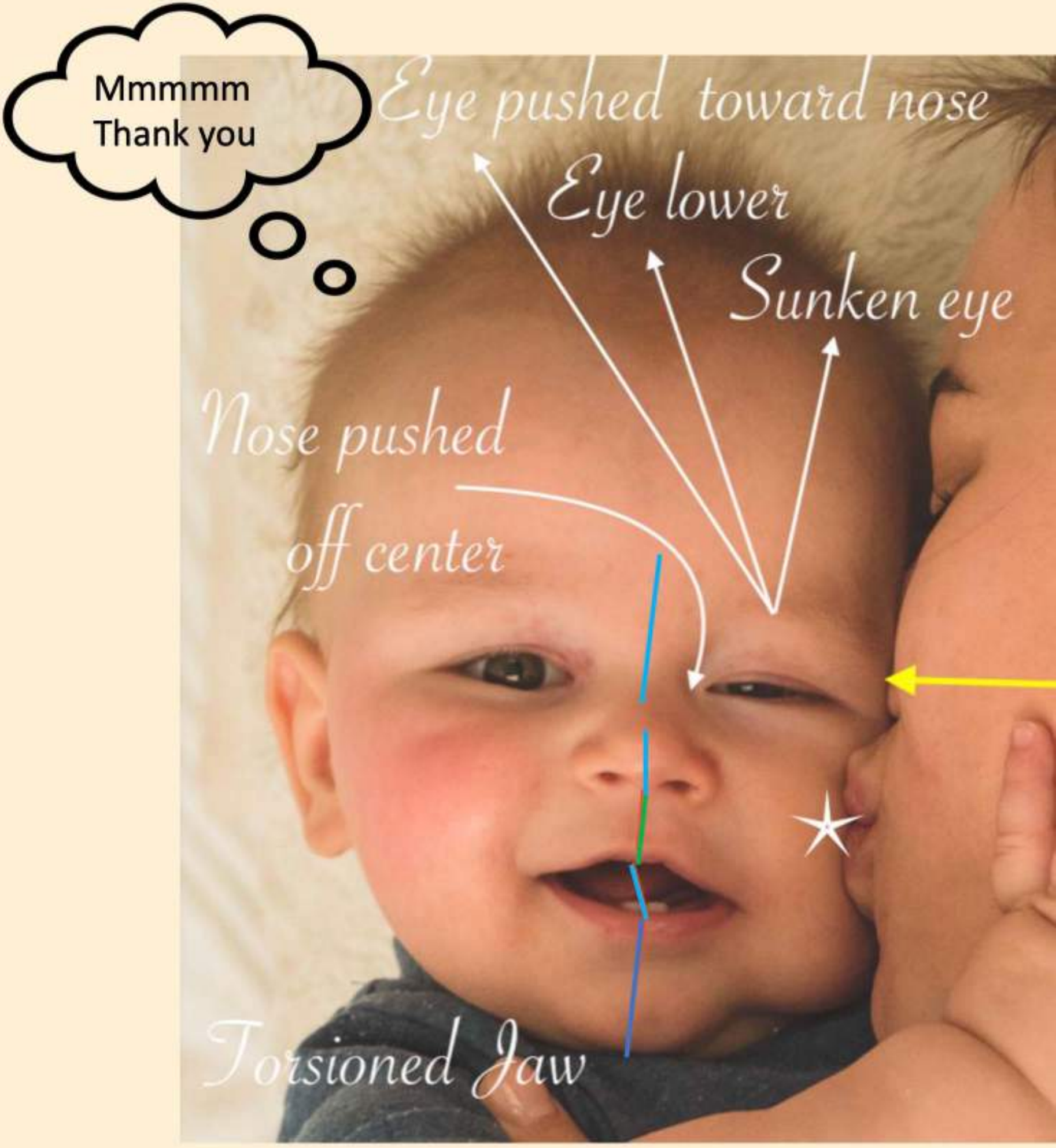
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PLOS ONE

RESEARCH ARTICLE

Maternal and paternal anxiety during pregnancy: Comparing the effects on behavioral problems in offspring

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Data Availability Statement: Due to Norwegian legislation, the researcher cannot make the data material on an individual level available to others at any time, including in connection with publication. According to the regulations in Norway and the National Institute of Public Health, no MoBa data on an individual or aggregated level may be uploaded into any repository or database at any time. Data from the Norwegian Mother, Father and Child Cohort Study and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway

Abstract

Prenatal maternal anxiety has been associated with both short and long-term mental health problems in the child. The current study aims to examine the association between maternal and paternal prenatal anxiety and behaviour problems in the child at 1.5 and 5 years, using three different approaches; (1) adjusting for covariates, (2) using fathers' anxiety during pregnancy as a negative control, and (3) using a sibling-comparison design, controlling for unmeasured family factors. We used data from the Norwegian Mother, Father and Child Cohort Study (MoBa) is used. MoBa is a cohort consisting of about 114 000 pregnancies (about 34000 siblings) recruited from 1999 to 2008. Self-reported measures on maternal anxiety were obtained twice in pregnancy and 6 months after birth, while paternal anxiety was reported prenatally at 17th weeks of gestation. Maternal reports on child behaviour problems were obtained at 1.5 and 5 years of age. Results suggests that prenatal exposure to maternal anxiety was associated with behaviour problems at 1.5 years: adjusted beta (β) = 0.13 (CI = 0.12, 0.15), and at 5 years: β = 0.11 (CI = 0.09, 0.14). However, paternal anxiety was also associated with behaviour problems at 1.5 years: β = 0.03 (CI = 0.01–0.03) and at 5 years β = 0.03 (CI = 0.02, 0.03). These associations were attenuated in the sibling comparison analyses: β = -0.02 (CI = -0.02–0.05) at 1.5 years and β = -0.05 (CI = -0.10, 0.02) at 5 years. In conclusions, the sibling analyses are not consistent with a direct effect of prenatal maternal anxiety on child behaviour problems. It is more likely that genetic or shared family environment explain this association.

Introduction

Exposure to maternal stress during pregnancy, such as anxiety, is a known risk factor for a wide range of developmental outcomes, and is associated with shortened gestation, restricted fetal growth, and increased emotional and behavioral difficulties in offspring [1–3]. The mechanism linking maternal exposures during pregnancy and offspring outcomes has been

(Norwegian Institute of Public Health) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with the EU General Data Protection Regulation (GDPR) and approval from the data owners. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply through helsedata.no.

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suggested to operate via the programming hypothesis [4]. This theory proposes that stress in the mother stimulates the release of the stress hormones corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids. These hormones cross the placenta barrier and influence fetal-brain development [5, 6]. The programming hypothesis suggests that if such exposure occurs during any sensitive period of fetal development, it may lead to increased risk of disease later in life [7]. According to the fetal programming hypothesis if such exposure occurs during any sensitive period of fetal development, it may lead to increased risk of a disease later in life [8]. For example, in a recent meta-analysis, maternal anxiety was found to increase the risk of socioemotional problems, such as behavior problems by 50% [9]. MacKinnon et al. found an increased risk of both hyperactivity and conduct disorder after exposure to prenatal distress [10]. These negative consequences of maternal prenatal anxiety have been suggested to continue beyond childhood [3]. However, solving the methodological problems by randomizing pregnant mothers to the exposure is clearly not possible.

Despite this evidence, the link between prenatal exposure to maternal anxiety and child behavior problems is not clear [11, 12], and findings have been mixed. On the one hand, DiPietro et al. [13] found that moderate anxiety in pregnancy was associated with more optimal child development, while others reported no association between maternal distress and child behavior problems [12]. Thus, the association between prenatal maternal anxiety and child behavior problems may be due to residual confounding either prenatally or postnatally. Prenatal maternal anxiety may for example relate to behavior problems only indirectly through postnatal maternal anxiety [14]. On the other hand, the association between prenatal maternal anxiety and child behavior could be due to genetic confounding (e.g., shared family effects). With regards to shared genes, while in our cohort a partial overlap in the genetic variance between maternal depression and child behavior problems has been previously demonstrated [15], such links have not been extensively studied in the context of maternal anxiety. As addressing residual confounding by randomizing pregnant mothers to the exposure is clearly not possible. Our purpose is therefore to investigate whether maternal prenatal anxiety is related to behavior problems using a non-exposed control design. We apply three approaches to account for unmeasured and measured confounding.

First, we adjust for covariates, previously shown to be related to behavior problems in the child, by multiple linear-regression analyses. For example, some studies have found prenatal anxiety and depression to be associated with birth-related outcomes, e.g. low birth weight or preterm birth [1]. Others have also found birth outcomes, such as low birth weight, to be associated with behavior problems in the child [16, 17]. Studies also suggest that the effect of exposure to maternal prenatal anxiety may not occur in infancy but at a later age [3]. Thus, whether maternal anxiety influences fetal development, in turn causing behavior problems later in childhood, remains unclear. Therefore, in the first analyses, we first controlled for several known prenatal and postnatal confounders.

Second, we used paternal prenatal anxiety as a negative control [11]. Thus, if there is a direct effect of maternal anxiety in utero, prenatal maternal anxiety should have a stronger effect on child-behavior problems than prenatal paternal anxiety. For example, Ramchandani and colleagues [18] found depression in fathers during the prenatal period to be associated with behavior problems in three-year-olds. They examined the association between prenatal and postnatal paternal depression for behavior problems. They did not, however, compare maternal prenatal depression with paternal prenatal depression, or examine anxiety. Van Batenburg-Eddes and colleagues [17] examined both maternal and paternal anxiety and depression in two large cohort studies and found similar effects of maternal or paternal anxiety/depression on child-inattention symptoms. Thus, their findings suggest that although

there was a direct effect of prenatal maternal depression and anxiety, most of the observed effects could be explained by residual confounding (i.e., either paternal symptoms or postnatal effects of parental symptoms). However, they did not examine behavior problems.

A third approach to account for confounding factors is to apply a sibling-comparison design. This approach may provide an effective control for familial factors that are constant (maternal genes and family context). Two large-scale studies that compared siblings differentially exposed prenatally to depression [19] or adverse life-events [20] did not find any association to offspring behavior. Similar findings emerged when the association between maternal prenatal anxiety and child emotional difficulties at 6 and 36 months was examined using a sibling design [21]. These studies found that the association was confounded by shared family effects. However, as maternal prenatal anxiety may differentially relate to child internalizing versus externalizing versus neurodevelopmental outcomes [18, 22], the biological pathway from prenatal exposure to maternal anxiety on child behaviour may differ depending on the specific outcome. Based on these previous studies, maternal prenatal anxiety seems to have a stronger influence on the development of externalizing difficulties (i.e. behaviour problems) compared to internalizing ones (i.e. emotional difficulties) [18, 22]. Studies also suggest that the effect of exposure to maternal prenatal anxiety may not occur in infancy but at a later age [23].

Building upon this earlier evidence, in the present study we examine whether the association between maternal prenatal anxiety and child behaviour problems in early childhood can be attributed to measured (known covariates, paternal prenatal anxiety) and unmeasured (shared genetic variance and environment) confounding. We aim to examine the association between maternal prenatal anxiety and behavior problems, using three different approaches: (i) adjusting for covariates and postnatal anxiety as a negative control, (ii) using fathers' anxiety during pregnancy as a negative control, and (iii) using a sibling-comparison design, controlling for unmeasured family factors. We aim to examine effects both in infancy and later in childhood by using behavior problems at both 1.5 and 5 years as the outcome.

Materials and methods

This study is a subproject of the Norwegian Mother, Father, and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health [24]. MoBa is a cohort comprising 114,247 pregnancies recruited from 1999 to 2008 with a participation rate of 40.6% [25]. All but two of the 52 hospitals across Norway agreed to participate in the recruitment for the study. Women were invited to participate when they attended the routine ultrasound examination that is offered to all pregnant women at 17–18 weeks of gestation (www.fhi.no/moba-en). The maternal-questionnaire response rates at the 17^{th} and 30^{th} weeks of gestation, and at 1.5 and 5 years after birth, were 95.1%, 91.4%, 87.0%, and 54.0%, respectively [25]. Written informed consent was obtained from all participating women. The Regional Committee for Medical and Health Research Ethics approved the study.

Within MoBa, 59,292 mothers of 68,602 children completed a series of questionnaires for each unique pregnancy, at the 17^{th} and 30^{th} weeks of gestation, and at 6 months and 1.5years after birth. The questionnaires included maternal anxiety level (17^{th} and 30^{th} weeks of gestation and 6 months after birth), paternal anxiety level (17^{th} week of gestation), and infant-behavior problems (1.5 and 5 years), along with other maternal characteristics such as age, education, marital status, smoking and drinking habits, and partner harmony. MoBa was also linked to the Medical Birth Registry of Norway (MBRN), which contains detailed medical information about newborn children (e.g., sex, birth weight, and gestational age) as well as their mothers (e.g., parity and birth complications).

In MoBa, there were 8,823 pairs of siblings at 1.5 years, and 3,428 of siblings at 5 years after birth with complete information. The mean age-difference between siblings was 2.7 years. The numbers dropped slightly after excluding half-siblings who had the same mother but different fathers (Fig 1). We used version 8 of the quality-assured data files; an overview of the questionnaires and items is available at https://www.fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/.

Measures

Maternal and paternal anxiety. Mothers reported on symptoms of anxiety using six items from the validated short version of the Hopkins Symptom Checklist, two from SCL-5 and four from SCL-8 [26]. Items from the SCL are scored on a Likert scale ranging from 1 (not at all bothered) to 4 (very much bothered) and have been validated with a correlation of 0.92 with the SCL-25 [26]. Maternal anxiety was assessed twice during pregnancy (at the 17th and 30th gestational weeks) and once after birth (when the child was six months old). The mean scores for the 17th and the 30th gestational weeks were calculated separately using the items of constantly "frightened or anxious," "nervous, inner turmoil," "feel tense or stressed," and "sudden fear without reason." The maternal prenatal anxiety score was defined as the mean of the anxiety score at the 17th and 30th weeks. Paternal anxiety was also assessed once at the 17th week of gestation using four items from the SCL-8.

Child-behavior problems. Child-behavior problems were measured by items from the Child Behavior Checklist (CBCL/TRF) [27]. A team of clinical and developmental psychologists selected the items from the CBCL used in MoBa. The selected items were based on theoretical and empirical representativeness and are representative with a correlation of 0.92 with the full scale [28]. Mothers responded to 8 items at 1.5 years and 10 items at 5 years on a three-point Likert scale, from not true ("0") to sometimes true ("1") to often true ("2"), and mean values were computed for each time point. Cronbach's alpha was 0.57 and 0.74 for 1.5 years and 5 years, respectively.

Potential confounders. The following variables were considered to be potential confounders: alcohol consumption during pregnancy (coded as never "0" and more than once a month "1"), smoking in pregnancy (coded as never "0," sometimes "1," and daily "2"), 10

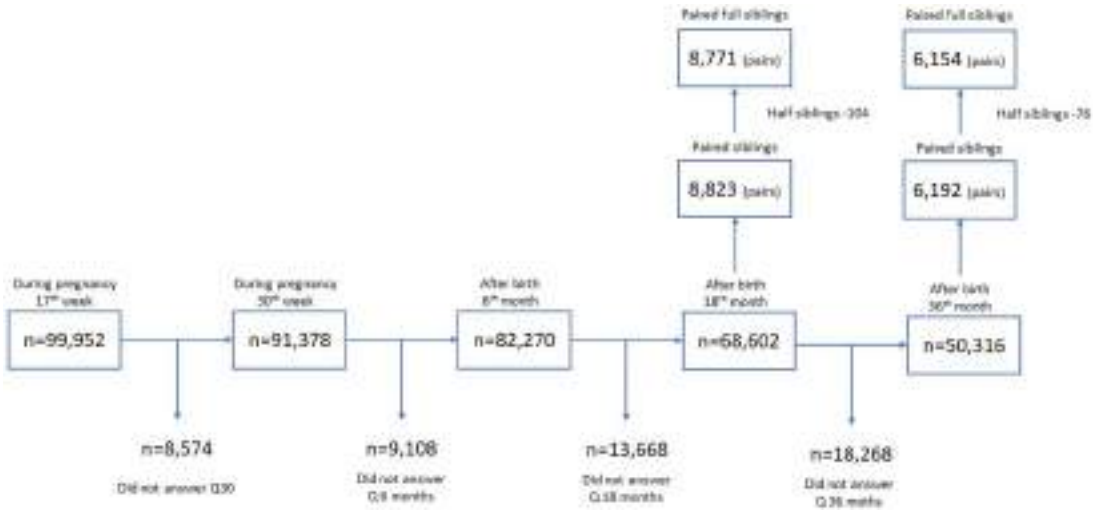

Fig 1. Flow chart of study sample. Note: The half siblings refer to the siblings with the same mother but different fathers.

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items regarding partner harmony from the Marital Satisfaction Scale (MSS) with response options ranging from 1 to 6 (the higher, the worse), marital status (married/living together "0" and single "1"), and low maternal education (coded as higher university degree +4 years "0," college/university 3 years "1," college 1–2 years "2," and secondary school "3"). We also controlled for the following variables extracted from the MBRN: parity (coded as 0, 1, 2, 3, and 4 +), birth complications (coded as yes "1" or no "0"), and child sex (girl "0," boy "1"). The Pearson correlations between the variables can be found in Fig 2.

Statistical analyses

In the full cohort, the associations of maternal anxiety with child-behavior problems at 1.5 and 5 years were estimated using two different regressions: 1) ordinary linear regression of the

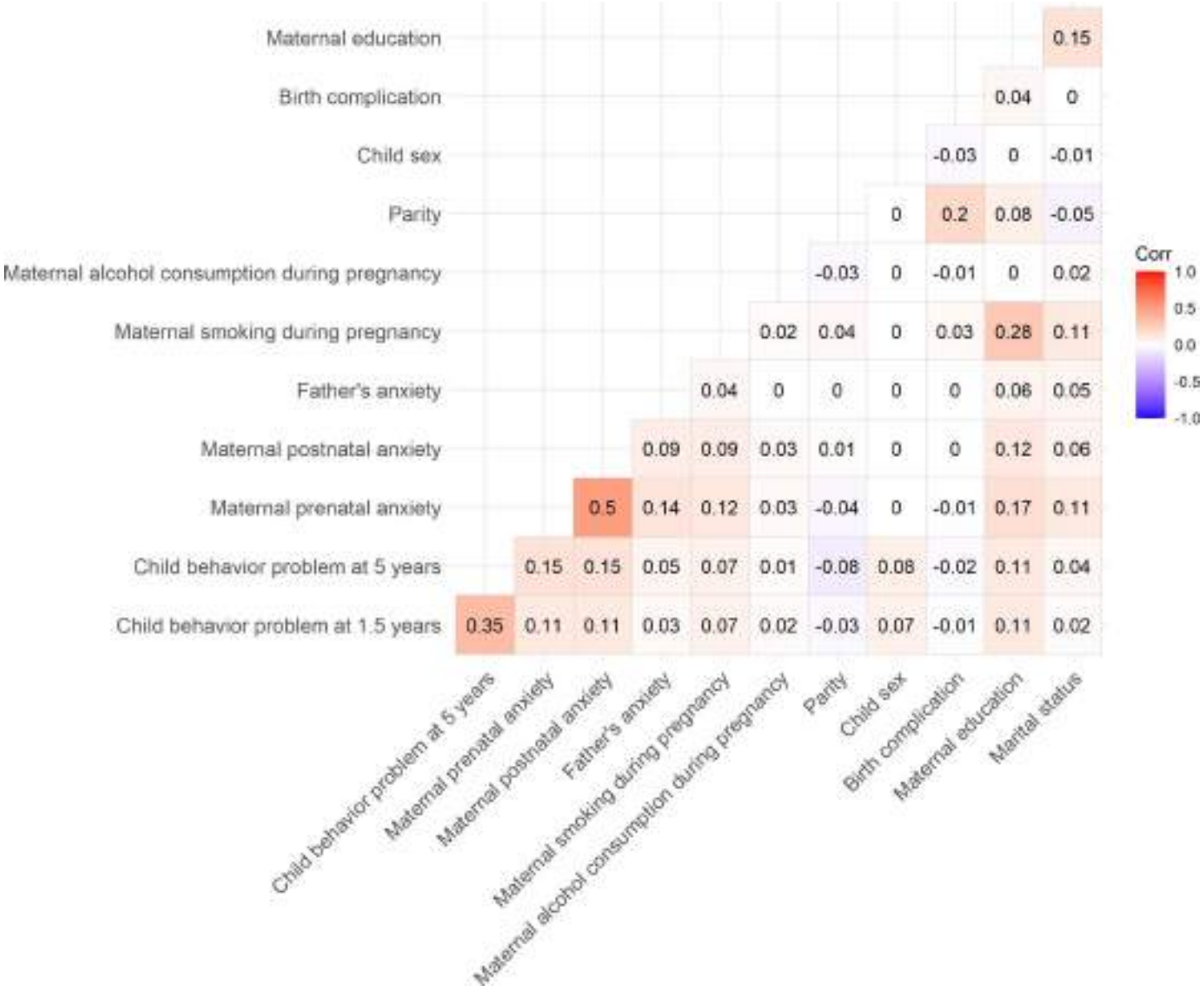

Fig 2. Pearson correlations between study variables.

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child-behavior problem score on the maternal-anxiety score and 2) logistic regression of the dichotomized child-behavior problem score on the dichotomized maternal-anxiety score. The two regression models were adjusted for maternal smoking, alcohol consumption, parity, parental education, marital status, birth complication, and the interaction term between maternal prenatal and postnatal anxiety. When the outcome variable was the child-behavior problem measured at 5 years, the regressions were further adjusted for the child-behavior problem at 1.5 years.

Adjusted model:

$$Y_{child-behavior\ at\ 1.5yrs} = \beta_0 + \beta_1 X_{mat-anx-pre} + \beta_2 X_{mat-anx-post} + \beta_3 \left(X_{mat-anx-pre} X_{mat-anx-post} \right) + \beta_4 X_{mat-smk} + \beta_5 X_{mat-alc} + \ldots + \epsilon$$

$$Y_{child-behavior\ at\ 5yrs} = \beta_0 + \beta_1 X_{mat-anx-pre} + \beta_2 X_{mat-anx-post} + \beta_3 \left(X_{mat-anx-pre} X_{mat-anx-post} \right) + \beta_4 Y_{child-behavior\ at\ 1.5yrs} + \beta_5 X_{mat-smk} + \beta_6 X_{mat-alc} + \ldots + \epsilon$$

Additionally, we focused on the association between the maternal/paternal anxiety score at the 17th week and the child-behavior problem. The child-behavior problem score was regressed on the maternal/paternal anxiety score at the 17th week with adjustment for the paternal/maternal anxiety score at the 17th week and the same set of adjusting variables used in the full cohort.

Mutually adjusted model:

$$Y_{child-behavior\ at\ 1.5yrs} = \beta_0 + \beta_1 X_{mat-anx\_w17} + \beta_2 X_{pat-anx-w17} + \epsilon$$

$$Y_{child-behavior\ at\ 5yrs} = \beta_0 + \beta_1 X_{mat-anx-w17} + \beta_2 X_{pat-anx-w17} + \epsilon$$

Fully adjusted model:

$$Y_{child-behavior\ at\ 1.5yrs} = \beta_0 + \beta_1 X_{mat-anx-w17} + \beta_2 X_{pat-anx-w17} + \beta_3 X_{mat-anx-6m} + \beta_4 X_{mat-smk} + \beta_5 X_{mat-alc} + \ldots + \epsilon$$

$$Y_{child-behavior\ at\ 5yrs} = \beta_0 + \beta_1 X_{mat-anx-w17} + \beta_2 X_{pat-anx-w17} + \beta_3 X_{mat-anx-6m} + \beta_4 X_{child-behavior\ at\ 1.5yrs} + \beta_5 X_{mat-smk} + \beta_6 X_{mat-alc} + \ldots + \epsilon$$

In the sibling design, the association between maternal anxiety and the child-behavior problem was estimated with an adjustment for the family-shared effect. We used two types of regression: 1) regression of the inter-sibling difference in the child-behavior score on the inter-sibling difference in the maternal anxiety score and 2) conditional-logistic regression of the dichotomized child-behavior problem score on the dichotomized maternal-anxiety score (fixed effect) and family identification (random effect). The same set of adjusting variables mentioned above was used.

Adjusted model:

i) Contrast regression

$$\left(Y_{child-behavior\ at\ 1.5\ yrs,\ \ sib1} - Y_{child-behavior\ at\ 1.5yrs,\ \ sib2}\right) = \beta_1\left(X_{mat-anx-pre,\ \ sib1} - X_{mat-anx-pre,\ \ sib2}\right) + \beta_2\left(X_{mat-anx-post,\ \ sib1} - X_{mat-anx-post,\ \ sib2}\right) + \beta_3\left(X_{mat-anx-pre,\ \ sib1} - X_{mat-anx-pre,\ \ sib2}\right)\left(X_{mat-anx-post,\ \ sib1} - X_{mat-anx-post,\ \ sib2}\right) + \beta_4\left(X_{mat-smk,\ \ sib1} - X_{mat-smk,\ \ sib2}\right) + \ldots + \epsilon$$

ii) Conditional logistic regression:

$$logit\left(P\left(Y_{child-behavior\ at\ 1.5yrs} = 1\right)\right) = \beta_1 X_{mat-anx-pre} + \beta_2 X_{mat-anx-post} + \beta_3 X_{mat-anx-pre} X_{mat-anx-post} + \beta_4 X_{mat-smk} + \beta_5 X_{mat-alc} + \ldots + \alpha_{family-ID}$$

Missing data

Information about the proportion of missing data is given in Tables 1 and 2. Missing data in MoBa have previously been examined by Nilsen et al. [29].

Results

Descriptive

Table 1 presents descriptive statistics for the full cohort. The mean score of child-behavior problems at 1.5 years increased with the severity of maternal prenatal and postnatal anxiety and paternal anxiety. The mean score of child-behavior problems at 1.5 years increased from 0.49 to 0.58 as maternal prenatal anxiety shifted from light to severe. Similarly, the mean score of child-behavior problems at 5 years increased from 0.35 to 0.51 with the severity of anxiety for the mothers measured postnatally (six months after birth). The mean score of child behavior at both 1.5 and 5 years also increased with the severity of paternal anxiety, but the inclination was not as large as that with maternal anxiety.

Among the 18,767 siblings (Table 2) with complete data on child-behavior problems at 1.5 years, the mean score of child-behavior problems increased and decreased (0.47 → 0.57 → 0.48) as maternal prenatal anxiety escalated from light to moderate to severe. We observed a similar pattern in the mean score of child-behavior problems at 5 years. However, the mean score of child-behavior problems at both 1.5 and 5 years increased as maternal postnatal (or paternal) anxiety became severe.

Prenatal and postnatal maternal anxiety

We found a moderately positive association between prenatal maternal anxiety and child-behavior problems at both 1.5 years ($\beta = 0.14$, 95% confidence interval [CI] 0.13, 0.16) and 5 years ($\beta = 0.19$, 95% CI 0.16, 0.21) (see Table 3). These associations remained significant after adjusting for potential confounders (maternal smoking, alcohol intake, parental education,

Table 1. Characteristics of full cohort.

		Behavior Problems at 1.5 years			Behavior Problems at 5 years		
		Counts n = 73,757	Mean μ = 0.49	(SD) (s = 0.28)	Counts n = 40,163	Mean μ = 0.35	(SD) (s = 0.28)
Mother's prenatal anxiety	1–2, Light	70,072	0.49	(0.28)	38,293	0.35	(0.28)
(score)	2–3	2,989	0.57	(0.31)	1,490	0.46	(0.33)
	3–4, Severe	308	0.58	(0.33)	132	0.51	(0.37)
	NA	388	0.54	(0.34)	248	0.39	(0.31)
Maternal postnatal	1–2, Light	67,552	0.48	(0.28)	37,053	0.35	(0.28)
Anxiety	2–3	2,761	0.57	(0.31)	1,260	0.47	(0.34)
(score)	3–4, Severe	361	0.59	(0.32)	167	0.50	(0.36)
	NA	3,083	0.52	(0.30)	1,683	0.38	(0.31)
Father's anxiety	1–2, Light	53,910	0.49	(0.28)	32,526	0.35	(0.28)
(score)	2–3	1,216	0.51	(0.29)	748	0.40	(0.30)
	3–4, Severe	123	0.53	(0.32)	61	0.43	(0.31)
	NA	18,508	0.49	(0.29)	6,828	0.36	(0.29)
Smoking	None	64,344	0.48	(0.28)	36,058	0.35	(0.28)
during pregnancy	Sometimes	2,928	0.54	(0.29)	1,259	0.41	(0.30)
	Daily	2,543	0.56	(0.31)	911	0.46	(0.31)
	NA	3,942	0.49	(0.30)	1,935	0.36	(0.29)
Alcohol consumption	Never	60,103	0.49	(0.28)	33,809	0.35	(0.28)
during pregnancy	1+/month	435	0.54	(0.28)	265	0.40	(0.30)
	NA	13,219	0.49	(0.30)	6,089	0.35	(0.29)
Parity	0	34,199	0.49	(0.28)	19,057	0.38	(0.29)
	1	25,626	0.50	(0.29)	13,984	0.35	(0.28)
	2	10,938	0.46	(0.28)	5,645	0.31	(0.27)
	3	2,298	0.46	(0.29)	1,138	0.31	(0.28)
	4+	696	0.46	(0.29)	339	0.30	(0.26)
Child sex	Boy	37,709	0.51	(0.29)	20,491	0.38	(0.30)
	Girl	36,047	0.47	(0.28)	19,672	0.33	(0.27)
	NA	1	1.40	-	0	-	-
Birth complication	No	53,581	0.49	(0.28)	29,827	0.36	(0.29)
	Yes	20,176	0.48	(0.28)	10,336	0.34	(0.28)
Education	University 4+	46,673	0.47	(0.27)	27,704	0.33	(0.27)
	College/University 3y	18,494	0.53	(0.29)	8,520	0.40	(0.30)
	College 1-2y	3,013	0.56	(0.30)	1,163	0.44	(0.32)
	Secondary school	1,393	0.58	(0.31)	514	0.46	(0.32)
	NA	4,184	0.50	(0.29)	2,262	0.37	(0.30)
Marital status	Married/Partner	71,097	0.49	(0.28)	38,785	0.35	(0.28)
	Single	2,660	0.52	(0.30)	1,378	0.41	(0.31)

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parity, marital status, and birth complication). We also found moderate associations between postnatal maternal anxiety and child-behavior problems at both 1.5 years (β = 0.15, 95% CI 0.13, 0.17) and at 5 years (β = 2.0, 95% CI 0.17, 0.22). A similar pattern was observed when logistic regressions were applied.

Fathers as a negative control

We compared the effects of maternal anxiety and paternal anxiety at the 17th week on child-behavior problems at 1.5 and 5 years (Table 4) because paternal anxiety was assessed at week 17 only. The effect size of paternal anxiety on child-behavior problems was smaller than that of

Table 2. Characteristics of sibling sub-sample.

		Behavior Problems at 1.5years			Behavior Problems at 5 years		
		Counts n = 18,767	Mean μ = 0.48	(SD) (s = 0.28)	Counts n = 10,922	Mean μ = 0.33	(SD) (s = 0.27)
Mother's prenatal anxiety	1–2, Light	18,143	0.47	(0.28)	10,596	0.32	(0.27)
(score)	2–3	495	0.57	(0.32)	247	0.43	(0.34)
	3–4, Severe	56	0.48	(0.29)	24	0.40	(0.29)
	NA	73	0.56	(0.29)	55	0.35	(0.25)
Maternal postnatal	1–2, Light	17,592	0.47	(0.28)	10,251	0.32	(0.27)
Anxiety	2–3	487	0.56	(0.31)	250	0.43	(0.35)
(score)	3–4, Severe	68	0.57	(0.33)	37	0.44	(0.39)
	NA	620	0.48	(0.28)	384	0.33	(0.28)
Father's anxiety	1–2, Light	15,369	0.47	(0.28)	9,381	0.33	(0.27)
(score)	2–3	274	0.48	(0.29)	172	0.35	(0.27)
	3–4, Severe	25	0.52	(0.33)	12	0.37	(0.37)
	NA	3,099	0.48	(0.29)	1,357	0.33	(0.27)
Smoking	None	17,075	0.47	(0.28)	10,139	0.32	(0.27)
during pregnancy	Sometimes	474	0.54	(0.30)	190	0.39	(0.32)
	Daily	382	0.56	(0.30)	147	0.39	(0.31)
	NA	836	0.48	(0.28)	446	0.34	(0.27)
Alcohol consumption	Never	15,854	0.47	(0.28)	9,411	0.33	(0.27)
during pregnancy	1+/month	73	0.51	(0.29)	40	0.41	(0.29)
	NA	2,840	0.48	(0.29)	1,471	0.32	(0.28)
Parity	0	8,071	0.48	(0.27)	3,761	0.34	(0.27)
	1	7,834	0.48	(0.28)	5,238	0.33	(0.28)
	2	2,257	0.45	(0.27)	1,515	0.30	(0.26)
	3	458	0.45	(0.30)	309	0.29	(0.27)
	4+	147	0.43	(0.29)	99	0.30	(0.24)
Child sex	Boy	9,657	0.49	(0.28)	5,637	0.35	(0.28)
	Girl	9,110	0.46	(0.27)	5,285	0.31	(0.26)
	NA	0	-	-	0	-	-
Birth complication	No	13,464	0.48	(0.28)	7,692	0.33	(0.27)
	Yes	5,303	0.47	(0.28)	3,230	0.32	(0.27)
Education	University 4+	13,359	0.46	(0.27)	8,300	0.31	(0.27)
	College/University 3y	3,848	0.51	(0.28)	1,873	0.36	(0.29)
	College 1-2y	474	0.56	(0.30)	191	0.40	(0.31)
	Secondary school	184	0.57	(0.31)	66	0.56	(0.37)
	NA	902	0.50	(0.28)	492	0.35	(0.27)
Marital status	Married/Partner	18,433	0.48	(0.28)	10,761	0.33	(0.27)
	Single	334	0.46	(0.28)	161	0.33	(0.30)

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maternal anxiety. The effect size of maternal anxiety on child-behavior problems at 1.5 years (0.06, 95% CI 0.06, 0.07) was twice the effect size of paternal anxiety (0.03, 95% CI: 0.02, 0.04). These maternal and paternal effects were reduced after adjustment for potential confounders, but remained significant.

Sibling comparisons

The associations between maternal anxiety and child-behavior problems were adjusted for family-shared effects in the sibling design (Table 5). The moderate associations observed in the full cohort (Table 3) almost vanished in the sibling design. For example, the adjusted effect of

Table 3. The effect of maternal anxiety on child behavior problems at 1.5 and 5 years (full cohort).

	Behavior Problems at 1.5 years		Behavior Problems at 5 years	
Multiple linear regression	Crude beta (95% CI)	Adjusted beta (95% CI)[1]	Crude beta (95% CI)	Adjusted beta (95% CI)[2]
Sample size (n)	n = 70,522	n = 52,175	n = 38,067	n = 27,224
No maternal anxiety	(reference)	(reference)	(reference)	(reference)
Prenatal anxiety only	0.14 (0.13, 0.16)	0.13 (0.12, 0.15)	0.19 (0.16, 0.21)	0.11 (0.09, 0.14)
Postnatal anxiety only	0.15 (0.13, 0.17)	0.15 (0.13, 0.173)	2.0 (0.17, 0.22)	0.13 (0.10, 0.16)
Logistic regression	Crude OR (95% CI)	Adjusted OR (95% CI)[1]	Crude OR (95% CI)	Adjusted OR (95% CI)[2]
Sample size (n)	n = 70,522	n = 52,175	n = 38,067	n = 27,224
No maternal anxiety	(reference)	(reference)	(reference)	(reference)
Prenatal anxiety only	1.5 (1.4, 1.6)	1.37 (1.25, 1.51)	1.87 (1.70, 2.07)	1.48 (1.30, 1.68)
Postnatal anxiety only	1.6 (1.5, 1.8)	1.60 (1.42, 1.79)	2.12 (1.88, 2.40)	1.68 (1.44, 1.97)

[1] Adjusted for maternal smoking, alcohol, parental education, parity, marital status, birth complication, and the interaction term between maternal prenatal and postnatal anxiety.

[2] Also adjusted for child behavior problems at 18 months.

[3] All estimates are significant = $p<0.05$

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prenatal anxiety on child behavior problems at 1.5 years was weak 0.02 (CI 95% -0.01, 0.05). The adjusted effect of prenatal anxiety on child-behavior problems at 5 years also appeared to be weak 0.02 (CI 95% -0.03, 0.05). Maternal prenatal and postnatal anxiety did not affect child-behavior problems after adjustment in this sibling design. We found consistent results from conditional logistic regressions.

Discussion

In this study, we applied three different approaches to control for unmeasured and measured confounding when examining the link between maternal anxiety during pregnancy and child-behavior problems. We found that behavior problems were higher when children had been exposed to maternal anxiety during pregnancy. Mothers' postnatal anxiety measured at six months was also associated with increased behavior problems at 1.5 and 5 years of age. Although the associations were somewhat weaker, they remained after adjusting for a number of potential confounders. The effect sizes are equivalent to those found in previous studies [9].

The second approach was to apply the father's anxiety measured during pregnancy as a negative control. Paternal anxiety operates as a negative control based on the assumption that

Table 4. The effect of prenatal anxiety on child behavior problems at 1.5 and 5 years.

	Behavior Problems at 1.5years			Behavior Problems at 5 years		
	Crude beta (95% CI)	**Mutually adjusted[1] beta (95% CI)**	**Fully adjusted[2] beta (95% CI)**	**Crude beta (95% CI)**	**Mutually adjusted[1] beta (95% CI)**	**Fully adjusted[3] beta (95% CI)**
Maternal anxiety at 17th week	0.06 (0.06, 0.07)	0.06 (0.06, 0.07)	0.03 (0.02, 0.03)	0.09 (0.08, 0.09)	0.08 (0.07, 0.09)	0.03 (0.02, 0.04)
Paternal anxiety at 17th week	0.03 (0.02, 0.04)	0.02 (0.02, 0.03)	0.02 (0.01, 0.03)	0.06 (0.05, 0.07)	0.05 (0.03, 0.06)	0.03 (0.02, 0.05)

[1] Adjusted for either maternal or paternal anxiety at 17th week.

[2] Adjusted for maternal anxiety 6 months, smoking, alcohol, parental education, parity, marital status and birth complication.

[3] Adjusted for maternal anxiety 6 months, child behavior problems at 1.5 years, smoking, alcohol, parental education, parity, marital status and birth complication.

All estimates are significant at $p< .05$

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Table 5. The effect of maternal anxiety on child behavior problems at 1.5 and 5 year (sibling design).

	Child behavior problems at 1.5 years		Child behavior problems at 5 years	
Contrast regression	Crude beta (95% CI)	Adjusted beta (95% CI)[1]	Crude beta (95% CI)	Adjusted beta (95% CI)[2]
Sample size (n)	(n = 7,378 pairs)	(n = 4,837 pairs)	(n = 3,237 pairs)	(n = 2,092 pairs)
No maternal anxiety	(reference)	(reference)	(reference)	(reference)
Prenatal anxiety only	-0.00 (-0.02, 0.03)	0.01 (-0.02, 0.05)	-0.02 (-0.06, 0.02)	-0.05 (-0.10, 0.01)
Postnatal anxiety only	0.01 (-0.01, 0.04)	0.02 (-0.01, 0.05)	0.01 (-0.03, 0.05)	0.02 (-0.03, 0.07)
Conditional logistic regression	Crude OR (95% CI)	Adjusted OR (95% CI)[1]	Crude OR (95% CI)	Adjusted OR (95% CI)[2]
Sample size (n)	(n = 18,122)	(n = 14,045)	(n = 10,526)	(n = 7,910)
No maternal anxiety	(reference)	(reference)	(reference)	(reference)
Prenatal anxiety only	1.06 (0.75, 1.50)	1.17 (0.74, 1.85)	1.16 (0.68, 1.97)	1.09 (0.52, 2.29)
Postnatal anxiety only	1.32 (0.88, 1.98)	1.07 (0.63, 1.80)	1.67 (0.90, 3.11)	1.36 (0.58, 3.19)

[1] Adjusted for maternal anxiety 6 months, smoking, alcohol, parental education, parity, marital status, birth complication, and the interaction term between maternal prenatal and postnatal anxiety.

[2] Also adjusted for child behavior problems at 1.5 years.

[3] All estimates at not significant ($p > .05$)

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paternal anxiety during pregnancy does not have any direct effect on the intrauterine environment coupled with the assumption that confounds are equally associated with both paternal and maternal anxiety [11]. We found that paternal prenatal anxiety was associated with child behavior. This suggests that the association between parental anxiety and child behavior could be confounded by shared environmental or genetic effects. However, this association was weaker than for maternal anxiety. This finding is in line with previous studies using paternal anxiety as a negative control [30] and points to the possibility of a direct biological effect of maternal anxiety through the intrauterine environment on child behavior [11].

To account for shared family effects, we applied a sibling-comparison design. In the sibling-comparison analyses, no associations were found for maternal anxiety measured either prenatally or at six months after birth. The implication is that maternal genetic and family-environmental factors that are shared by siblings may explain the consistent associations found in epidemiological studies examining the fetal-programming hypothesis. This finding is in line with previous studies examining relationships between depression during pregnancy and offspring mental health [16, 19]. However, no previous studies have examined paternal anxiety as a negative control, the timing of exposure, and maternal anxiety and associations with short- and long-term child behavior.

Strengths and limitations

A major strength of this study was applying a sibling-comparison design. Sibling designs can reveal spurious effects of the explanatory variables, since many of these factors are similar through successive pregnancies and thus exposed to each sibling. While non-twin sibling designs cannot completely control for genetic effects, they do offer a relatively effective control for shared genetic influences as well as non-measured shared family confounds. However, an advantage of the non-twin sibling design over the MZ-twin design is that it provides an opportunity to examine different environmental exposures in utero.

Another example is extrapolating from animal models to complex human traits. Whether the stress response in rodents and humans shares similar mechanisms is subject to debate. This is particularly so in light of findings that imply the possibility that effects of stress during pregnancy in humans may be due to confounding factors not taken into consideration in

animal research. Because we used data from a large population-based dataset, we were able to control for a number of covariates, such as birth complications, smoking and alcohol consumption during pregnancy, and maternal age and education.

One of the limitations of our study is the potential lack of representation due to the selection bias of MoBa participants. However, a study examining the effect of recruitment bias using data from the MoBa study showed that even though prevalence estimates of exposures and outcomes were not always equal to that of the background population, estimates of associations were not biased [29]. The women participating with more than one pregnancy in the cohort might also represent an element of selection bias. As has been suggested by Sjölander et al., [30] there is a possibility that the first pregnancy influences the second. Additionally, since we used self-reports from the mothers, the associations may be biased by common-method variance. For instance, highly anxious mothers may be poor judges of their children's difficult behavior compared to mothers experiencing less anxiety. However, since we examine the outcomes of young children, mothers were deemed to be the individuals with the most knowledge about their child's behavior, outweighing the possibility of bias through halo effects. Using the same informant–the mother–is often unavoidable in large cohort studies. Furthermore, as the behaviors measured were mostly observable child behaviors, they seemed less liable to bias than other child traits might be.

A third limitation is that we used short scales with few items to measure anxiety when broader measures of anxiety and clinical diagnostic interviews would have been optimal. However, in large-scale studies with over 100,000 pregnancies, clinical interviews would be extremely time-consuming and costly. Furthermore, these items were found to correlate highly with the longer version of the shortened scale [28].

In sum, this study suggests that the well-established association found for prenatal maternal anxiety and child behavior difficulties was no longer present, once stable confounding factors was accounted for in a sibling comparison design. Our findings push forward our thinking about early experiences and precursors for child difficulties in the first five years of life. Pregnant women of today may feel more confident that fetal psychological experiences may be less risky than previously thought because we have improved the study design and methodology.

Conclusions

In this large prospective cohort, we found that both maternal and paternal anxiety were associated with behavior problems, after adjusting for multiple controls. However, this association was attenuated within full-sibling pairs. Our findings suggest that the association between prenatal maternal anxiety and behavioral difficulties is confounded by genetic and/or other family factors.

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Effects of Paternal Obesity on Fetal Development and Pregnancy Complications: A Prospective Clinical Cohort Study

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Objectives: To evaluate the association between paternal obesity and fetal development and pregnancy complications.

Study Design: This prospective cohort clinical trial analyzed data from 7683 women with singleton pregnancies. All study subjects were sequentially divided into four groups based on paternal BMI. We compared the differences in fetal growth and pregnancy complications between different paternal BMI groups by univariate logistic regression and independent t-test. Finally, the independent predictors of SGA and macrosomia were determined.

Results: The incidences of preeclampsia, cesarean section, SGA, macrosomia, and postpartum hemorrhage in the paternal obesity group were significantly higher than the normal BMI group. With the increase of paternal BMI, fetal ultrasound measurement parameter, neonatal and placental weight showed an increasing trend (trend $P < 0.05$). However, these differences disappeared in the obese group. The test for interaction showed the effect of paternal obesity on SGA and macrosomia was significantly affected by maternal obesity. We also found paternal obesity was an independent predictor of both SGA and macrosomia. Based on the above results, we plotted the Nomograms for clinical prediction.

Conclusion: Paternal obesity can affect fetal growth parameters and placental development, which has an adverse impact on pregnancy outcomes. Optimizing the paternal BMI will help improve the health of the next generation.

Keywords: paternal obesity, macrosomia, SGA, preeclampsia, cohort study

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INTRODUCTION

Over the past 40 years, a global debate on population obesity has emerged, and many countries are now suffering from an obesity epidemic. Worldwide, more than 155 million people are overweight, and about 40 million children and adolescents are obese (1). The effects of obesity on individuals are well documented and involve an increased risk of cardiovascular disease, diabetes, and stroke.

In recent decades, the rapid increase in obesity cannot be explained exclusively by genomic DNA mutations or selection (2). This suggests the involvement of other causes, including gene expression of epigenetic modifications, which can occur over the life cycle of numerous individuals in a population and can therefore be immediately transmitted to a large number of offspring in the next generation (3). Although the developmental planning of mothers for the health of their offspring is widely accepted, women are thus described as being primarily responsible for the intergenerational transmission of obesity (4, 5). However, through a structural review of recent studies examining epigenetic and social mechanisms of obesity risk transmission, we suggest that the role of fathers in influencing obesity risk in early childhood has been underestimated. Previous reports did not consider the potential impact of paternal obesity, which would cause bias (6, 7). Although the design and execution of epidemiological studies on patrilineal exposure before pregnancy face challenges, especially in terms of selection bias and recruitment, we believe it is feasible and necessary (8). There is a growing awareness that parental obesity may have a negative impact on fetal development (9, 10). A review of studies on mouse models and human male obesity has clarified that male obesity has a significant negative impact on sperm motility, DNA damage and embryos in various key early developmental stages (11). Paternal obesity can not only induce epigenetic changes of sperm before conception, but also affect the development process during pregnancy (12). Recent data also suggest that paternal nutrition and weight status can alter placental function in offspring. In a high-fat diet-induced mouse model of obesity, paternal obesity is associated with placental weight loss, fetal growth restriction, and changes in placental genes expression associated with lipid metabolism. Although few studies have assessed the effects of paternal obesity on human placental function, several research groups have reported showing that paternal body mass index (BMI) is a predictor of offspring placental and birth weight (13). Future human cohort studies must collect reliable health information for both partners and include it appropriately in statistical analyses to determine true parental impact. At present, no study has used a large birth cohort to evaluate the impact of paternal obesity on fetal development and perinatal complications. Therefore, the aim of this study was to investigate the influence of paternal obesity on fetal development (BPD, FL, APAD, TAD, AC, birthweight, and body length), placenta development (weight and area), pregnancy complications (GDM, ICP, preeclampsia, preterm delivery), and pregnancy outcomes (delivery mode, neonatal asphyxia, postpartum hemorrhage).

MATERIAL AND METHODS

Participants

We invited a total of 8210 Chinese women who delivered their babies at the obstetric department of the International Peace Maternity and Child Health Hospital between November 2020 to August 2021 to participate in the study. Pregnant women with singleton pregnancies who had regular antenatal examinations were included in this prospective study. In the present study, only single pregnancy outcomes were investigated. After excluding cases that did not meet the inclusion criteria or were unwilling to follow-up, we finally included 7767 remaining cases. The Ethics Committee of the International Peace Maternity and Child Health Hospital approved the study procedures (reference number GKLW 2021-23). This study was registered with the China Clinical Trials Registry (www.clinicaltrials.gov) (registration number ChiCTR2000037885). All participants provided written informed consent and the ethics committee approved the consent procedure.

Inclusion and Exclusion Criteria

The inclusion criteria for this prospective study were:(1) Chinese nationality, (2) singleton pregnancy, (3) maternity files had been established in hospital, (4) regular antenatal examination, (5) complete follow-up data are available, (6) signed informed consent forms.

The exclusion criteria were:(1) foreign nationality, (2) multiple pregnancies, (3) inability to have regular maternity visits, (4) other hospital deliveries, (5) with contraindications to pregnancy such as gynecological oncology.

BMI Grouping

In 2006, the China Obesity working group, China office, international society for Life Sciences summarized and analyzed the relationship between body mass index and the prevalence of related diseases according to the large-scale measurement data of the Chinese population, put forward the limits for Chinese adults to judge the degree of overweight and obesity. This study adopted the body mass index (BMI) in the guidelines for the prevention and control of overweight and obesity in Chinese adults. The cut-off point value was used to determine the degree of obesity. The accuracy of height is 0.1cm and the accuracy of weight is 0.1kg. BMI = weight (kg)/height^2 (m^2). According to the suggestions, BMI is divided into four groups (14, 15): BMI < 18.5 is underweight, 18.5 ≤ BM < 24 is normal, 24 ≤ BMI < 28 is overweight, and BMI ≥ 28 is obesity.

Clinic Data Collection

All the participants' data were recorded by assigned persons and filed electronically, including age, gravidity and parity, BMI, personal and family history, IVF-ET, multiple pregnancies, weight gain during pregnancy, gestational age at delivery, pregnancy complications. All participants received regular follow-up visits. Weight gain during pregnancy was determined as the difference between the pre-pregnancy weight and the last measured weight before delivery. Paternal BMI figures were calculated from self-reported height and weight. Biometric data for newborns and placentas are routinely measured immediately after delivery. The birth weight, body length, placental weight and placental area of newborns were collected and recorded. Delivery mode and pregnancy outcomes were also recorded after the delivery, including postpartum hemorrhage, mode of delivery, Apgar score and amniotic fluid

volume. We also took some measures to minimize observer bias. For example, we used masking to hide the research purpose of all observations and used different data collection sources for data triangulation. We used multiple observers and conducted unified training to ensure the reliability of data records and standardized observation procedures.

Ultrasound Measurements During Pregnancy

Collect and record the fetal biparietal diameter, femoral length, transverse abdominal diameter, anterior-posterior abdominal diameter and abdominal circumference measured by ultrasound (16) within one week before delivery. Professional ultrasound doctors conduct ultrasonic diagnostic examination and analysis to ensure the quality of data. The diameter of biparietal bone is measured from the outer edge of parietal bone near the probe to the inner edge of parietal bone on the other side on the cross section of fetal brain. The main signs include hyaline membrane cavity, thalamus, third ventricle and accumbent compartment. Using the ellipse function of the ultrasonic instrument, measure the head circumference on the same plane as the biparietal diameter. The abdominal circumference was measured in a plane perpendicular to the level of the fetal umbilical plexus, including the spine, gastric vesicles, liver, umbilical vein, skin, and subcutaneous fat. In the scan, the femoral length was measured from the greater trochanter to the lateral condyle, and the bones at both ends were clearly visible.

Definition of Pregnancy Complications

Pre-eclampsia is defined according to the International Society for the Study of Hypertension in Pregnancy (17). Previously normotensive women should have a systemic systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg after 20 weeks of gestation, both at least 4 hours apart. Hypertension should be accompanied by ≥300 mg of proteinuria in 24 hours or, if no 24-hour urine collection is available, 2 readings of at least ++ on a midstream or catheter urine specimen. Gestational age is calculated from the first day of the last normal menstrual period and is confirmed by an ultrasound scan in the first trimester of pregnancy. SGA refers to the birth weight is under the lightest 10% of birth weights for all babies born at the same number of gestation weeks of pregnancy. Macrosomia is defined as the birth weight of a newborn equal to or greater than 4000 grams. Preterm birth is defined as birth before 37 weeks of pregnancy. Postpartum Hemorrhage is defined as blood loss ≥1000 ml after vaginal or cesarean delivery (18, 19). GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. ICP is characterized by pruritus and elevated serum bile acid concentrations and usually develops in the third trimester of pregnancy and resolves rapidly after delivery (20).

Statistical Analysis

Data were analyzed with SPSS version 21.0 (IBM Corp., Armonk, NY) and R software version 3.6.1 (R Development Core Team, July 2019; http://www.r-project.org). Quantitative data were expressed as means ± standard deviation and compared using the independent samples t-test. Qualitative data were expressed as rates and compared using the chi-square test. Univariate logistic regression was used to compare pregnancy complications and outcomes in different paternal BMI groups by using forward stepwise. Multivariate regression analysis was used to adjust for confounding variables known to independently affect SGA and macrosomia. Risk ratios (ORs) with 95% confidence intervals (CIs) were calculated to identify risk factors and assess their impact. The nomogram was established based on results of the multivariate logistic regression analysis using software R 3.0.3 by using the "rms" package. P-value < 0.05 was considered significant.

RESULT

Description of the Cohort

Of the 7767 eligible women, 84 lost the chance of follow-up (48 delivered in other hospitals, 21 stillbirths and 15 withdrew from follow-up for personal reasons). **Figure 1** showed the progress of participants through the study. Finally, 7683 participants with a singleton pregnancy completed the whole follow-up process. We finally included 7683 father/mother/child triplets with 3932 newborn boys and 3751 newborn girls, respectively. The mean paternal age was 32.7 ± 4.6 years and their mean body mass index was 24.1kg/m^2, whereas the mean maternal age was 31.3 ± 3.8 years and the mean BMI at early pregnancy was 21.1 kg/m^2. At the pregravid assessment, paternal BMl increased progressively across the groups from the lowest to the highest of BMI. Among them, a total of 201 (2.7%) were in the underweight group, 3813 (49.6%) were in the normal BMI group, 2913 (37.9%) were in the overweight group and 756 (9.8%) were in the obesity group. Maternal BMI was also divided into four groups, including 1116 in underweight (14.5%), 5495 in normal (71.5%), 893 in overweight (11.6%) and 179 in obesity (2.3%). The baseline characteristics of the study population (such as parental age, gravidity, parity, parental education, mode of conception, maternal BMI and maternal disease history) are shown in **Table 1**, stratified into four groups based on paternal BMI.

Effects of Paternal BMI on Pregnancy Complications and Delivery Outcomes

Table 2 showed the results of univariate logistic regression, which compared the differences of pregnancy complications and delivery outcomes in different paternal BMI groups by forward stepwise. The intergroup p value represented the univariate logistic regression results compared with the reference (normal BMI group). The results showed that the incidences of preeclampsia, SGA, macrosomia, cesarean and postpartum hemorrhage in paternal obesity group were significantly higher than in normal BMI group. The rates of macrosomia and cesarean section in paternal overweight group were also significantly higher than those in normal BMI group. And the SGA rate in paternal underweight group was significantly higher than in normal BMI group. In addition, trend p values represented the linear

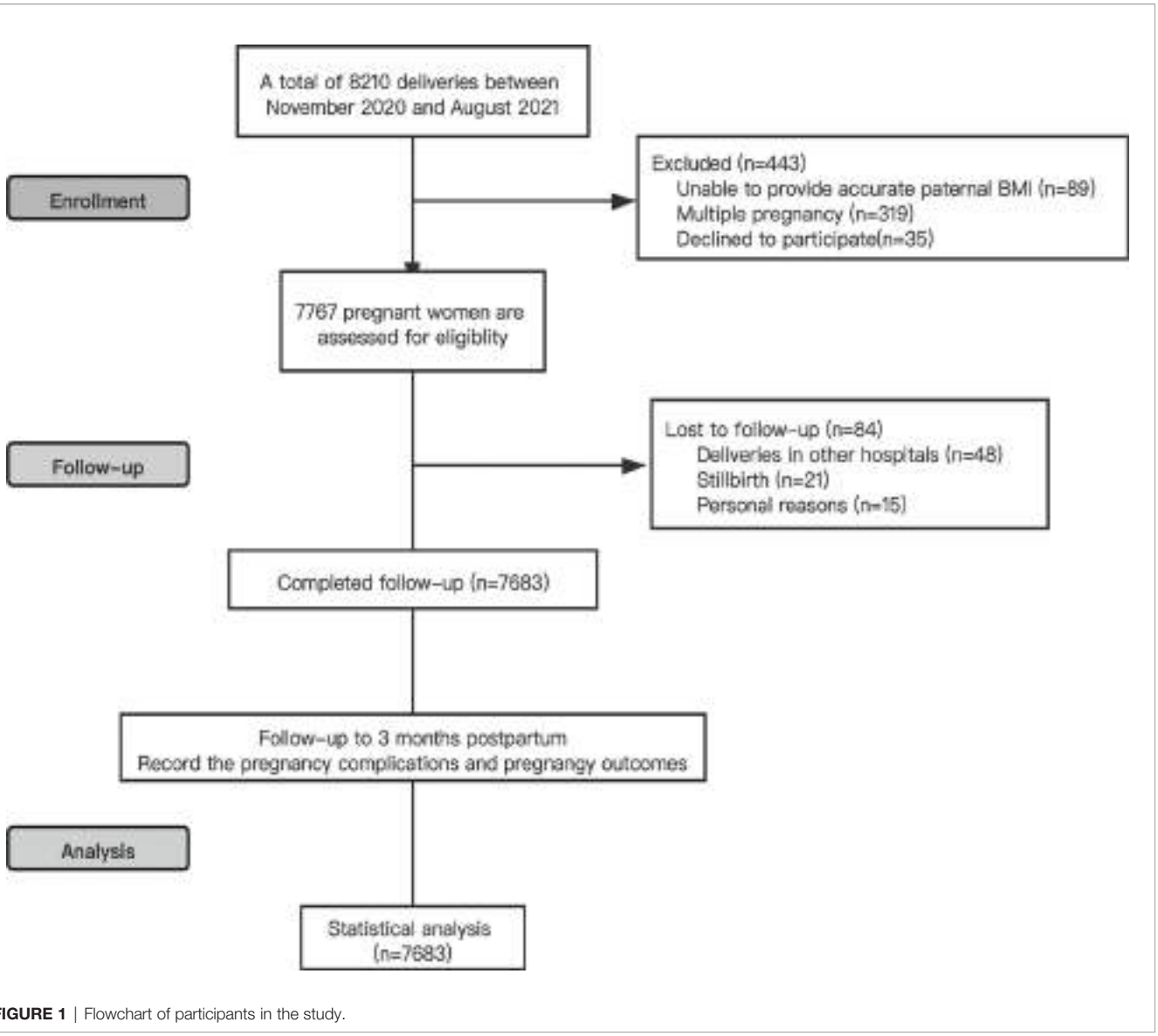

FIGURE 1 | Flowchart of participants in the study.

relationship between paternal BMI and pregnancy outcomes across the different categories. It reflected that with the increase of paternal BMI, the higher the rate of preeclampsia, SGA, macrosomia, and cesarean section.

Effect of Paternal BMI on Fetal Growth and Placental Development

Ultrasonography was performed within one week before delivery. **Table 3** illustrates the comparison of fetal ultrasound parameters and postpartum measurements in different paternal BMI groups. The trend test results showed that with the increase of paternal BMI, fetal BPD (biparietal diameter), FL (femoral length), TAD (transverse abdominal diameter), APAD (anteriorposterior abdominal diameter), AC (abdominal circumference), birth weight, placental weight and placental area showed an increasing trend (trend $P < 0.05$). Compared with the normal paternal BMI group, BPD, AC, placental weight and placental area decreased in the underweight group, and increased significantly in the overweight group. However, the above indicators showed no significant difference in the obesity group compared with the control group.

Value of Paternal Obesity as an Independent Factor in Predicting Macrosomia and SGA

Firstly, paternal BMI and the risk of SGA/macrosomia was analyzed by univariate and multivariate logistic regression, stratified by maternal BMI (**Table 4**). The test for interaction showed that the effect of paternal obesity on SGA and macrosomia was significantly affected by maternal obesity ($P < 0.005$). For maternal underweight, paternal underweight can significantly increase the incidence of SGA. For maternal BMI normal and overweight, paternal underweight and obesity can significantly increase the occurrence of SGA, while paternal

TABLE 1 | Baseline characteristics of patients in the study.

		Paternal BMI (kg/m^2)			
		Underweight (n = 201)	**Normal (n = 3813)**	**Overweight (n = 2913)**	**Obesity (n = 756)**
Maternal age (y)		29.79 ± 3.90	31.17 ± 3.68	31.50 ± 3.77	31.56 ± 3.87
Paternal age (y)		30.97 ± 4.03	32.54 ± 4.62	32.97 ± 4.56	33.08 ± 4.86
Gravidity (%)	<3	172 (85.6%)	3066 (80.4%)	2300 (79.0%)	595 (78.7%)
	≥3	29 (14.4%)	747 (19.6%)	613 (21.0%)	161 (21.3%)
Parity (%)	<2	171 (85.1%)	2793 (73.2%)	2085 (71.6%)	546 (72.2%)
	≥2	30 (14.9%)	1020 (26.8%)	828 (28.4%)	210 (27.8%)
Maternal education (%)	High school and below	22 (10.9%)	236 (6.2%)	167 (5.7%)	68 (9.0%)
	Bachelor's degree	143 (71.2%)	2601 (68.2%)	1984 (68.1%)	532 (70.4%)
	Master degree or above	36 (17.9%)	976 (25.6%)	762 (26.2%)	156 (20.6%)
Paternal education (%)	High school and below	15 (7.4%)	225 (5.9%)	160 (5.5%)	60 (7.9%)
	Bachelor's degree	158 (78.6%)	2501 (65.6%)	1992 (68.4%)	521 (68.9%)
	Master degree or above	28 (14.0%)	1087 (28.5%)	761 (26.1%)	175 (23.2%)
Conception (%)	Natural	184 (91.5%)	3451 (90.5%)	2607 (89.5%)	660 (87.3%)
	IVF	17 (8.5%)	361 (9.5%)	306 (10.5%)	96 (12.7%)
Maternal BMI	Underweight	55 (27.4%)	603 (15.8%)	373 (12.8%)	85 (11.2%)
(kg/m^2)	Normal	131 (65.2%)	2783 (73.0%)	2077 (71.3%)	504 (66.7%)
	Overweight	11 (5.5%)	374 (9.8%)	382 (13.1%)	126 (16.7%)
	Obesity	4 (1.9%)	53 (1.4%)	81 (2.8%)	41 (5.4%)
Maternal medical history (%)	Chronic hypertension	0 (0%)	17 (0.4%)	15 (0.5%)	7 (0.9%)
	Diabetes	0 (0%)	0 (0%)	3 (0.1%)	2 (0.3%)
	Heart disease	0 (0%)	2 (0.1%)	2 (0.1%)	2 (0.3%)

Data are given as number (percentage) or as the mean ± SD. BMI, body mass index.

overweight and obesity can significantly increase the incidence of macrosomia. However, for maternal obesity, paternal BMI had little effect on the incidence of both SGA and macrosomia. We next performed logistic regression analysis to determine the independent determinants of macrosomia and SGA. **Figure 2** represented the forest plot of logistic regression analyses of the risk of SGA and macrosomia. (A) and (B) represented independent predictors of SGA and macrosomia respectively. Data were presented as odds ratio per standard deviation change in the indicated variable. For SGA, the important independent predictors were paternal obesity (P<0.001), maternal obesity (P=0.044), preeclampsia (P<0.001) and paternal underweight (P<0.001). For macrosomia, the independent predictors were paternal obesity (P=0.005), maternal obesity (P<0.001) and maternal weight gain during pregnancy (P<0.001). The result showed that both paternal obesity and maternal obesity were important independent predictors in macrosomia and SGA.

Development of a Nomogram for Predicting the Probability of Macrosomia and SGA

The nomogram was developed using predictors from the multivariate analysis and significant variables pregravid and during pregnancy from univariate analysis to predict macrosomia and SGA risk. The nomogram for predicting SGA consisting of paternal underweight, paternal obesity, maternal obesity, preeclampsia, and maternal age (**Figure 3A**). The nomogram for predicting macrosomia consisting of paternal obesity, maternal obesity, GDM, maternal weight gain (**Figure 3B**). The total score calculated from the above variables was used to estimate status of SGA or macrosomia. These results suggested that the nomogram can be clinically useful in predicting the probability of the occurrence of macrosomia and SGA. This shows that paternal obesity is of great significance for the occurrence of both SGA and macrosomia.

DISCUSSION

The effects of maternal obesity on pregnancy and child health have been extensively studied, and systematic evaluations have found an increased incidence of pregnancy complications in pregnancy, including gestational diabetes (21), preeclampsia (22), hypertension, depression (23), cesarean section, preterm delivery, surgical site infections, and neonatal complications including perinatal death (24), macrosomia (25), and fetal defects. The impact of paternal obesity on pregnancy and child health has received less attention. Although most investigations have focused on the maternal environment, there is evidence that exposure to paternal obesity also predisposes offspring to metabolic disorders later in life (26). Obesity is a complex multifactorial disease involving genetic, epigenetic, and environmental factors (27, 28). The effect of epigenetic changes in sperm cells on fetal gene expression has been studied in animal models, and paternal environmental conditions have a negative impact not only on sperm but also on pregnancy success and offspring health. In reviewing the literature, some scholars (29) have emphasized the need to explore and recognize paternal contributions to the health of their offspring within the developmental origins of health and disease hypothesis and have referred to this new concept as the Paternal Origins of the Health and Disease paradigm (30) (POHaD). A better understanding of the preconception origins of disease through paternal exposure models will provide evidence-based public health recommendations for future fathers (30). However, so far,

TABLE 2 | Univariate logistic regression comparing pregnancy outcomes in different paternal BMI groups by using forward stepwise.

		Underweight (BMI <18.5)	Normal (BMI = 18.5~23.9)	Overweight (BMI = 24.0~27.9)	Obesity (BMI ≥ 28)	P value for trend[b]
GDM	Incidence (%)	17.4	14.3	15.0	16.5	0.821
	P[a]	0.221	Reference	0.438	0.112	
	OR (95%CI)	1.264 (0.868-1.841)	1	1.055 (0.921-1.210)	1.188 (0.961-1.469)	
ICP	Incidence (%)	1.0	0.7	0.8	0.5	0.851
	P[a]	0.569	Reference	0.627	0.690	
	OR (95%CI)	1.523 (0.358-6.474)	1	1.153 (0.649-2.049)	0.806 (0.280-2.323)	
Preeclampsia	Incidence (%)	3.0	2.2	2.8	4.6	0.001*
	P[a]	0.484	Reference	0.107	<0.001*	
	OR (95%CI)	1.350 (0.582-3.127)	1	1.286 (0.947-1.747)	2.129 (1.425-3.181)	
Premature birth	Incidence (%)	4.0	3.9	4.1	3.2	0.745
	P[a]	0.925	Reference	0.603	0.415	
	OR (95%CI)	1.036 (0.501-2.141)	1	1.068 (0.833-1.369)	0.833 (0.537-1.293)	
SGA	Incidence (%)	18.9	2.9	3	8.5	<0.001*
	P[a]	<0.001*	–	0.806	<0.001*	
	OR (95%CI)	7.848 (5.257-11.717)	Reference	0.806 (1.036-0.779)	3.113 (2.264-4.282)	
Macrosomia	Incidence (%)	2.5	3.1	5.7	6.6	<0.001*
	P[a]	0.601	–	<0.001*	<0.001*	
	OR (95%CI)	0.785 (0.317-1.943)	Reference	1.872 (1.473-2.379)	2.180 (1.552-3.061)	
Cesarean delivery	Incidence (%)	39.8	41.8	46.2	47.8	<0.001*
	P[a]	0.580	Reference	<0.001*	0.002*	
	OR (95%CI)	0.921 (0.690-1.231)	1	1.199 (1.088-1.321)	1.274 (1.089-1.489)	
Neonatal asphyxia	Incidence (%)	0.5	0.6	0.4	0.4	0.433
	P[a]	0.884	Reference	0.462	0.542	
	OR (95%CI)	0.862 (0.116-6.424)	1	0.772 (0.388-1.536)	0.687 (0.205-2.300)	
Postpartum hemorrhage	Incidence (%)	0.3	0.5	0.3	0.8	0.178
	P[a]	0.601	Reference	0.879	0.046*	
	OR (95%CI)	1.728 (0.222-13.452)	1	1.071 (0.443-2.588)	2.765 (1.019-7.500)	

BMI, body mass index; GDM, gestional diabetes mellitude; ICP, intrahepatic cholestasis of pregnancy; SGA, small for gestational age; OR, odds ratio;95% CI, 95% confidence interval of the estimated trend.

[a]*The p-values taken from univariate logistic regression compared with the referent (normal BMI).*

[b]*P values for trend across categories of different paternal BMI.*

**P<0.05 was considered statistically significant.*

little is known about the potential role of paternal environmental impact on offspring's health. Imprinted genes are well-known parents' "conflict theory" that controls fetal growth. It is proposed that father-expressed genes (PEGs) promote nutrition from the mother, while mother-expressed genes (MEGs) restrict children's use of resources (31). Imprinted genes are also thought to play an essential role in many biological processes and diseases, including intrauterine growth restriction (IUGR), obesity, and diabetes mellitus. Observational studies have found that increased paternal body mass index during pregnancy alters fetal cord blood methylation patterns, decreases neonatal IgM levels (32), is associated with delayed personal and social functioning in three-year-old children (33), increases the incidence of type II diabetes and insulin resistance (34), and is associated with the severity of obesity in childhood (35). Studies have found that obesity in the father during pregnancy alters birth weight (36–38) and increases the child's susceptibility to metabolic syndrome (36), subfertility (39), fatty liver (40), kidney disease (41), and hypertension (42) while reducing the child's cognitive function (43). It is widely believed that these factors have the potential to influence early embryonic and fetal growth and development, leading to the hypothesis that paternal obesity can influence pregnancy and child health outcomes long after pregnancy through epigenetic alterations. Paternal obesity has been shown to be associated with increased weight and body fat and metabolic disturbances in offspring prepubertal children (44). Recent studies have shown that paternal high-fat diet programs b-cell dysfunction in female rat offspring through epigenetic mechanisms (45). A similar paternal obesity effect was also found in the mouse model of paternal obesity. More and more evidence mainly come from animal experiments, which shows that Father also plays an essential biological role in fetal programming, but so far, only a few human epidemiological data support this concept. The clinical community still generally does not recognize the impact of father obesity on pregnancy and child health. This study will focus on the evidence of the effects of paternal obesity on pregnancy outcomes and fetal development to standardize and optimize paternal health to improve health outcomes in the next generation, creating a theoretical basis and enabling conditions for primary prevention of chronic disease.

Effect of Paternal Obesity on Placental Development and Pregnancy Complications

The placenta is known to be a dynamic regulator of fetal nutrient transport and growth and is a unique organ because it is influenced by three genomes: the mother, the father, and the fetus. The paternal genome, especially the epigenome, plays a crucial role in the development and function of the placenta,

TABLE 3 | Comparison of fetal growth and placental development in different paternal BMI groups.

Measurements		Paternal BMI (kg/m^2)					P for trend[b]
		Group	Underweight (BMI < 18.5)	Normal (BMI = 18.5~23.9)	Overweight (BMI = 24.0~27.9)	Obesity (BMI ≥ 28)	
Ultrasound measurements	BPD	Mean ± SD	93.04 ± 5.12	94.20 ± 3.73	94.59 ± 3.79	94.51 ± 3.62	<0.001*
		P[a]	0.019*	[reference]	0.002*	0.106	
	FL	Mean ± SD	68.73 ± 4.05	69.45 ± 2.89	69.61 ± 2.99	69.72 ± 2.83	0.001*
		P[a]	0.011*	[reference]	0.108	0.07	
	APAD	Mean ± SD	101.50 ± 7.50	103.81 ± 6.81	104.28 ± 6.97	104.14 ± 7.08	<0.001*
		P[a]	0.001*	[reference]	0.038*	0.362	
	TAD	Mean ± SD	99.68 ± 7.28	101.42 ± 6.60	101.71 ± 6.77	102.04 ± 6.34	0.001*
		P[a]	0.007*	[reference]	0.191	0.069	
	AC	Mean ± SD	316.86 ± 20.60	323.24 ± 17.70	324.44 ± 18.47	324.73 ± 18.21	<0.001*
		P[a]	0.002*	[reference]	0.044*	0.115	
Placental measurements	Placental weight	Mean ± SD	564.68 ± 25.66	607.78 ± 34.33	616.42 ± 42.63	613.59 ± 36.17	<0.001*
		P[a]	<0.001*	[reference]	<0.001*	0.125	
	Placental area	Mean ± SD	231.16 ± 15.87	241.76 ± 14.09	245.02 ± 16.12	242.76 ± 16.14	0.015*
		P[a]	0.025*	[reference]	0.045*	0.692	
	Umbilical cord length	Mean ± SD	58.24 ± 7.27	59.88 ± 8.85	57.94 ± 6.28	63.61 ± 9.79	0.428
		P[a]	0.793	[reference]	0.236	0.332	
Newborn measurements	Birthweight	Mean ± SD	3116.22 ± 441.712	3284.65 ± 407.59	3331.12 ± 422.06	3339.23 ± 429.72	<0.001*
		P[a]	<0.001*	[reference]	<0.001*	<0.001*	
	Body length	Mean ± SD	49.29 ± 1.64	49.74 ± 1.48	49.83 ± 1.47	49.88 ± 1.51	0.747
		P[a]	<0.001*	[reference]	0.008*	0.014*	

BMI, body mass index; BPD, biparietal diameter; FL, femoral length; TAD, transverse abdominal diameter; APAD, anteriorposterior abdominal diameter; AC, abdominal circumference
The data are presented as the mean values ± standard deviations.
[a]*The p-values taken from independent samples t-test and the reference group in this analysis was normal BMI group.*
[b]*P values for trend across categories of different paternal BMI.*
**P < 0.05 was considered statistically significant.*

which in turn regulates fetal growth (46). The interaction between paternal factors and placental development has been most extensively studied in preeclampsia. Recent data also suggest that paternal nutrition and weight status can alter placental function in offspring. Several research groups have reported that paternal BMI is the predictor of placental and birth weight in the offspring (13). Therefore, more studies are needed to fully understand the role of paternal nutritional status in shaping placental function. There is evidence that fathers play an essential role in the development of preeclampsia. The existence of a "paternal antigen" has been proposed and paternal obesity has also been suggested as a risk factor for preeclampsia (47). Fetal HLA-G variants from fathers increase immune incompatibility with mothers and are also significantly associated with preeclampsia in multiple pregnancies. Epidemiological, clinical, immunological, and genetic evidence supports the role of the father in the development of preeclampsia (47). The study demonstrates that paternal obesity in mice is associated with impaired embryonic development and significantly reduces fetal and placental weight (48). Placental and fetal growth retardation associated with paternal obesity is opposite to the effect of maternal obesity on pregnancy, which is significantly associated with the incidence of older than gestational age infants. Placental growth deceleration generally precedes fetal growth deceleration (49), and placental size has been identified as an independent determinant of intrauterine fetal growth and birth weight (50). Paternally expressed imprinted genes tend to enhance placental growth (51). Thus, imprinting errors or epigenetic changes during spermatogenesis may affect the placenta and subsequent fetal growth associated with paternal obesity. In mice's high-fat diet-induced obesity model, paternal obesity was associated with reduced placental weight, fetal growth restriction, and altered placental expression and DNA methylation of genes related to lipid metabolism. In mice, hypermethylation of just one parentally expressed imprinted gene is sufficient to induce FGR (52). In addition, global methylation changes of non-imprinted genes and altered gene expression have also been found in FGR placentas (53). SGA (small for gestational age) is a major obstetric complication caused by placental dysplasia and is an important cause of perinatal mortality and morbidity. SGA is mainly due to

TABLE 4 | Paternal BMI and the risk of SGA/macrosomia was analyzed by logistic regression, stratified by maternal BMI.

Maternal BMI		Paternal BMI		Crude		Adjusted		P for Interaction[c]
		Group	Incidence (%)	OR (95% CI)[a]	P value	OR(95% CI)[b]	P value	
SGA	**Underweight**	Underweight	5.0	9.324 (4.766-18.238)	<0.001*	9.435 (4.733-18.809)	<0.001*	<0.001
		Normal	53.7	Ref		Ref		
		Overweight	33.6	0.715 (0.382-1.338)	0.294	0.708 (0.373-1.342)	0.290	
		Obesity	7.7	0.834 (0.834-0.287)	0.738	0.645 (0.211-1.975)	0.443	
	Normal	Underweight	2.4	5.416 (2.931-10.007)	<0.001*	4.962 (2.664-9.241)	<0.001*	
		Normal	50.4	Ref		Ref		
		Overweight	37.9	1.113 (0.760-1.626)	0.584	1.128 (0.770-1.654)	0.537	
		Obesity	9.3	3.781 (2.493-5.734)	<0.001*	3.837 (2.517-5.850)	<0.001*	
	Overweight	Underweight	1.3	23.357 (4.834-112.855)	<0.001*	19.147 (3.518-104.211)	0.001*	
		Normal	41.7	Ref		Ref		
		Overweight	42.9	1.637 (0.588-4.555)	0.346	1.718 (0.610-4.837)	0.306	
		Obesity	14.1	8.990 (3.424-23.602)	<0.001*	8.861 (3.285-23.899)	<0.001*	
	Obesity	Underweight	2.4	16.000 (0.791-323.701)	0.071	14.445 (0.673-310.198)	0.088	
		Normal	29.7	Ref		Ref		
		Overweight	44.3	2.057 (0.208-20.371)	0.537	1.938 (0.193-19.413)	0.574	
		Obesity	23.6	4.000 (0.399-40.059)	0.238	3.989 (0.395-40.241)	0.241	
Macrosomia	**Underweight**	Underweight	5.0	0	0.998	0	0.998	0.006
		Normal	53.7	Ref		Ref		
		Overweight	33.6	2.269 (0.714-7.209)	0.165	3.294 (0.765-14.187)	0.110	
		Obesity	7.7	2.827 (0.539-14.830)	0.219	1.501 (0.131-17.208)	0.744	
	Normal	Underweight	2.4	1.078 (0.388-2.996)	0.886	0.847 (0.2201-3.573)	0.821	
		Normal	50.4	Ref		Ref		
		Overweight	37.9	1.618 (1.190-2.199)	0.002*	1.677 (1.157-2.433)	0.006*	
		Obesity	9.3	1.639 (1.018-2.639)	0.042*	1.749 (1.002-3.053)	0.049*	
	Overweight	Underweight	1.3	2.65 (0.247-17.256)	0.503	0	0.999	
		Normal	41.7	Ref		Ref		
		Overweight	42.9	2.385 (1.321-4.306)	0.004*	2.054 (1.046-4.034)	0.037*	
		Obesity	14.1	2.209 (1.020-4.780)	0.044*	2.314 (1.001-5.348)	0.050*	
	Obesity	Underweight	2.4	0	0.999	0	0.999	
		Normal	29.7	Ref		Ref		
		Overweight	44.3	1.075 (0.330-3.507)	0.905	1.211 (0.331-4.436)	0.773	
		Obesity	23.6	3.185 (0.982-10.329)	0.054	2.714 (0.704-10.460)	0.147	

BMI, body mass index; SGA, small for gestational age; OR, odds ratio;95% CI, 95% confidence interval of the estimated trend.

[a]Univariate logistic regression compared with the referent (norma paternal BMI).

[b]Estimated using multivariate logistic regression. Model for SGA adjusted for maternal BMI, preeclampsia, maternal age. Model for macrosomia adjusted for maternal BMI, GDM, maternal weight gain.

[c]P values for Interaction showed the interaction effect of paternal obesity and maternal obesity on the risk of SGA/macrosomia.

**P < 0.05 was considered statistically significant.*

placental insufficiency, which reduces the supply of nutrients and oxygen to the developing fetus (54). Fetal adaptation to this altered uterine environment results in permanent changes in glucose-insulin metabolism (55). Reduced hypothalamic satiety pathways in younger than fetal age children lead to programmed overeating and a self-perpetuating cycle of obesity (56). SGA infants are also associated with an increased risk of NCDs in offspring (57). Individuals with growth restriction are at increased risk of developing metabolic syndromes in later life, including obesity, hypertension, cardiovascular disease, and type 2 diabetes (58, 59). It has been shown that embryos from paternal obesity have a tendency for fertilization arrest, delayed preimplantation development, mitochondrial dysfunction, reduced blastocyst formation, reduced cell numbers, and abnormal cell lineage assignment to the trophoblastic ectoderm (TE) or inner cell mass (ICM) (60). Also, obese fathers have significantly smaller fetal development, delayed limb morphology, and a substantially smaller placenta (61, 62). In addition, paternal obesity increases the likelihood of metabolic syndrome in the offspring (63). Our study showed that paternal obesity was significantly associated with the incidence of preeclampsia, with a progressive increase in preeclampsia as paternal BMI increased in a linear association (P<0.001). In addition, paternal obesity is an independent predictor of both SGA (OR=2.866, 2.091-3.930) and macrosomia (OR=1.690, 1.168-2.444). All these results confirm the adverse effects of paternal obesity on placental development and pregnancy complications.

Effect of Paternal Obesity on Fetal Development

At birth, both SGA and macrosomic infants are associated with increased fetal complications, including increased NICU and fetal mortality (64, 65). They also increase the risk of developing chronic diseases later in life. It should be noted that early signs of these chronic disease states have been shown in the offspring of animal models with obese fathers (66, 67). The study showed an increased likelihood of both SGA and macrosomia with paternal obesity (68), which may be why other studies have generally found no effect on average birth weight. The existing literature reports two diametrically opposite birth weight results for fetal development of obese fathers: macrosomia (69) and SGA (70),

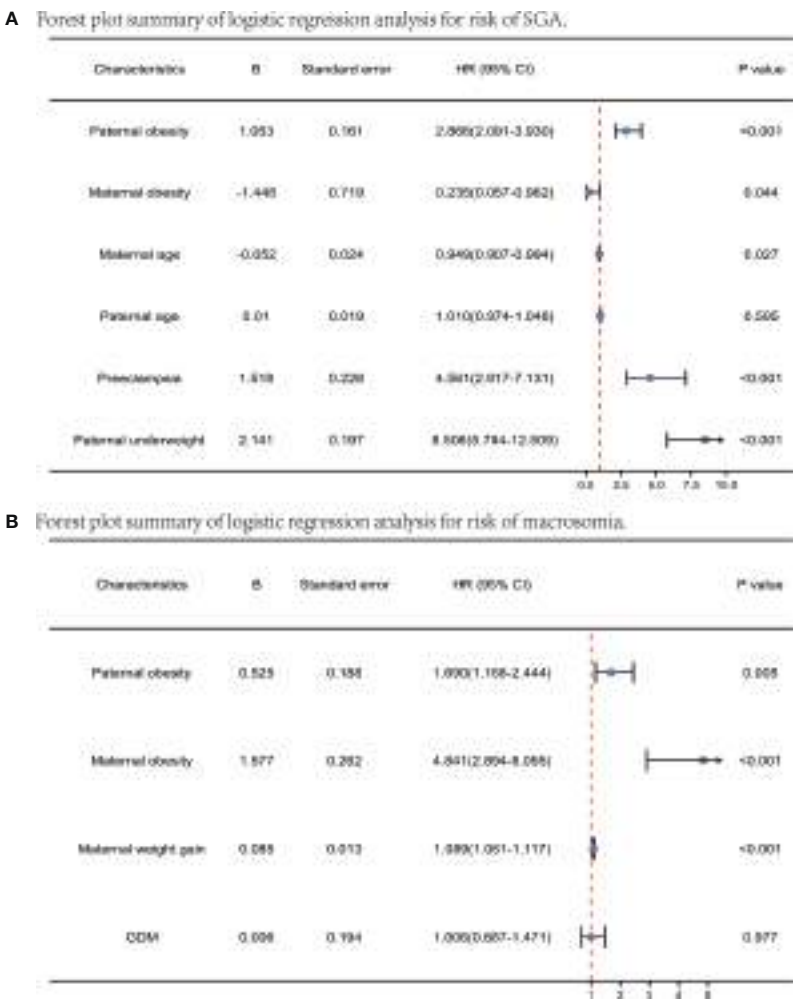

FIGURE 2 | Forest plot summary of logistic regression analysis for risk of SGA and macrosomia. Predictors of SGA **(A)** and macrosomia **(B)** pregravid and before pregnancy. Data were presented as odds ratio per standard deviation change in the indicated variable.

and both have statistical differences. McCowan et al. (70) found that obese men (BMI ≥ 30 kg/m^2) were more likely to have SGA than non-obese men. Conversely, paternal underweight (<18.5 kg/m^2) is independently associated with SGA (71).

In contrast, Yang et al. conducted a case-control study and found that overweight and obese fathers were significantly associated with the risk of macrosomia (72). After a study included linear interaction, it was found that paternal obesity weakened the positive correlation between maternal obesity and newborn birth weight. When the father is obese, the increase in average birth weight associated with maternal obesity is weakened (73). And those studies that assessed birth weight as a continuous measure did not find any consistent association, because the association between paternal obesity and SGA may be masked by the co-occurrence between paternal obesity and macrosomia (74). Chen et al. (75) showed that paternal BMI was significantly associated with birth weight, biparietal diameter, head circumference, abdominal diameter, abdominal circumference, and chest diameter of male offspring. Therefore, cohort studies are needed to confirm whether the findings are similar in humans and investigate the effect of paternal BMI on the distribution of birth weight beyond mean differences and bipolar categories. We use the ultrasound measurements to describe the body shape of newborns, because it is known that the birth process will affect some anthropometric parameters immediately after birth (76) (e.g. head circumference, etc.). Our study showed that there was a positive linear relationship between paternal BMI and BPD, FL, APAD, TAD, AC, placental weight, and placental area (p for trend<0.05), but in the group of paternal obesity, there was no difference in the above indicators compared to normal controls. These results confirmed the above conjecture that high paternal BMI increased the frequency of unhealthy extremes, including macrosomia and SGA, but had a relatively small impact on the average. Our study also showed by logistic regression analysis that paternal obesity was the independent risk factor for the development of both SGA and macrosomia, which also confirmed the above theory. The interaction test showed that the effect of paternal obesity on SGA

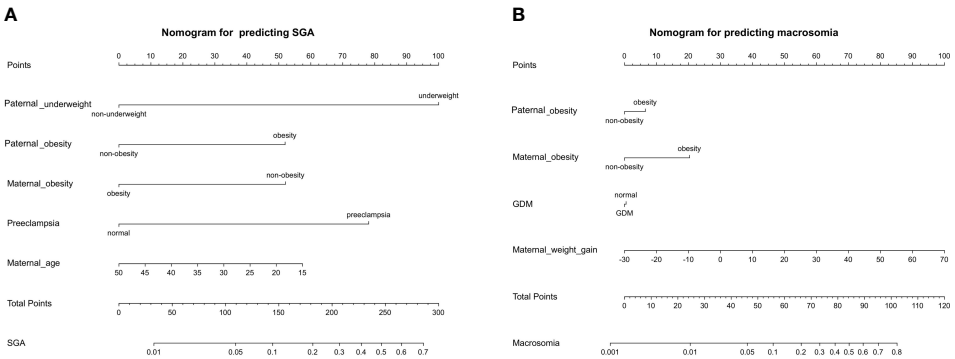

FIGURE 3 | The nomogram was developed to predict the incidence rate of SGA **(A)** and macrosomia **(B)** based on the significant predictors in the multivariable analysis. Draw an upward vertical line from each variable axis to obtain the point of each variable. Calculate the sum of each variable score and draw an upward vertical line from the total score axis to obtain the predicted incidence of SGA or macrosomia.

and macrosomia was significantly affected by maternal obesity. For maternal BMI normal and overweight, paternal obesity can significantly increase the occurrence of SGA and macrosomia. However, for maternal obesity, paternal BMI had little effect on the incidence of both SGA and macrosomia.

Future Prospect

In many media and government campaigns, women remain the primary target for improving the health of their pregnancies and offspring (77) and ignore the contribution of the fathers. In reviewing available guidelines and recommendations, no country has yet issued separate specific guidelines for men (78). The lack of research interest in the role of fathers is evident in human studies, as most of the literature related to early exposure does not have a section on paternal influence. Epigenetic modifications are a continuous process, and some changes may be reversible. Experiments have shown that preconception dietary and exercise interventions improve sperm function and embryonic development in a paternally obese mouse model (79). Human studies have also shown that exercise can improve male fertility (80). Weight loss following bariatric surgery has also been shown to reshape sperm DNA methylation patterns (81). These findings provide new insights into the shared responsibility of parents for the intergenerational origins of obesity. There is an urgent need to define this new concept and its mechanistic basis in embryonic programming, identify effective interventions for obese parents before pregnancy, and optimize paternal health to improve the health outcomes of the next generation, creating exciting new opportunities for chronic disease prevention (82). Future comprehensive studies should include paternal epidemiology and epigenetic studies to understand the underlying intergenerational mechanisms of early human exposure. The paternal obesity status dramatically alters the sperm epigenome, which may have important implications for the susceptibility of offspring to metabolic diseases. In addition to clarifying the epigenetic mechanism of paternal obesity affecting intrauterine development, future research directions can also focus on whether pre-pregnancy diet and exercise intervention can improve and reverse the adverse effects on offspring, optimize the status of paternal obesity to improve the health outcomes of the next generation, and create opportunities for the prevention of chronic diseases.

Strengths and Limitations

Our study has several advantages, such as a relatively large sample size, and our data cover the measurements of fetal growth, neonatal weight, neonatal body length, as well as placental area and weight entirely. In addition to the stratification of maternal BMI, we also studied the interactive effects of paternal obesity and maternal obesity on the incidence of SGA and macrosomia, which has not been seen in the previous studies. All participants were Chinese, minimizing genetic susceptibility differences in birth weight and gestational age. The advantage of our study also lies in its prospective and rigorous method. In analyzing the impact of paternal BMI on fetal development and pregnancy complications, we have controlled for parental age, maternal BMI, weight gain during pregnancy, and other influencing factors. Importantly, our study enables us to address the potential contribution of paternal obesity to a range of fetal anthropometric indicators and placental function, which is rare so far. Information on birth outcomes and maternal complications during pregnancy comes from medical records, minimizing misclassification. In this study, the maternal BMI was measured by instruments, but the paternal BMI was calculated by self-report. This is also a limitation that may increase the risk of bias and the risk of deviation. However, a previous study showed that the self-reported anthropometric index was accurate enough among European adults (83). One study showed that the average weight of young men changes by 0.6 kg over the course of a year (84), which is considered unlikely to change within a few months of obtaining paternal measurements.

CONCLUSION

Our study showed that there was a positive linear relationship between paternal BMI and fetal BPD, FL, APAD, TAD, AC, placental weight, and placental area (trend $P < 0.05$), but there was no difference between obese father group and normal control

group. These results confirm our conjecture that the high BMI of fathers increases the frequency of unhealthy extremes, including macrosomia and SGA, but has a relatively small impact on the average fetal birth weight. In addition, paternal obesity was significantly associated with the incidence of preeclampsia, macrosomia, and SGA. Although the effect of paternal obesity on SGA and macrosomia was significantly affected by maternal obesity, paternal obesity was still an independent predictor of SGA and macrosomia. All these results confirm the adverse effects of paternal obesity on placental development and pregnancy complications. Optimizing the paternal BMI will help improve the health of the next generation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the International Peace Maternity and Child Health Hospital (reference number GKLW 2021-23). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HH contributed to the design of the study, collection, interpretation of data, and revising the manuscript. JL participated in the design of the study, analyzed the data and drafting the manuscript. WG was responsible for the collection and interpretation of data. WG and JL conceived the study and reviewed/edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.826665/full#supplementary-material

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"Parental advisory: maternal and paternal stress can impact offspring neurodevelopment"

Short title: Parental stress can impact offspring neurodevelopment

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Abstract

Parental stress exposures are implicated in the risk for offspring neurodevelopmental and neuropsychiatric disorders, prompting critical examination of preconception and prenatal periods as vulnerable to environmental insults such as stress. Evidence from human studies and animal models demonstrates the influence that both maternal and paternal stress exposures have in changing the course of offspring brain development. Mechanistic examination of modes of intergenerational transmission of exposure during pregnancy has pointed to alterations in placental signaling, including changes in inflammatory, nutrient-sensing, and epigenetic pathways. Transmission of preconception paternal stress exposure is associated with changes in epigenetic marks in sperm, with a primary focus on the reprogramming of DNA methylation, histone post-translational modifications, and small non-coding RNAs. In this review, we discuss evidence supporting the important contribution of intergenerational parental stress in offspring neurodevelopment and disease risk, and the currently known epigenetic mechanisms underlying this transmission.

Keywords; Stress; Intergenerational transmission; PTSD; placenta; sperm; epigenetics

Introduction

Early life stress is a well-established risk factor for neuropsychiatric disorders across the lifespan. '*Stress'* encompasses various environmental challenges that disrupt organismal homeostasis and result in physiological and/or behavioral responses (1). In humans, stressors can include metabolic challenges (e.g. famine), immune challenges (e.g. illness), and perceived psychological threats (e.g. social/emotional distress). In preclinical animal studies, stress can be imparted using psychological and/or physical challenges, including immobilization, social defeat, and isolation (2). During pregnancy, maternal stress alters the maternal milieu, which can directly or indirectly impact fetal development (3-4). Because the impact of stress is transmitted from parent to offspring, the term intergenerational transmission has been applied (5). However, preconception stress in either parent can impact germ cells, thus influencing development in one or more generations, resulting in transgenerational effects (6-7). As the most recent studies focusing on germ cell epigenetic transmission have been largely examined in paternal models, we discuss these studies in detail regarding stress programming of sperm as causal in offspring phenotypes.

Understanding the mechanisms by which parental stress exposure is ultimately communicated to the developing offspring brain is critical for elucidating the etiology of mental health disorders. Epigenetic control of gene expression, including DNA methylation, histone post-translational modifications (PTMs), and non-coding RNAs, evolved to regulate and establish cell- and tissue-specific gene expression programs and to control normal cellular functions (8-9). Stress experienced during critical developmental windows when these epigenetic patterns are generated can result in reprogramming of cellular epigenomes, leading to long-term changes in patterns of gene expression and cellular function. More specifically, stress exposure can lead to such epigenetic alterations in sperm and oocytes, resulting in transmission of altered marks to the zygote (7). Following conception, stress exposure can also directly alter epigenetic programming of the fetus by disrupting the function of extra-embryonic tissues, including the placenta, to promote alterations in key developmental signals throughout gestation. Thus, parental stress exposures during the preconception and prenatal windows can have lasting consequences on offspring development and, subsequently, adult outcomes.

In both human studies and animal models, intergenerational transmission of stress exposures have been associated with endophenotypes of stress-related neuropsychiatric disease in adult offspring, including disruption of the hypothalamus-pituitary-adrenal (HPA) stress axis. The HPA stress axis is important for

glucocorticoid production in response to physiological and psychological challenges, and its dysregulation is an underlying feature of most neuropsychiatric disorders (10-11). Thus, many studies have focused on understanding developmental programming of the HPA stress axis as a readout of intergenerational transmission of stress exposure. In this review, we discuss the impact of maternal and paternal stress exposure on offspring neurodevelopmental outcomes, with a focus on offspring programming of the HPA stress axis. Moreover, we focus our discussion on the epigenetic mechanisms by which intergenerational transmission of stress exposure may be signaled to developing offspring.

Maternal Mechanisms of Intergenerational Stress Transmission

Stress during pregnancy is associated with an increased risk for autism spectrum disorders (ASD), schizophrenia, affective disorders, and attention deficit hyperactivity disorder (ADHD) in offspring, largely related to the specific stage of pregnancy in which stress experience occurred (4). For instance, epidemiological and clinical studies report that early pregnancy, when epigenomic patterning is established, has the greatest impact on offspring brain development (12–16). Risk and outcome of stress exposure is also related to fetal sex, such that males whose mothers experience psychological stress during the first and second trimesters show an increased risk for schizophrenia and ASD (13–15), whereas female offspring exposed to high levels of cortisol during early pregnancy are at higher risk for affective disorders (16). Moreover, late gestation may be a sensitive period wherein stress exposure can lead to long-term alterations in cognitive function and risk for ADHD, particularly in females (17–19). Although fetal development differs between species, rodent models of maternal stress exposure are valuable for elucidating the proximate mechanisms on programming offspring stress sensitivity. Our lab and others have shown that stress during early pregnancy has the greatest long-term impact on the offspring HPA stress axis, cognitive, and metabolic function, particularly in male offspring (20–25).

Numerous biological mechanisms converge to impart sex-specific alterations on offspring neurodevelopment following maternal stress, including effects on the maternal milieu, the placenta, and the developing fetus. While these factors have been explored for their contributions to offspring brain development, they are so tightly intertwined that alterations in one environment typically produce changes in the others. For instance, the placenta is a key source of corticotropin-releasing factor (CRF) (26), which feeds back to both the

fetal and maternal pituitary (27-28). Placental CRF is critical for regulating the fetal HPA axis, and for proper production of glucocorticoids and androgens from the fetal adrenal gland (27; 29). These steroids are necessary for organ maturation (30). Maternal stress enhances placental CRF production and signaling, which in turn modifies fetal HPA feedback and development (31). Rodent studies using treatment with the synthetic glucocorticoid, dexamethasone, during pregnancy demonstrate that potentiation of the maternal HPA axis reduces HPA axis sensitivity in adult offspring by attenuating the expression of glucocorticoid (GR) and mineralocorticoid receptors (MR) in the hippocampus, and enhancing anxiety-like behaviors and stress responsivity (32-33).

Similar to maternal stress, maternal infection during pregnancy is associated with an increased risk for ASD and schizophrenia, suggesting that these insults may have overlapping mechanisms that promote long-term changes in development (34–39). Interestingly, rodent models of maternal immune activation produce offspring phenotypes similar to those observed with maternal stress (40). Both maternal stress and infection promote an inflammatory state by increasing cytokine production during pregnancy, weakening the maternal immune system (41). In mice, signaling of the pro-inflammatory cytokine, interleukin-6 (IL-6) is enhanced by both of these maternal insults, and inhibiting IL-6 signaling rescues the impact of maternal infection on offspring development (42-43). Prenatal stress exposure increases IL-6 specifically within the male placenta, and sensitizes the HPA stress axis and metabolic dysfunction in male offspring (44). Treatment of pregnant mice with a nonsteroidal anti-inflammatory drug during stress exposure ameliorates the programmatic dysfunction observed in male offspring, suggesting that maternal/fetal immune signaling mediates the effects of maternal stress exposure on placental and/or fetal brain development (44). Activation of the HPA axis is also known to interact with the maternal immune system, with glucocorticoids acting as important immunomodulators (45-46). For example, thymocytes, monocytes, and neutrophils express GR, which mediates the transcriptional effects of glucocorticoids and can alter migration, differentiation, and proliferation (46-47). Clinical studies also report that psychosocial stress during pregnancy decreases lymphocyte activity (48). Other neuropeptide and neuroendocrine factors resulting from activation of the HPA axis can interact with immune cells as well, such as CRF regulation of mast cell degranulation (46; 49). For a more comprehensive review on maternal immune regulation of fetal development, see (40; 50).

Placental epigenetics and neurodevelopmental programming

At the interface of maternal experience and the developing fetus lies the placenta, a tissue that serves as a gatekeeper of maternal signals, admitting critical nutrients and gasses from maternal circulation while blocking pathogenic intruders including viruses and bacteria (51). Here we focus our discussion on the evidence for epigenetic mechanisms in the placenta to promote sex-specific offspring responses to prenatal stress. For additional discussion on the involvement of the placenta in transmitting maternal signals to the developing fetal brain see reviews (51–54).

The fetally-derived trophoblast lineage is the first to differentiate following fertilization, forming the outer blastocyst trophectoderm layer and eventually becoming the dominant cell type of the placenta (55). Male and female placentas express differences in gene expression, largely originating from the X and Y chromosomes (51; 56). Of particular interest are the numerous X- and Y-linked genes that encode epigenetic machinery, including genes that affect the methylation status of the histone transcriptional repressor, H3K27, such as the histone demethylases, UTX and UTY, and the X-linked enzyme, O-linked N-acetylglucosamine transferase (OGT) (57). Differential expression of these and other broad epigenetic mediators are able to establish widespread sex differences in gene expression patterns within male and female trophoblast lineages (58). These sex differences may contribute to sex-specific susceptibility to prenatal perturbations, such as early prenatal stress, where males are more vulnerable (59).

Evidence supporting this hypothesis has been demonstrated in rodents, wherein maternal stress significantly modifies placental gene expression and function in a sex-specific manner (56; 60–62). We previously identified OGT as a placental mediator of the sex-specific effects of prenatal stress on HPA stress axis and metabolic programming (63). OGT is a nutrient-sensing enzyme that biochemically modifies thousands of proteins to promote widespread effects on cellular signaling, cell cycle regulation, proteosomal activity, transcriptional regulation and additional critical cellular functions (for review see (64)). Further, OGT is a known mediator of epigenetic repression via its structural stabilization of the histone H3K27 methyltransferase, EZH2 (65–67), as well as epigenetic activation via its association with the TET proteins at activational histone marks (68–70).

Female placental tissue (mouse and human) has nearly double the level of OGT as male tissue (60). In addition, placental OGT levels are reduced in response to early prenatal stress exposure in both male and

female tissue. Might low levels of placental OGT be responsible for producing altered HPA function and endophenotypes of autism and schizophrenia in males exposed to early prenatal stress? To test this hypothesis, we reduced OGT levels in placental trophoblasts in both sexes and found a recapitulation of the stress axis and metabolic dysregulation phenotype found previously only in males (63). Thus, placental OGT activity appears to be a critical mediator of the sex-specific effects of prenatal stress exposure on offspring neurodevelopmental programming. However, as OGT targets myriad proteins and cellular processes, the downstream mechanisms involved in OGT's sex-specific programming are still unknown.

Maternal preconception stress

Unlike the effects of paternal preconception stress, less is known about the mechanisms by which maternal preconception stress programs offspring outcomes. However, epidemiological evidence suggests that traumatic events prior to conception, such as childhood abuse and development of PTSD, are associated with poor neuropsychiatric outcomes in offspring (71–73). Studies in children whose mothers survived the Holocaust suggest one mechanism whereby maternal preconception stress may affect future generations via alterations in DNA methylation of stress regulatory genes, FKBP5 and GR, associated with enhanced HPA stress axis sensitivity (73-74). Another recent study found that maternal childhood abuse correlates with greater placental CRF production during pregnancy (75), an intriguing finding that suggests integration of stress experience with the female reproductive tract. Further studies are needed to determine how traumatic preconception events alter maternal biology to allow for transmission to future generations.

Paternal Mechanisms of Intergenerational Stress Transmission

The number of studies examining the interaction of stress with the paternal germline to impact the programming of offspring development has grown in the last decade, with fascinating results implicating male life experiences in intergenerational transmission. The majority of epigenetic patterning of the male germ cell occurs prenatally, with some *de novo* DNA methylation and histone modifications occurring postnatally, prior to puberty (for review, see (76)). During spermatogenesis, sperm histones are actively replaced by protamines, highly charged proteins that allow condensation of sperm chromatin to one-tenth that of somatic cells (77). As a result, mature sperm become transcriptionally inert, and are considered resistant to external influences.

However, recent studies have now turned the dogma upside down, demonstrating that mature sperm are responsive to homeostatic challenges, including dietary disruption, stress or trauma, and exposure to drugs of abuse, during the sperm maturation stage that occurs in the epididymis (78–82). In the following section we discuss the evidence from human studies and relevant animal models of intergenerational transmission of environmental perturbations through the paternal germline and the potential attributed epigenetic mechanisms. We focus on stress and trauma as these have been the most widely studied exposures in paternal transmission.

Human Studies and Animal Models of Paternal Stress

Retrospective epidemiological studies offer compelling evidence linking stress exposures during the male lifetime with disease risk in subsequent generations. Studies using birth measures and food supply records from the Swedish Famine in 1836 made the first claims for both intergenerational and transgenerational effects occurring through the male lineage. These studies established associations between food supply during early childhood in males with altered health outcomes, including disease risk and longevity, in their sons and grandsons (83–85). Further, studies of a cohort of Holocaust survivors and their adult offspring found an increased prevalence of neuropsychiatric disorders, such as depression and PTSD, and reduced cortisol levels and GR sensitivity in offspring whose fathers were survivors (74; 86). Interestingly, as many of these children were conceived decades following the Holocaust, these outcomes support that traumatic stress promotes lasting effects through the paternal germline (74). Studies of males exposed to chemicals from smoking, high-fat diets, and environmental toxicants also compared germ cell outcomes and reported associated epigenetic changes in sperm (87–89). Human studies investigating molecular signatures of stress in the male germline have not been completed, but would provide valuable insight into novel mechanisms of intergenerational transmission resulting from paternal stress exposures.

Animal models of stress transmission via the paternal lineage provide a unique opportunity to identify germ cell epigenetic mechanisms without the major confounding factor of paternal behavior to consider. In most rodent models, males do not participate in offspring rearing, allowing researchers to isolate the specific contribution of epigenetic changes in paternal germ cells. For example, in our studies, male mice breed with females for a maximum of three days and are removed from the female's cage immediately following

observation of a copulation plug, significantly limiting the impact the stressed male may directly have on maternal behavior or investment (79; 90). Such studies have found that male mice exposed to chronic variable stress, dietary challenges, social defeat stress, and odor-paired fear conditioning have a number of altered epigenetic marks in their germ cells, including increased specific small noncoding RNA and changes in DNA methylation (78; 79; 82; 91–93). Further, these altered epigenetic marks are associated with offspring behavioral, physiological, and metabolic outcomes characteristic of endophenotypes of stress-related neuropsychiatric disorders.

Interestingly, rodent studies have demonstrated germ cell susceptibility to stressful environments across the paternal lifespan. For instance, male mice exposed to maternal separation stress during the perinatal period sired offspring with depressive-like behaviors (94). Our lab has shown that male mice exposed to early prenatal stress present with altered stress coping behaviors and a heightened HPA stress response and transmit this phenotype only to their male, but not female, offspring in the next generation (95). These were two of the first rodent studies demonstrating that male germ cells can be reprogrammed by stress experience during early development. Sperm has distinct periods of differentiation, development, and maturation, and therefore the timing of stress exposure likely impacts distinct mechanisms (7). During the prenatal and perinatal periods, development and epigenetic patterning of germ cell precursors and the surrounding reproductive tissues is dynamic; therefore, stress exposure during these critical windows may disrupt the organization of important processes unique to this period (76).

Other studies examining paternal transmission have demonstrated that stress exposure of adolescent and adult animals alters germ cell programming. For example, male mice exposed to chronic variable stress sire male and female offspring that exhibit a significantly blunted HPA stress response, an endophenotype reflected in subsets of patients with major depressive disorder or PTSD (96-97). Interestingly, this paternal effect occurred whether the sires were exposed to stress over the pubertal window or solely during adulthood, suggesting that stress exposures post-puberty (i.e. following maturation of the male reproductive system) evoke similar mechanisms. In contrast, retrospective studies from Swedish famine cohorts associated nutritional challenge during preadolescence with changes in grandson longevity, while such challenges later in life produced no transgenerational effects (98). This disparity in the timing of germ cell vulnerability between our findings in stress-exposed rodents and the findings from the Swedish cohorts may be dependent on

species, timing, or type of perturbation (e.g. psychosocial vs nutritional). Therefore, further studies are needed in order to identify the windows of germ cell vulnerability in humans.

Stress Programming of Epigenetic Marks in Sperm

The observation that stress exposures across the male lifespan can lead to programming of offspring phenotypes has brought mounting attention to examination of epigenetic marks in sperm (99). Epigenetic marks have been described in mature sperm in both humans and rodents, including DNA methylation, histone PTMs, and small noncoding RNAs, and have been implicated in transmitting environmental information to the next generation (7; 100). In this section, we discuss the evidence supporting the role of sperm epigenetic marks in the transmission and programming of offspring development following paternal stress exposures.

Sperm DNA methylation patterns are well described in normal germ cell development, and specific changes to these patterns have been reported in response to paternal stress exposure, such as maternal separation stress and odor-paired fear conditioning (91; 94). During embryogenesis, the developing germ cell undergoes global erasure of DNA methylation marks. Following this process, *de novo* DNA methyltransferases specify germ cell methylation patterns that are distinct from those in somatic cells (76). An additional wave of active DNA demethylation of the paternal gamete occurs immediately post-fertilization in the zygote (101). Importantly, some genomic loci are resistant to demethylation, a process of genomic imprinting critical for normal development, as mistakes at imprinted loci can result in neurodevelopmental disorders, including Angelmans and Prader-Willi syndromes (102-103). Changes to sperm DNA methylation have been reported in rodent models of chronic stress experience (91-92; 94). For example, males that experienced odor-paired fear conditioning as adults had decreased DNA methylation at the specific genomic locus of the corresponding odor receptor in their sperm, suggesting a mechanism by which stress experience may produce offspring with specific behavioral changes (91). Intriguingly, in the same study, these sperm DNA methylation changes corresponded to increased offspring behavioral sensitivity to the associated odor. However, DNA methylation changes at this odor receptor were not present in the brains of these offspring, suggesting sperm DNA methylation changes may influence other epigenetic mechanisms, such as histone PTMs, to program the offspring brain. In another study, males exposed to maternal separation stress early in life sired offspring with depressive-like behaviors (94). These altered behaviors were also associated with changes in DNA

methylation patterns at loci related to stress regulatory genes and epigenetic pathways in both the paternal germ cell and in the offspring brain. However, how stress induces such site-specific sperm methylation changes and how these changes influence the programming of adult offspring tissues to produce behavioral phenotypes are not known.

Despite the central dogma that mature sperm are transcriptionally inert, populations of small noncoding RNAs (~22-34 bp) have been well described in the mature sperm of humans and animals, including microRNA (miRs), PIWI-associating RNAs, and transfer RNA-derived fragments (tRFs) (104–107). Specifically, sperm miRs are critical for normal embryogenesis, where inhibition of sperm-borne miR-34c in the zygote resulted in zygotic arrest (108). In our studies, male mouse chronic stress experience significantly increased 9 miRs in sire sperm (79). Remarkably, microinjection of these same 9 miRs into fertilized zygotes completely recapitulated the blunted HPA stress axis phenotype reported in our model of paternal stress, providing causal evidence for the role of stress-altered miRs in sperm (109). Other labs have corroborated the crucial role of stress-sensitive sperm RNAs in programming offspring phenotypes via microinjection of total sperm RNA and tRF populations, a class of small non-coding RNAs derived from tRNAs (80; 110-111). The mechanisms by which sperm small noncoding RNAs influence offspring neurodevelopment are not clear. Following zygote miR microinjection, we found a significant reduction of specific stored maternal mRNA populations at the 2-cell stage, supporting sperm miR canonical function in the embryo (109). Intriguingly, in this study, the two most repressed genes were *Sirt1* and *Ube3a,* epigenetic regulators that have been associated with neurodevelopmental and metabolic disorders in humans (112-113). In another study, zygote microinjection of tRFs altered by paternal dietary challenge resulted in changes in zygote gene expression, in particular the repression of endogenous retro-elements (111). Therefore, sperm small noncoding RNAs may alter critical genes during the pre-implantation stages of embryogenesis, resulting in a cascade of cellular events that ultimately reprograms the offspring. Due to the relative instability of RNA molecules compared to more long-lasting epigenetic marks, such as DNA methylation, it is unlikely sperm-derived RNAs are maintained past early stages of embryogenesis, but rather produce a dynamic change in the developmental landscape, possibly additional epigenetic changes, that shapes the embryo trajectory.

Considering the exciting new evidence that sperm noncoding RNAs are changed by paternal perturbations and reprogram offspring development, mechanistic studies to determine how the male

reproductive tract senses changes in the environment and alters sperm content are necessary before interventions can be considered. The source of RNA in mature sperm was previously assumed to be residual from spermatogenic processes (114). However, in the epididymis, the site of important post-testicular sperm maturation, a novel role of epithelial cell extracellular vesicles has recently been proposed in the delivery of small non-coding RNA to maturing sperm (115). For instance, the content of these 'epididymosomes' was shown to alter sperm tRFs in response to paternal dietary challenge, supporting that epididymal epithelial cells may be the dynamic mediators between paternal environmental exposures and sperm RNA changes (111).

Lastly, histone PTMs are also potential epigenetic signals in sperm. Roughly 1% of histones in mice and 10% of histones in humans are retained in sperm chromatin following the active exchange of histones with protamines (77; 116). Importantly, retained histones have been mapped to regions of important developmental genes, suggesting they designate those that are critical for post-fertilization function in the zygote (117). As evidence to this point, disruption of the specific histone mark, H3K4me2, in sperm altered gene expression in the two-cell zygote and severely impaired offspring development (118). In addition, sperm from male rats that were administered chronic cocaine showed increased H3 acetylation specifically at the *Bdnf* promoter in both paternal sperm and in the offspring brain, supporting the hypothesis that retained histone PTMs may denote genes important to offspring development (81; 119). In addition to histone PTMs, protamine biochemical modifications have also been reported, supporting a potential protamine code in sperm that may impart transcriptional effects on embryo development (120). However, as protamines are rapidly replaced with maternal histones post-fertilization (121), how such protamine modifications could influence embryogenesis requires further investigation.

Conclusions

The focus of stress as a risk factor for neuropsychiatric and neurodevelopmental disorders and the mounting evidence for the intergenerational transmission of parental stress exposure brings to light exciting new mechanisms involved in transmission of sex-specific stress signals. Many affected tissues are extra-embryonic and easily accessible (e.g., placenta, semen), and thus the translational potential from animal models to prospective human studies may facilitate development of necessary predictive disease biomarkers. The potential to identify at-risk individuals may then inform clinical decisions, including altering prenatal care

and earlier interventions for children. However, the discussion here only begins to appreciate the incredibly complex and multifaceted etiology that contributes to disease risk or resilience. Despite the growing evidence supporting intergenerational inheritance, there remains skepticism as to whether the transmission of parental experience is truly mediated by epigenetic mechanisms in the germ cell. For example, stress exposure may also impact offspring development via changes to parental care (e.g. maternal investment). Further, in paternal inheritance studies, the “sick sperm” hypothesis suggests stress exposure can alter sperm maturation or motility and that offspring development may be affected by the integrity of fertilization or pre-implantation events (122). Therefore, more studies with careful examination of these potentially complex factors are needed to determine the mechanism by which parental stress programs offspring development. Moreover, large prospective cohort studies in which gene x environment influences are considered, such as the NIH-launched initiative Environmental Influences on Child Health Outcomes (ECHO) and the Avon Longitudinal Study of Parents and Children (123–125), will be invaluable to our ability to identify causal mechanisms, who may be at-risk, and in designing prevention and therapeutic measures.

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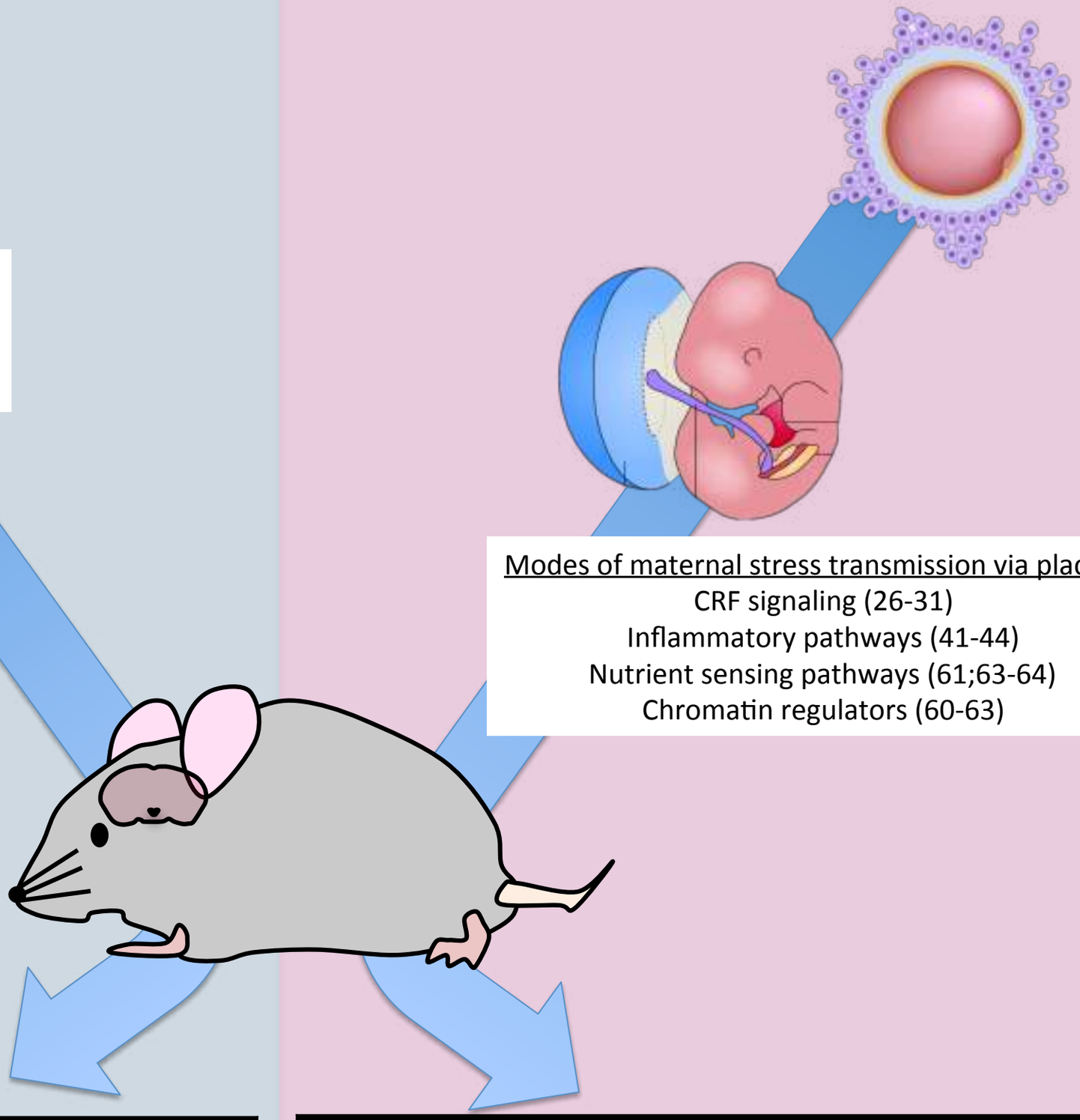
Figure Legend

Figure 1. Intergenerational transmission of maternal and paternal stress can impact offspring neurodevelopment. Paternal stress exposures influence offspring outcomes (left table), potentially through changes in sperm epigenetic marks. Maternal stress during pregnancy alters placental signaling to reprogram offspring neurodevelopment (right table). Few studies to date have examined maternal preconception stress effects on the oocyte, likely due to current technical barriers.

<u>Modes of paternal stress transmission via sperm</u>
DNA methylation (82; 91-92; 94)
Small non-coding RNAs (79-80; 109-111)
Histone post-translational modifications (81; 118)

<u>Modes of maternal stress transmission via oocyte</u>
No mechanisms have yet been described, likely due to technical limitations



<u>Modes of maternal stress transmission via placenta</u>
CRF signaling (26-31)
Inflammatory pathways (41-44)
Nutrient sensing pathways (61;63-64)
Chromatin regulators (60-63)

Exposure	Species	Offspring outcomes	Ref
Swedish famine	Humans	Increased longevity and decreased risk for cardiovascular disease in grandsons	83-85; 98
Preconception trauma	Humans	Reduced cortisol levels, reduced GR sensitivity, increased risk of depression and PTSD	74; 86
Chronic variable stress	Mice	Reduced HPA stress axis responsivity in male and female offspring	79
Social defeat	Mice	Increased depressive-like and anxiety-like behaviors, increased glucocorticoid levels	93
Odor-paired fear conditioning	Mice	Increased odor behavioral sensitivity in males	91
Maternal separation	Mice	Increased depressive-like behaviors; altered exploratory behavior	94
Dietary challenge	Mice	Metabolic dysfunction, developmental defects	78; 80; 82

Exposure	Species	Offspring outcomes	Ref
Psychological stress during pregnancy	Humans	Increased risk of ASD and schizophrenia in males; increased risk for affective disorders in females	13-19
Infection during pregnancy	Humans	Increased risk of ASD and schizophrenia in males	34-40
Childhood abuse	Humans	Increased disruptive behavior, externalizing behavioral problems	71-72; 75
Preconception trauma	Humans	Poor perceived emotional health, increased depressive and anxiety symptoms, increased PTSD risk, greater glucocorticoid sensitivity	73-74; 86
Prenatal chronic variable stress	Mice	Increased HPA stress axis sensitivity, cognitive dysfunction, metabolic dysfunction in males	21-23; 60
Prenatal infection	Mice	Social deficits; altered exploratory behavior; increased repetitive behaviors	42-43
Prenatal glucocorticoids	Rats	Impaired coping and learning; reduced growth	32-33

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Fetal Origins of Adult Disease

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Abstract

Dr. David Barker first popularized the concept of fetal origins of adult disease (FOAD). Since its inception, FOAD has received considerable attention. The FOAD hypothesis holds that events during early development have a profound impact on one's risk for development of future adult disease. Low birth weight, a surrogate marker of poor fetal growth and nutrition, is linked to coronary artery disease, hypertension, obesity, and insulin resistance. Clues originally arose from large 20th century, European birth registries. Today, large, diverse human cohorts and various animal models have extensively replicated these original observations. This review will focus on the pathogenesis related to FOAD and examines Dr. David Barker's landmark studies, along with additional human and animal model data. Implications of the FOAD extend beyond the low birth weight population and include babies exposed to stress, both nutritional and non-nutritional, during different critical periods of development, which ultimately result in a disease state. By understanding FOAD, health care professionals and policy makers will make this issue a high healthcare priority and implement preventative measures and treatment for those at higher risk for chronic diseases.

Introduction

David Barker's keen observations have been popularized as the "Barker hypothesis," or "Fetal Origins of Adult Disease" (FOAD). It was his group that noted that low birth weight (LBW) serves as proxy not just for fetal, but also adult health. Today, LBW is associated with a host of chronic diseases ranging from coronary artery disease (CAD), Type II diabetes mellitus (T2DM), cancer, and osteoporosis to various psychiatric illnesses (See Table I.).[1–7] FOAD is based on the premise of "developmental plasticity"—a single genotype, influenced by specific intrauterine events, has the capability to produce different phenotypes. This theory relies on the fact that there exist specific developmental periods whereby an organism is "plastic" or "sensitive" to its environment. Diversity is maximized to provide the best fit between phenotype and environment. For example, when faced with the adversity of malnutrition, a fetus will undergo remodeling thereby altering structure and function of various organs to preserve neurodevelopment and promote survival. These

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adaptations prepare the fetus for extrauterine life where additional stressors may be encountered. It must be recognized, however, that over time, this evolutionary advantage of "plasticity" is lost, and one's response to environmental or pathological challenges becomes constrained. This phenomenon, known as "programming," refers to the fact that stimuli, when applied during early development, generates permanent changes that persist throughout one's lifespan. Programming is not just limited to the in-utero environment, but extends into childhood, where different organs and systems continue to adapt to various cues.

The FOAD theory was originally supported by large birth registries and human cohorts where gestating women and their offspring faced severe malnutrition in the form of famines.[1,4,8,9] These large registries recorded the birth history of men and women, and these subjects were then identified later in life. This allowed investigators to correlate birth weight and childhood growth with adult onset diseases. These findings were found to be independent of confounders such as tobacco use, diet, exercise, socioeconomic status, and family history. Although numerous epidemiological studies across various cultures and ethnicities support the link between LBW and future adult disease, LBW is not necessarily a prerequisite.[10–13] Those with "normal" birth weights, or appropriate for gestational age (AGA), may still be at risk depending on the type, timing, and duration of the original insult. Moreover, insults are not limited to malnutrition. Famines or severe calorie restriction merely provide a model for other afflictions. Alterations in diet composition, inflammation, infection, glucocorticoids, hypoxia, stress, and toxins also play a vital role in shaping the adult phenotype.[14–20] Although the literature tends to focus on the LBW, or small for gestational age (SGA) baby, special consideration must be given to the stressed AGA, large for gestational age (LGA), and premature neonate. And lastly, the transgenerational and socioeconomic implications of FOAD have far-reaching repercussions that cannot be underestimated; further research is still needed to unravel its complexities.[21–23]

The aim of this review is to provide the general clinician with a foundation to better understand how nutritional and non-nutritional perturbations result in chronic disease. Since Barker's original observations, numerous epidemiological and human studies, further reinforced by animal models, have provided a plethora of support.[12,19, 24–31] Mice, rats, sheep, and monkeys have been subjected to adverse conditions during gestation to mimic the human condition. Models include global calorie or specific macronutrient or micronutrient restriction, hypoxic-ischemia induced by uterine artery ligation, and glucocorticoid exposure. The data, as a whole, force the clinician and researcher to question and discover how developmental stressors permanently alter structure, metabolism, and genetic expression resulting in cognitive, behavioral, and body composition changes ultimately leading to future disease. The literature points to opportunities for public health prevention, future pharmaceutical therapies, and innovative alternative nutritional/environmental strategies that could maximize population based well-being.

Background

The Helsinki and Hertfordshire cohorts from the1930s and 1940s, which comprised over 20,000 subjects collectively, linked poor fetal growth with CAD, hypertension, and insulin

resistance in adult men and women.[1,2,9] Differential mortality rates have been associated with variation in birth weights (Fig 1). Specifically, a LBW in either gender or a documented lower weight for males at 1 year of age was associated with an increased death rate from CAD. A similar trend was noted in both sexes for insulin resistance.[2] Moreover, these effects have been noted to extend beyond the first generation of offspring (F1 generation), with both short- and long-term health implications in future generations.[21–23]

During the relatively short Dutch famine of 1944–1945, the daily nutritional intake of pregnant women was reduced to approximately 400–1000 calories. The timing during pregnancy of this famine (early, mid, or late gestation) was linked to differential birth weights and subsequent development of adult disease. Infants who were subjected to mid or late gestation calorie restriction were lighter, while those who endured the famine in early gestation had normal birth weights. In addition, adults whose mothers were exposed to the famine during mid or late gestation demonstrated reduced glucose tolerance, while those whose mothers were exposed to the famine during early gestation revealed a more atherogenic lipid profile and higher body mass index (BMI).[4,9] Thus, although birth weight in some cases serves as a surrogate marker for the development of adult disease, it is the in utero environment that sets the trajectory for the subsequent acquisition of childhood or adult diseases.

Conversely, the Leningrad famine spanned more than 800 days and provided yet another opportunity to study how severe malnutrition during pregnancy and early infancy, both periods of critical development, affect adult disease. During this siege, fetuses subjected to severe calorie restriction also experienced malnutrition during infancy. However, these subjects, unlike their Dutch counterparts, did not demonstrate increased rates of insulin resistance, dyslipidemia, hypertension, or CAD.[8] These two famines, although similar at first glance, differed in the duration and severity of the malnutrition the population endured. These two infamous natural disasters, with effects documented in large European databases, provided David Barker and others with clues to what subsequently was described by the term FOAD, or known as the “Barker hypothesis.” Even today, despite a plethora of human and animal data, scientists continue to debate the mechanistic link(s) between abnormal growth and adult disease. In addition, in humans, the genetic make-up and environment cannot be dismissed, and it has been a challenge to separate these influences from each other.

“The Mismatch Concept”

The contrast between two natural disasters, namely the Dutch famine and Leningrad siege, highlights the “mismatch concept.” Fetal survivors of the Leningrad siege developed a “thrifty phenotype” that served them well in their extrauterine life.[32] In other words, the superimposed stress of malnutrition in their intrauterine environment was well-matched to the malnutrition experienced outside the womb, and may have offered a form of “protection” from future adult disease. The Dutch, by contrast, exhibited “catch-up” or compensatory growth during infancy. Their intrauterine environment which supported short-term survival was ill matched with their subsequent extrauterine environment. Thus, the Dutch fetuses paid the price for their intrauterine adaptation—“there is no short term gain

without long term pain." In other words, when there is a "match" between the predicted and the actual environment, survival is maximized. Conversely, when the two environments are "mismatched" a predisposition to disease may result; an individual's full potential may not be realized because of maladaptation to the new disparate extrauterine environment predisposing to disease states (Fig 2).

This concept of "mismatch," and its subsequent consequences, also applies to contemporary times. The World Health Organization estimates that over 30 million infants are born LBW, defined as a weight less than 2.5 kg.[33] In addition, many poorly resourced countries are being industrialized or swept over by the "Mc Donald's" fast food phenomenon. This "mismatch" is not confined to poor resourced nations; it also plagues well resourced societies with access to modern health care and high standards of living. High-calorie and high-fat diets coupled with limited active play and excessive media viewing have become the norm in Western nations. In the USA, obesity has more than doubled among children and adolescents. In comparing the two periods 1976–1980 and 2003–2006, the percentage of obese adolescents increased from 5% to 17.6%.[34] Insulin resistance is intimately linked to T2DM, CAD, hypertension, and dyslipidemia. T2DM is now a global epidemic affecting over 170 million people; by 2030 this number is expected to double.[35]

Considering these statistics, one may ask—what developmental "hits" are considered detrimental? And during which time periods? When is too much truly too much? And practically speaking, how should the pediatrician, obstetrician, and neonatal-perinatal subspecialist promote growth during pregnancy and the various postnatal periods (neonatal, infancy, and childhood)? How should clinicians monitor the fetus, and later the infant, child, and adult when an adverse environment is experienced early in gestation? Can these negative outcomes be prevented or reversed?

Catch-up Growth

Today, numerous human and animal studies have revealed that LBW followed by exponential childhood growth increases the risk for the metabolic syndrome, which is characterized by obesity, insulin resistance, dyslipidemia, and hypertension.[2,32,36,37] This tendency to "catch-up" in growth reflects the body's natural response to nutrient deprivation. Moreover, both the parents and clinician may not understand the dangers of rapid weight gain and may actually promote it. Catch-up growth, however, is associated with increased visceral adiposity.[38,39] Recent findings in a group of racially diverse American children mimicked those of the 1930–1940s' English cohort revealing an association between the tendency to store fat intra-abdominally and LBW. In this study specific markers of central adiposity, as measured by central-to-peripheral and subscapular-to-tricep skinfolds, were increased in LBW children as early as 5–11 years of age.[38] Similarly in a cohort of Hispanic and non-Hispanic Caucasians, LBW was associated with elevated fasting insulin levels and truncal obesity. For each tertile decrease in birth weight, the risk for "insulin resistance syndrome" increased 1.72.[10]

Studies of children with T2DM have revealed that many of them were characterized as being small at birth, but during childhood and adolescence they began to cross growth

percentiles. The odds ratio for developing T2DM was 1.38 for each 1 kg decrease in birth weight, and 1.39 for each increase in weight standard deviation between 7 and 15 years of age.[37] Therefore, the thin toddler who begins to rapidly gain weight, or finally "catches-up" to his peers, is at the same risk, if not greater, for developing T2DM compared to his overweight age-matched peer.

Anthropometric data for over 1,400 men and women from Delhi, India, was collected during the first 3 decades of their life from 1970 to 2000. This Indian study conducted during modern times is reminiscent of the Dutch famine. The authors describe this period in India as a "transition" to a more Western lifestyle—a lifestyle marked by increased food availability and reduced physical activity. Results of this study revealed that those individuals with increased insulin resistance were more likely to be small at birth, grow slowly during the first couple of years in life, and then develop "an adiposity rebound".[12] These children however were not described as overweight or obese with this "rebound" growth. Instead, they were described as rapidly gaining body mass. This "catch-up fat" during childhood and early adulthood occurs at a disproportionately faster rate in comparison with lean body mass, and is one of the main promoters of early insulin resistance.

This "nutritional transition" is not solely limited to India but has occurred on all continents. The quantity and quality of the world's food supply varies from country to country, and even neighborhood to neighborhood; while some individuals face starvation, others consume high-calorie, high-fat meals that lack significant nutritional value, which in itself is a different form of starvation.

The tendency for the LBW infant to store fat, particularly in the abdominal compartment, has received considerable attention.[10,38,40,41] LBW infants are known to have adipocytes that demonstrate increased numbers of insulin receptors, glucose uptake, and basal and insulin-stimulated insulin-receptor substrate 1 (IRS-1)-associated phosphatidylinositiol 3-kinase (PI3K).[42,43] Moreover, these adipocytes are resistant to insulin and demonstrate serine phosphorylation of IRS-1, resulting in a state of anti-lipolysis.[43] In addition, increased central adiposity is associated with increased free fatty acids, which stimulate the production of cholesterol and glucose, which in turn decrease insulin sensitivity.[24] As fat deposition progresses in the liver, permanent structural hepatic changes occur.[44]

This molecular "switch" in insulin signaling "protects" the LBW fetus and neonate by promoting storage of fat, a calorically dense nutrient. However, over time this altered metabolism sets the stage for the development of disease. Considering its impact on childhood growth, a clinician may then question whether replacing this quick "rebound" with slow steady measured growth could result in increased lean body mass rather than fat accumulation. Moreover, could any of these cellular aberrations resulting in chronic disease be avoided?

Biological Basis

Growth is largely determined by a mother's ability to nourish her fetus. The provision of this nourishment depends on the maternal diet, the placenta's ability to supply nutrients (amino

acids, glucose, fat, oxygen, and growth-stimulating hormones), and the mother's own in utero experience.[21–23] In other words, the effect of FOAD extends beyond the first (F1) generation. Considering the medical and socio-economic implications of programming, it is critical that all health professionals promote healthy pregnancies to maximize each child's potential and growth trajectory.

So why would growth or other insults in early life alter one's disease potential? First, cell number and growth are exquisitely sensitive to their metabolic and hormonal milieu. Undernourished animals and babies have reduced renal volumes and nephrons, which can result in hypertension. Autopsies of hypertensive humans who died in motor vehicle accidents have demonstrated reduced numbers of, but hypertrophic, glomeruli.[45–47] Similar to humans, growth-restricted animals have decreased numbers of glomeruli and develop chronic renal disease later on in life. Moreover, measurements of mammalian target of rapamycin, a nutrient sensing biomarker, are reduced in growth-restricted kidneys.[48] Second, any stress can alter hormonal concentrations, hormone receptors, and hormonal responses. Receptors can be down- or up-regulated and mutations may result in structural transformations. Hormonal responses can be blunted, or exaggerated.

Consistent with this paradigm is the SGA child who later develops T2DM. These individuals have a reduced number and function of pancreatic β-cells resulting in decreased insulin production and consequently a high glucose/insulin ratio. This outcome leads to abnormal skeletal muscle, liver, and adipocyte insulin signaling and/or glucose production with each of these perturbations resulting in insulin resistance. The same is true with leptin, a critical hormone secreted by adipocytes. Leptin acts on the central nervous system to decrease food intake and increase energy expenditure. The SGA neonate has decreased leptin concentrations at birth, but with increased adiposity becomes hyperleptinemic during the period of "catch-up" exponential growth. This hyperleptinemic state is associated with decreased and/or resistant hypothalamic leptin receptors, which result in hyperphagia and decreased energy expenditure. Dysregulated insulin and leptin serve as two examples of how hormonal perturbations predispose the SGA infant to T2DM and other co-morbidities.

Small for Gestational Age Infant

It is important to acknowledge the spectrum of LBW, which includes SGA, intrauterine growth restriction (IUGR), and very low birth weight (VLBW) infants, some who are not only born prematurely but at times also with superimposed IUGR. While SGA is defined as a birth weight or birth length less than the 10th percentile with respect to gestational age, IUGR refers to an infant who does not reach his or her predetermined genetic potential because of some pathologic insult. This insult can be categorized as maternal, placental, or fetal, with the most common etiology thought to be placental insufficiency. Although IUGR infants may be SGA, all SGA infants are not necessarily IUGR.

Not surprisingly, prenatal and postnatal periods are exquisitely sensitive to any factor that can affect growth as these are periods of exponential cell replication, division, and growth. Infants born SGA are at increased risk for developing obesity, T2DM, CAD, hypertension, kidney disease, premature pubarche, and Polycystic Syndrome (PCOS), dyslipidemia, short

stature, and osteoporosis.[1–4,13,32,37,45,46,49–50] Many of these phenotypic changes are known to be secondary to or associated with insulin resistance.

Height

Although fetal growth is usually discussed in terms of birth weight, it is important not to dismiss the aspect of birth length. Infants with low birth length, LBW, or premature birth are more likely to be short adults.[49–52] Most neonates who fall 2 standard deviations below the growth curve for length, however, are likely to "catch-up" to their peers during childhood. At 1 year and 18 years of age, respectively, only 13.4% and 7.9% of short babies remain stunted.[53] Those that remain short often are referred after the age of 2 to the pediatric endocrinologist for growth hormone therapy or at an older age for evaluation of the metabolic syndrome because of their increased risk of obesity.

It is difficult to separate out the individual contributions of low birth length, LBW, prematurity, and other important factors such as parental height on the individual's ultimate height and the associated complications, such as obesity and T2DM. Each characteristic may have an additive, synergistic, or independent effect. When only females were examined, being short for gestational age was associated with a fivefold increase in short adult stature, while being SGA was associated with only a twofold increase. Interestingly, females who are short at birth, not SGA, are at higher risk for obesity.[49] At the other extreme, larger and longer babies are even more likely to become heavier adults in comparison with light and short babies.[54] As is seen in infants born to mothers with gestational diabetes (GDM) secondary to maternal hyperglycemia, the GDM fetus becomes hyperinsulinemic, resulting in accelerated in utero growth. For every 1 kg increase in birth weight, full-term babies have a 50% increase in adolescent obesity.[55] Short and large babies, both at risk for insulin resistance, are two distinct, separate populations, and are most likely the result of two different programming mechanisms.

Bone growth affects not only one's ultimate height and risk for obesity, but also bone disease. Osteoporosis is linked to fractures, which are linked to a high risk for morbidity and mortality later in life. In a study of a Finnish cohort of patients admitted to the hospital for fractures, low birth length and slow growth were correlated with increased fracture risk during adult life.[56] SGA status and slow growth during the first year of life predict decreased adult bone mass even after adjustment for other predictors of osteoporosis and osteopenia.[6] Studies of twins have proven to be very useful in supporting the FOAD hypothesis. Twin studies are valuable as they help correct for well-known genetic and environmental confounders. The dizygotic or monozygotic co-twin with LBW is more likely to have a lower bone mineral density at specific sites.[57] This data, along with results from other twin studies, suggest that even in genetically identical monozygotic twins, the co-twin with the lower birth weight is predisposed to lower adult bone mass and to developing the metabolic syndrome.[58]

Growth hormone, other insulin-like growth factors, and vitamin D are among many factors that influence a child's growth and bone mass. The growth hormone/insulin-like growth factor-1 axis and receptors are most likely altered in individuals who fail to realize their growth potential. Adults with decreased bone mineral density are more likely to have

decreased growth hormone and to have been smaller children.[59] Other investigators have explored this area even further and have discovered a strong interaction between SGA, poor adult bone mass, and certain single nucleotide polymorphisms (SNPs) in the growth hormone, vitamin D, and calcium-sensing receptor.[60–64] In a SNP analysis, the insulin-like growth factor-1 receptor was altered in 2 short children with low birth weights and postnatal growth restriction.[64] Reduced insulin-like growth factor receptors impact not only a child's ultimate height, but also the child's ability to maintain glucose homeostasis and sustain good brain growth. In summary, like weight, length at birth and height serve as predictors for future disease.

Insulin Resistance/Diabetes

While LBW is undoubtedly associated with insulin resistance, the search for a mechanistic link continues. Many investigators suggest that the pancreas is "programmed" resulting in decreased β-cell mass and function and over time skeletal muscle becomes insulin resistant. Some authors, by contrast, have failed to replicate or generate data to support this theory and believe that insulin resistance, not production, is the primary culprit.[65, 66] In their opinion, once insulin resistance sets in, the pancreas increasingly is stressed to produce more insulin and over time responds to its overwhelming exhaustion with progressive failure of its β-cells.

Pancreas—In support of the former theory, many studies have demonstrated decreased insulin secretion and normal insulin sensitivity in young SGA adults. In one study of adults born with LBW, insulin secretion was reduced by 30%, while insulin sensitivity was determined to be normal.[27] In examining this phenomenon more closely, the IUGR population was noted to have pancreatic dysfunction even before birth; this was evidenced by decreased insulin, glucose, insulin/glucose ratios, and β-cell number and function.[67–69] Interestingly, in some studies, this reduction in β-cell function was initially accompanied by increased insulin sensitivity.[70] These changes persisted after birth and were accompanied by further alterations. When rats are subjected to calorie restriction in-utero, β-cell mass is initially reduced by approximately 35%. When caloric restriction extends into the neonatal period, impaired β-cell development persists with a 40–66% reduction. Later as adults, these animals are described as glucose intolerant.[68,71] Moreover, pancreatic duodenal homeobox-1 (Pdx-1), a well-known transcription factor controlling pancreatic development, is reduced. At 28 days of life, insulin secretion and Pdx-1 protein expression is reduced when compared with controls.[30]

In another commonly used IUGR model, the uterine artery of pregnant rats is ligated, resulting in a severe, abrupt reduction of uteroplacental blood flow. These IUGR rats are growth-restricted at birth but later demonstrate accelerated weight gain, surpassing their age-matched controls. As they age, the rats become insulin resistant and glucose intolerant. Studies have demonstrated that early on, their β-cell mass is equivalent to that of controls. However by 26 weeks, the rats pancreatic mass is notably decreased to approximately 50% of their control counterparts. Using this same model, deterioration in the rats' β-cell function is accompanied by mitochondrial dysfunction, as evidenced by decreased adenosine triphosphate (ATP) production, increased reactive oxygen species, and mitochondrial point

mutations. In addition, all of these markers demonstrated a steady increase over the first 15 weeks of life.[19] When faced with undernutrition, cell division is slowed (as evidenced by decreased Pdx-1 and β-cell-mass) and cell function is altered (as evidenced by decreased hormonal supply and cellular damage).

An alternative hypothesis to FOAD is the "fetal insulin hypothesis." T2DM is known to have a strong genetic component. According to this theory, because insulin is key for fetal growth, any genetic variant that impairs insulin secretion may reduce birth weight and simultaneously result in T2DM. In other words, the genotype, not LBW, predisposes one to T2DM. Supporting this theory, Freathy et al, using SNPs, demonstrated that alleles for increased T2DM risk that reside at two separate loci, *CDKAL1 and HHEX-IDE*, also were associated with LBW.[72]

Although one cannot ignore the genetic component to T2DM, SGA humans and growth restricted animal studies clearly have served as models for FOAD and insulin resistance. Evidence is now accumulating about specific nutritional and non-nutritional alterations that may or may not alter growth and result in a similar pancreatic phenotype. This is the case with essential amino acids, glucose, and micronutrient deficiencies.[14,73,74] Thus, clinicians must be aware that perturbations, small or large, in the fetal and postnatal environment can have long-term consequences.

Skeletal muscle, liver, and fat—Although the debate still continues whether the pancreas or skeletal muscle is the key instigator behind the T2DM FOAD theory, evidence from both camps is convincing. Taken together, human and animal studies highlight the importance of crosstalk between pancreas, skeletal muscle, liver, adipose tissue, and brain. Skeletal muscle, one of the principal sites of action for glucose and insulin, is prone to dysregulation in T2DM. LBW infants have decreased lean body mass and increased visceral adiposity.[75–77] This "sarcopenic obesity" is considered one of the major culprits in the development of T2DM.[39,75–77] Fat tends to accumulate viscerally and in ectopic sites, such as the liver. When children with nonalcoholic fatty liver disease were examined, close to 40% of the population was born SGA and this subset also was more likely to progress to non-alcoholic steatohepatitis.[44] In addition to an increased risk for hepatic disease, it is hypothesized that LBW infants and later adults have increased hepatic glucose production. In fact, in the uterine artery ligation model, IUGR rats exhibited increased hepatic glucose production as evidenced by impaired oxidation of pyruvate and increased phosphoenolpyruvate carboxykinase before the onset of T2DM.[78]

Like many of the features in FOAD, there is subtle evidence of future pathology before clinical presentation. With respect to skeletal muscle, programming affects multiple areas—skeletal muscle development and/or fiber composition, glucose uptake, downstream insulin signaling molecules, glycolysis, and glycogen synthesis. Non-diabetic SGA young adults, when compared with age matched controls, demonstrate hyperinsulinemia at baseline and during oral glucose tolerance tests.[24] When challenged with a hyperinsulinemic-euglycemic clamp, those born small have decreased peripheral glucose uptake and reduced activation of PI3K/Akt proteins.[24,79,80] Looking more closely at muscle histology, LBW was associated with increased fast-twitch, glycolytic type IIx fibers, and larger type IIa and type I slow-

twitch, oxidative fibers.[81] Larger fiber size and a shift toward more type II fibers are associated with skeletal muscle insulin resistance. When examining the insulin signaling pathway, we and others have noted decreased protein expression of several key proteins, protein kinase C (PKC) ζ, p85, and insulin responsive glucose transporter (GLUT4), in both LBW adults and growth restricted rats.[28,30,79,80] No difference was noted in insulin receptor expression, suggesting the defect lies downstream.[80] To examine muscle glycolysis in LBW adult females, investigators analyzed ATP production with ^{31}P-magnetic resonance spectroscopy and found that ATP production was reduced in LBW adults subjected to exercise.[82]

With regards to adipose tissue, adipocytes are smaller in the SGA/IUGR fetus and neonate and with aging increase in size and number.[83] Moreover, as the SGA child accumulates more adipose tissue in extraneous sites, alterations in lipid metabolism occur and derangements in total cholesterol, low-density lipoprotein, and high-density lipoprotein become apparent.[13,25,84–86] When the SGA population is examined as a whole, those who become obese adults are more likely to have abnormally high total cholesterol and low-density lipoprotein serum concentrations.[86]

How birth weight alters adipokines, adiponectin and leptin, and the implications of these changes remains an area of active research. Adiponectin, an insulin-sensitizing and anti-inflammatory protein, is inversely correlated with fat mass and is decreased in diabetic states. Although adiponectin's role in adult disease is well-defined, its role in children and specifically in LBW infants is less clear. SGA fetuses have increased circulating adiponectin, and over time concentrations decrease. As expected, in the SGA population adiponectin is negatively correlated with weight, height, and BMI.[87–89] In a series of studies, however, no difference in adiponectin in SGA and AGA children was noted.[87–89] When a sub-group analysis was conducted, however, adiponectin was statistically higher in SGA subjects who did not exhibit "catch-up" growth or who were severely growth restricted at birth.[87]

In contrast to adiponectin, leptin concentrations correlate closely with fat mass and insulin resistance. Leptin, a satiety factor, acts on the hypothalamus and is responsible for regulating food intake and energy expenditure via a negative feedback loop. At birth IUGR neonates have decreased leptin, and by 1 year of age, leptin is increased compared with AGA controls.[90–92] All neonates, undergo a "leptin surge," and this surge occurs prematurely in growth-restricted rodents and sheep.[26,93] In normal two-week-old sheep, leptin concentrations are inversely related to feeding activity. In other words, as leptin decreases, feeding activity increases. However, in growth-restricted sheep, this relationship is reversed, and plasma leptin correlates with increased suckling.[26] As adults, LBW infants have abnormally high leptin concentrations even when BMI is taken into account.[94] This hyperleptinemia, at various stages of the life cycle, may represent a form of "leptin resistance," which acts to increase energy intake and decrease energy expenditure. When faced with the stress of a high fat diet, growth-restricted rats become obese and have higher leptin concentrations and decreased energy expenditure when compared to growth-restricted rats consuming standard chow or non-growth restricted rats on a high fat diet.[26]

Perinatal stress has been shown to alter neuronal circuitry. Studies have shown that intrauterine nutritional imbalances affect the rat/mouse hypothalamic orexigenic peptide, neuropeptide Y and anorexic peptide, cocaine- and amphetamine-regulated transcript.[95] In addition, emerging evidence supports perturbations of circadian oscillator genes, or "clock genes." Recently, a hyperphagic, hypoactive, preobese mouse was found to have altered clock genes in the brain and liver.[29] Thus, undernourished fetuses are programmed for abnormal eating behaviors and energy metabolism and bear a predisposition towards obesity.

As emphasized above the FOAD hypothesis centers around reshaping the individual's metabolism and body composition. To promote survival during periods of starvation, food intake increases, basal metabolic rate decreases, and energy is preferentially stored as fat. To increase glucose availability, pancreatic insulin production decreases, skeletal muscle and adipose tissue become insulin resistant, and hepatic glucose production is increased. This results in a state of hyperglycemia and increased de novo lipogenesis, which is further complicated by impaired action of growth and steroid hormones and leptin resistance. Overall, these events create a vicious cycle of adipose deposition (Fig 3). These adaptations are aimed at conserving energy and diverting scarce nutrients to vital organs. However, if there is "mismatch" in environments, or a transition from a nutritionally poor to nutritionally rich state, organ dysfunction and later disease become apparent.

A LBW neonate, symbolic of a perturbed in utero state, is at increased risk for developing insulin resistance/T2DM. In addition, the individual's growth during infancy, childhood, and adolescence, whether it is rapid, slow, or steady, at any stage, can further modify the eventual phenotype. The trajectory of one's growth and future disease profile may be significantly impacted very early, even before conception. However, we have demonstrated that interventions with exercise and drug therapy suppress hepatic glucose production and increase skeletal muscle insulin responsiveness in the IUGR animal.[96,97] Understanding how and why insulin resistance occurs in this population is key to developing strategies to reduce the burden of the metabolic syndrome and other associated diseases.

Puberty

Considering the implications of reduced fetal growth on the endocrine axis, it appears plausible that LBW children could have gonadal dysfunction and disturbed sexual maturation. In one study of SGA females, puberty and menarche occurred earlier than in the control population.[98,99] Other studies, however, have demonstrated that SGA children enter puberty at the appropriate age, but progress more rapidly through puberty.[100] In contrast to these observations, other studies have demonstrated that birth weight had no effect on the timing or progression through puberty.[101,102] When height was taken into account, it was noted that SGA children enter puberty at "the normal age," but this was not "normal" when considering their short stature.[103] There has also been a recent trend, specifically in Western countries, for earlier menarche. As a result, it is difficult to dissect environmental influences, perhaps related to exposure to endocrine disruptors, from the programming effect. There are limited studies on how LBW affects fertility and menopause in females, and the onset of puberty in males.

Ibanez et al published a collection of articles describing the hormonal dysfunction of Northern Catalonian Spanish girls. In these studies, LBW status was linked with precocious pubarche and adrenarche.[104,105] Adrenarche is characterized by the maturation of adrenal glands, and the production of sex steroids, such as dehydroepiandrosterone, which are responsible for pubarche. The hallmark of pubarche is the appearance of pubic hair, which usually occurs after the age of 8. These reports describe a "sequence of events" beginning with reduced growth, which progresses to pronounced adrenarche and precocious puberty, followed by ovarian hyperandrogenism, and finally insulin resistance. In these studies SGA girls have higher concentrations of dehydroepiandrosterone compared with AGA girls. Girls diagnosed with precocious puberty are more likely to have LBW status, and those with precocious puberty are more likely to have hyperandrogenism and hyperinsulinemia/insulin resistance.[104,105]

It is unclear if the link between precocious puberty and polycystic ovarian syndrome with SGA is secondary to early alterations of endocrine set points and/or a consequence of rapid weight gain during childhood.[50] In an Australian cohort of children with precocious puberty, 65% were obese and 35% were SGA.[98] As described above, exponential childhood growth is associated with central adiposity and insulin resistance, which is known to increase androgen and IGF-1 production.[10,38,39]

Overall, the link between LBW and premature precocious puberty and associated abnormalities appears plausible, but studies are limited by small, non-heterogeneous populations. Moreover, two other studies by different investigators have failed to replicate some of these results.[101,102] Further work is needed before unequivocal conclusions can be reached.

Premature Infant

Equally challenging for the clinician is the preterm infant. The VLBW infant, and specifically the extremely low birth weight infant, is at high risk for postnatal growth failure during their intensive care stay, which is intimately linked to poor cognitive outcomes. VLBW is defined as a birth weight less than 1.5 kg; extremely low birth weight infant is defined as a birth weight less than 1 kg. In one investigation of infants studied at 36 weeks corrected gestational age, 100% of neonates with a birth weight < 1000 g were characterized as having postnatal growth restriction, and the majority remained restricted at 36 months.[106] Despite aggressive, early parenteral nutrition and the introduction of enteral nutrition, the smallest infants remain small throughout childhood and neurodevelopmentally delayed.[106–109]

On the converse, preterm babies whose growth does not falter early demonstrate better cognitive outcomes. With the introduction of preterm formula, which is higher in calories and protein compared to term formula or breast milk, as an intervention in a preterm population, data revealed that males had higher verbal IQs and larger caudate volumes; however, both sexes demonstrated increased insulin resistance with higher split proinsulin levels and also higher diastolic blood pressures.[110,111] In another study of VLBW infants as young adults, they were found to have a 6.7% increase in their 2 hour glucose concentration,

a 16.7% increase in their fasting insulin concentration, a 40% increase in their 2-hour insulin concentration, and a 4.8 mm Hg increase in systolic blood pressure when compared to controls.[112] However in another study, individuals with better weight gain post-hospitalization or after reaching term were noted to have better intelligence scores, and a small, possibly clinically irrelevant increase in blood pressure.[113]

So the question remains, when and how should postnatal growth be fostered? Breast milk is considered the gold standard nutrition for the full-term, AGA infant. However, if term formula does not meet the needs of the growing premature infant, will breast milk? Does fortified breast milk carry any unforeseen risks? In a recent study LBW babies were assigned to exclusive breast milk feedings or fortified breast milk. Those that received exclusive breast milk demonstrated less weight gain, but had lower fasting glucose and insulin concentrations at 3 months of age.[114] Others have demonstrated that breast milk protects against rapid, exponential childhood growth.[115] However, how that applies to the VLBW and/or premature population remains unclear, and longitudinal follow-up studies are still needed.

Before the 1950s, few preterm infants survived. Today, with use of mechanical ventilation, surfactant replacement, antibiotics, and state-of-the-art neonatal intensive care nurseries, these children are reaching adulthood. Opportunities now are available for investigators to study the programming effects of prematurity in children, adolescents, and adults. These effects are far-reaching, and extend beyond cardiovascular, metabolic, and cognitive perturbations, and affect the family and society as a whole. Follow-up studies of VLBW infants have revealed that they are less likely to graduate from high school or obtain a university degree; however, rates of employment do not differ between those who were VLBW and non-VLBW infants.[116–118] Researchers have found that thoughts of depression and anxiety are more common in the follow-up of female VLBW infants, while males who were VLBW infants are more likely to exhibit attention deficit and hyperactivity disorder.[116,119,120] In studies of the Helsinki Cohort, depressive symptoms increased in a linear fashion with decreased gestational length, and growth restriction was associated with increased anxiety traits.[121] Additional evidence from a large Swedish cohort confirmed that infants born prematurely were more likely to suffer from psychiatric disorders and exhibit suicidal behavior.[122,123] Thus, while the provision of suboptimal nutrition has deleterious effects perhaps in a gender-specific manner on the preterm's cognitive development, prematurity also is associated with serious psychiatric implications. This is not necessarily surprising given that a good portion of CNS development occurs outside the womb in a foreign environment.

Other stressors, such as infections, hypoxia, and exogenous glucocorticoids, can permanently alter the neuroendocrine system.[15,16,124] When faced with chronic or repeated perinatal and postnatal stress, the hypothalamic pituitary axis (HPA) is activated, resulting in elevated adrenocorticotrophic hormone (ACTH) and adrenal hypertrophy.[125,126] An altered HPA carries significant long-term implications for atherosclerosis, dyslipidemia, T2DM, and immunosuppression. Prenatal glucocorticoids have been demonstrated to reduce hepatic production of insulin-like growth factor binding protein 1, which affects the child's height, can alter hepatic gluconeogenesis and increase blood pressure.[127] Providing yet another link

between birth weight and adult insulin resistance, studies have demonstrated that LBW infants have elevated plasma cortisol concentrations as adults.[128]

Considering that the HPA is intimately tied to behavior, it is not surprising that HPA programming can lead to aberrant behavior and thoughts. If subjected to a hostile environment, a pregnant mother produces a "stress response," which is transmitted to the fetus. When gestating rats were exposed to light and noise stress, their offspring had increased corticosterone levels and demonstrated impaired hippocampal function. This effect is most likely secondary to a reduction in pyramidal neurons and decreased synaptogenesis.[17]

Postnatal manipulations, like prenatal manipulations, can result in imprinting. When fetal rats are exposed to high levels of glucocorticoids in utero, their birth weights are reduced. As adults their HPA is chronically activated, and they exhibit anxiety-like and depressive behaviors.[15] Increased in utero exposure to glucocorticoids, which can be seen with maternal protein restriction, is associated with increased blood pressure in offspring.[129] There now is a growing body of evidence linking viral CNS infections with the development of schizophrenia, and glucose deprivation with autistic-like behaviors.[130,131]

Large for Gestational Age Infant

The other end of this spectrum finds the neonate born LGA, or with a birth weight greater than the 90th percentile secondary to gestational diabetes or idiopathic macrosomia. The obese or diabetic pregnant mother represents another form of programming. LGA, like SGA, is linked to future obesity and insulin resistance. LGA children are less likely to receive breast milk and exhibit rapid weight gain in the first 6 months of life.[112,132] Although exclusive breast milk feeding appears to provide some protection from obesity, not all epidemiological studies consistently support this finding. LGA infants have been tracked to be heavier children with increased mid upper arm circumference at the level of the triceps and subscapular sites, and they are more likely to develop hypertension and hypertriglyceridemia and become obese adults.[55,132–136]

Mothers with GDM are at increased risk for delivering an LGA or SGA neonate. GDM is a spectrum; severe GDM is characterized by vasculopathy and nephropathy, both of which are known to produce IUGR fetuses. In most cases, however, GDM produces an increased delivery of glucose and other macronutrients to the fetus, resulting in increased fetal production of insulin, the dominant fetal growth hormone. Infants born to mothers with GDM have increased adiposity and elevated insulin and leptin levels.[137,138] GDM also is hallmarked by maternal transmission; GDM mothers are more likely to have been born to mothers with T2DM, and GDM offspring are more likely to develop T2DM.[31,139]

It is important to remember that birth weight is merely a "symptom" of FOAD. In other words, it may or may not be a presenting feature or sign. It is imperative to recognize and acknowledge the AGA neonate born to a GDM mother. Although they appear "normal," they too were subjected to in utero compromise and are at increased risk for future disease.[31] Their in utero environment results in an increased secretion of hormones that promote the

deposition of adipose tissue and increased insulin secretion early in life, thereby setting the fetus up for an abnormal body composition and future disease.

Cancer

In addition to being at increased risk for developing metabolic derangements, being LGA at birth is associated with an increased risk of cancer. As a result, fetal determinants are receiving new attention. Birth weight has been speculated to be associated with the development of breast, ovarian, prostate, testicular, and colon cancers. While fetal growth factors, such as insulin, are regulated by maternal substrates, it is also known that maternal concentrations of estrogen and testosterone can alter the offspring's hypothalmic-pituitary-testicular/ovarian axis. By altering a specific tissue's exposure to nutrition and steroid hormones, the risk for tissue dysplasia and subsequent cancer can be altered. Unlike insulin resistance, which demonstrates a U-shaped curve with respect to birth weight, colon cancer exhibits a J-shaped curve, with the heaviest babies carrying the largest risk.[140,141] In a population-based cohort of over 10,000 men and women, macrosomia carried a hazard ratio of 2.57, while VLBW infants carried a modest, yet statistically significant, increase in incidence.[141] Studies have demonstrated that when rats fed excessive calories were then exposed to carcinogens, they exhibited an increased number of colorectal tumors in comparison with similar controls who received a calorically appropriate diet.[142]

The strongest evidence for cancer and FOAD exists for breast cancer.[5,143–150] A case-control study nested within the US Nurses' Study revealed that those individuals at birth who weighed less than 2.5 kg were half as likely as those who weighed greater than 4 kg to subsequently develop breast cancer.[5] Similarly, in a cohort of 2221 British women, a birth weight > 3.5 kg was associated with an increased risk for cancer, specifically pre-menopausal breast cancer, even after adjusting for confounders.[145] Trichopoulos first proposed that in utero exposure to high levels of estrogens, either endogenous or exogenous, increased the number of stem cells and/or mitogenic activity of undifferentiated breast tissue. Consistent with this theory, mothers with advanced age, dizygotic gestations, or macrosomic or preterm babies demonstrate higher concentrations of estrogen. As a consequence, their fetuses are at an increased risk for breast cancer development.[148,149] Conversely, mothers diagnosed with pregnancy-induced hypertension have decreased estrogen concentrations, and therefore, their offspring are relatively protected from breast cancer. In fact, in one study, pre-eclampsia/eclampsia was associated with a substantially lower breast cancer rate ratio of 0.24.[150] Moreover, women who are taller in childhood and have higher growth rates seem to carry an even higher risk. For every 5-cm increase in height, there is an 11% increase in breast cancer, thus implicating growth factors, such as the insulin-like growth factor, potentially yet another carcinogenic culprit.[146]

Epigenetics

Cancer, like the metabolic syndrome, is a complex and multifactorial disease. Genetic mutations and environmental triggers are not sufficient to explain the pathogenesis and the rising incidence of cancer, obesity, and T2DM. Epigenetics, which means "on top of genes," describes how the environment interacts with the genome to produce heritable changes resulting in phenotypic variation without altering the DNA of the genome. Epigenetic

processes include DNA methylation and demethylation and post translational processes such as, acetylation phosphorylation and methylation of core histones, which result in an altered histone code. The DNA methylation of cytosine-guanine dinucleotides is commonly described in the literature. DNA methyltransferase enzyme isoforms (Dnmt 1, 3a, 3b) methylate DNA, causing the DNA to be tightly coiled or wound (i.e., heterochromatin). This state results in transcriptional repression and is maintained by heterochromatin protein, HP1. Methylation is maintained by the methyl donors, methionine, choline, and various cofactors, such as folic acid. By contrast, loosely wound DNA, known as euchromatin, allows active transcription (Fig 4).

Epigenetic changes, previously well-described in the field of cancer, are now implicated in the pathogenesis of obesity and insulin resistance. Epigenetic modifications have been implicated in the SGA neonate, affecting promoters of glucose transporter 4, Pdx-1, glucocorticoid receptor, and peroxisomal proliferator activated receptor-α genes.[151,152] Whether methyl donor supplementation before or during pregnancy can reverse the SGA phenotype remains to be elucidated. While epigenetic modifications have been described in various animal studies, replications in human samples have proven to be challenging. This is perhaps related to the fact that human samples have been limited to blood cells while most of the epigenetic changes have been observed to be tissue-specific.[153]

Summary

To curb the epidemic of rising chronic diseases, some attention must be given to FOAD. David Barker's observations continue to stand the test of time across multicultural populations subjected to various constraints. The FOAD hypothesis has far-reaching implications as indicated by the following statement by the World Health Organization, "The global burden of death, disability and loss of human capital as a result of impaired fetal development is huge and affects both developed and developing countries."[154] The purpose of this review was to summarize some of the epidemiological, human, and animal data and provide pediatricians with a more complete understanding of the pathogenesis of chronic disease that are making their appearance earlier in childhood rather than waiting until adulthood.

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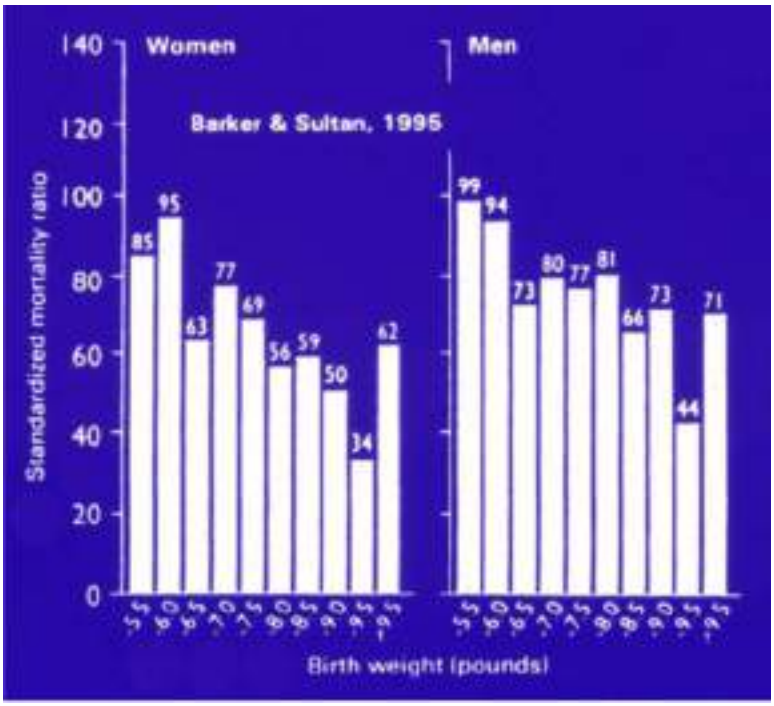

Figure 1.

Standardized mortality ratio by gender based on birth weight in pounds. (Reprinted with permission from Barker DJ, Sultan HY. Fetal programming of human disease. In: Hanson M, et al, editors. Fetus and neonate physiology and clinical applications: growth. Vol. 3. Cambridge: Cambridge University Press; 1995.)

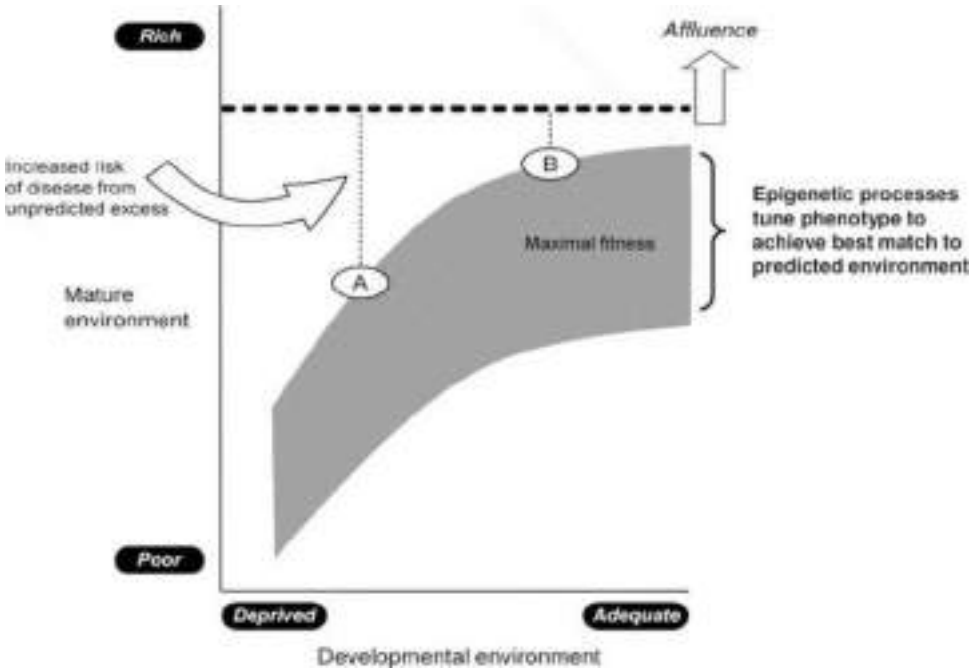

Figure 2.

The “thrifty hypothesis.” Schematic representation of risk of disease based on the “mismatch concept,” which focuses on the degree of disparity between the intra- and extrauterine environment. During the period of developmental plasticity, epigenetic processes are thought to alter gene expression in the fetus based on maternal environmental cues to produce phenotypes in the offspring best suited for the environment. Greater mismatch between pre- and post birth environments results in greater risk of disease (e.g., development in a poor environment followed by transition to an affluent Western lifestyle with unpredicted excessive richness of high calorically dense food with sedentary lifestyle as seen in A versus B). (Reprinted with permission from Godfrey KM, et al. Epigenetic mechanisms and the mismatch concept of the developmental origins of the health and disease, Pediatr Res 61:5R, 2007).

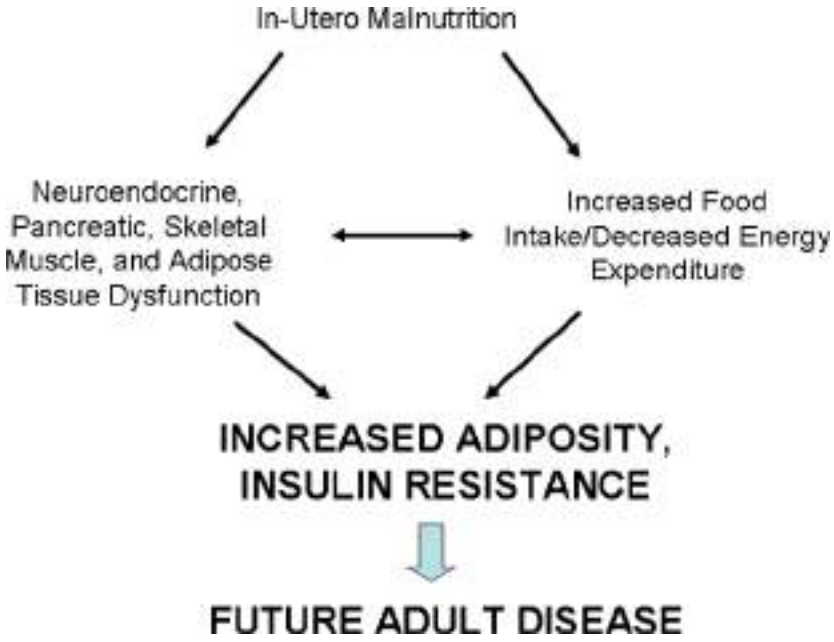

Figure 3.

Schematic representing the pathogenesis of Fetal Origins of Adult Disease (FOAD.) In-utero malnutrition results in neuroendocrine, pancreatic, skeletal muscle, and adipose tissue dysfunction, and increased food intake and decreased energy expenditure. This leads to increased adiposity and insulin resistance, and ultimately future adult disease.

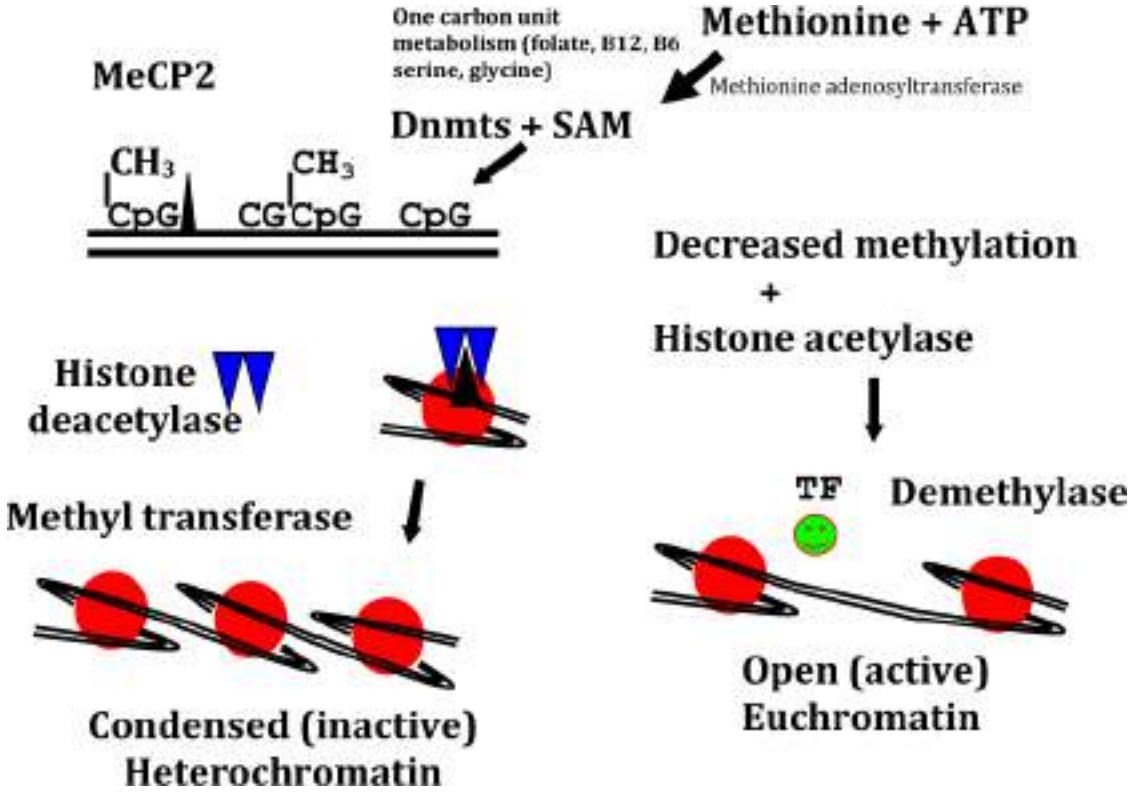

Figure 4.

Simplistic scheme showing methylation (CH_3) of CpG islands achieved by DNA methyltransferases (Dnmts) and S-adenosyl-L-methionione. Methylated DNA attracts methylated CpG binding protein (MeCP2), which recruits histone deacetylases and histone methylases, resulting in histone deacetylation and methylation. This process occuring in a gene promoter causes heterochromatin formation, resulting in failure of gene expression, which further is stabilized by the binding of the heterochromatin protein (HPI). In contrast, hypomethylation of DNA attracts histone actetylases and demethylases, which results in the oppositie effect with increased euchromatin formation, transcription factor binding, and the activation of gene transcription adenosine triphosphate (ATP). (Reprinted with permission from Devaskar SU, Thamotharan M. Metabolic programming in the pathogenesis of insulin resistance. Rev Endocr Metab Disord 2007; 8:105).

Table I

Chronic diseases associated with the Fetal Origins of Adult Disease (FOAD) hypothesis

Chronic diseases attributed to "Developmental Origins"
Diabetes Mellitus
Obesity
Dyslipidemia
Hypertension
Coronary Artery Disease
Stroke
Kidney Failure - glomerulosclerosis
Liver Failure – cholestasis, steatosis
Lung Abnormalities – BPD, reactive airway disease
Immune Dysfunction
Reduced Bone Mass
Alzheimer's Disease
Depression, Anxiety, Bipolar Disorder, Schizophrenia
Cancer

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REVIEW
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Collective Trauma and the Social Construction of Meaning

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Collective trauma is a cataclysmic event that shatters the basic fabric of society. Aside from the horrific loss of life, collective trauma is also a crisis of meaning. The current paper systematically delineates the process that begins with a collective trauma, transforms into a collective memory, and culminates in a system of meaning that allows groups to redefine who they are and where they are going. For victims, the memory of trauma may be adaptive for group survival, but also elevates existential threat, which prompts a search for meaning, and the construction of a *trans*-generational collective self. For perpetrators, the memory of trauma poses a threat to collective identity that may be addressed by denying history, minimizing culpability for wrongdoing, transforming the memory of the event, closing the door on history, or accepting responsibility. The acknowledgment of responsibility often comes with disidentification from the group. The dissonance between historical crimes and the need to uphold a positive image of the group may be resolved, however, in another manner; it may prompt the creation of a new group narrative that acknowledges the crime and uses it as a backdrop to accentuate the current positive actions of the group. For both victims and perpetrators, deriving meaning from trauma is an ongoing process that is continuously negotiated within groups and between groups; it is responsible for debates over memory, but also holds the promise of providing a basis for intergroup understanding.

Keywords: collective trauma, meaning, social identity, victimization, collective memory

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INTRODUCTION

The term *collective trauma* refers to the psychological reactions to a traumatic event that affect an entire society; it does not merely reflect an historical fact, the recollection of a terrible event that happened to a group of people. It suggests that the tragedy is represented in the collective memory of the group, and like all forms of memory it comprises not only a reproduction of the events, but also an ongoing reconstruction of the trauma in an attempt to make sense of it. Collective memory of trauma is different from individual memory because collective memory persists beyond the lives of the direct survivors of the events, and is remembered by group members that may be far removed from the traumatic events in time and space. These subsequent generations of trauma survivors, that never witnessed the actual events, may remember the events differently than the direct survivors, and then the construction of these past events may take different shape and form from generation to generation. Such collective memory of a calamity suffered in the past by a group's ancestors may give rise to a *chosen trauma* dynamic that weaves the connection between trauma, memory and ontological security (Volkan, 1997). These chosen traumas are conceptualized as narratives emphasizing that 'walking through blood' is necessary

on the path to freedom, independence and group security (Resende and Budryte, 2014). In this paper I illustrate how the collective memory of traumatic events is a dynamic social psychological process that is primarily dedicated to the construction of meaning. The creation and maintenance of meaning comprises a sense of self-continuity, a connection between the self, others and the environment (Baumeister and Vohs, 2002; Heine et al., 2006), and the feeling that one's existence matters. It is a processes of identity construction that comprises the sense of self-esteem, continuity, distinctiveness, belonging, efficacy, and ultimately a sense of meaning (Vignoles et al., 2006). Accordingly, the current article relies on these principles to trace the process of meaning-making following historical trauma at the collective level and among both victim and perpetrator groups.

Much of the theory and research presented in this paper focuses on the Holocaust because it is considered to be the prototypical 20th century genocide, and has attracted more attention and scholarship than other collective traumas (Mazur and Vollhardt, 2015). Can the Holocaust be compared to other cases of genocide and mass murder and should it? According to eminent Holocaust historian, Yehuda Bauer, the Holocaust, in spite of its unique attributes, can and must be compared to other events of a similar nature, otherwise why should a public school system in Philadelphia, New York, or Timbuktu teach it (Bauer, 1979)? Based on the notion that every specific trauma is unique, but the lessons derived can be universal, this paper discusses the common long-term consequences of different forms of collective victimization.

For victims of collective trauma meaning is established by: (a) passing down culturally-derived teachings and traditions about threat that promote group preservation; (b) these traditions of threat amplify existential concerns and increase the motivation to embed the trauma into a symbolic system of meaning; (c) trauma fosters the sense of a collective self that is transgenerational thereby promoting a sense of meaning and mitigating existential threat; (d) the sense of an historic collective self also increases group cohesion and group identification that function to create meaning and alleviate existential concerns; (e) the profound sense of meaning that is borne out of collective trauma perpetuates the memory of the trauma and the reluctance to close the door on the past; (f) Over time collective trauma becomes the epicenter of group identity, and the lens through which group members understand their social environment.

For members of perpetrator groups, collective trauma represents an *identity threat* (Branscombe et al., 1999), as it creates tension between the desire to view the group in a positive light (Tajfel and Turner, 1979), and the acknowledgment of severe moral transgressions in its past. The inability to reconcile the character of the group in the present with its character in the past may motivate group members, primarily high identifiers, to perceive an historical discontinuity of the group that serves to distance present group members from past offenders (Roth et al., 2017). Sometimes this discontinuity is reflected in the motivation to close the door on history and never look back (Imhoff et al., 2017), and sometimes the thorny chapters of a group's history are glossed over creating an uncomfortable gap in collective memory – an absence suggesting a presence. Members of perpetrator groups may deal with the dark chapter in their history by thoroughly denying the events, disowning them and refusing to take any responsibility for them. But, more often than not, reactions to an uncomfortable history will take on a more nuanced form with group members reconstructing the trauma in a manner that is more palatable, and representing the trauma in a manner that reduces collective responsibility. In some cases, the dissonance between current group values and past behavior are so great that disaffiliation from the group remains the only viable option (Čehajić and Brown, 2010; Hirschberger et al., 2016b).

Understanding the impact of trauma on collective meaning becomes even more complex when considering what Primo Levi defined as the *gray zone* (Levi, 1959) – a nebulous area wherein the distinction between victims and perpetrators is not always clear cut, and victims may behave as perpetrators and perpetrators are victims. Members of groups that exist in this region of collective memory are often motivated to defensively represent their history in a manner that highlights their sacrifice and downplays their crimes (Bilewicz et al., 2014; Hirschberger et al., 2016b). These groups may also engage in competitive victimhood dynamics with other groups demanding to be recognized as the veritable victim (Noor et al., 2012). Sometimes the victimization of one group poses such a threat to another unrelated victimized group because of the sense that its' victimization is overshadowed and does not receive due attention and acknowledgment. For example, sub-Saharan African immigrants in Belgium who felt a lack of recognition of their group's victimization expressed more antisemitism as a form of competitive victimhood with Jews whose victimization receives more recognition (De Guissmé and Licata, 2017). The current paper offers a perspective suggesting that the intra- and inter-group tribulations over a dark chapter in history represent more than an attempt to abdicate responsibility for past crimes, or quarrel over the benefits of the victim status. The need to come to terms with a dark past represents a crisis of meaning that must be resolved for the group to deconstruct and reconstruct its sense of collective self and assume an identity that offers continuity, coherence and significance. The memory of historical crimes threatens fundamental values, current notions of self-worth, and the sense of having a constructive collective purpose (Baumeister, 1991; Vignoles et al., 2006). The quest for meaning must, therefore, involve the reconstruction of these basic elements.

This analysis of meaning borne out of trauma for both victim and perpetrator groups offers the provocative suggestion that trauma is not merely a destructive event, but also an irreplaceable ingredient in the construction of collective meaning. Accordingly, for victim groups there may be secondary gains to collective trauma, that are often overlooked, that function to keep the memory of trauma alive, and lead subsequent generations to incorporate the trauma into their collective self. For perpetrator groups, the trauma functions as a catalyst that stimulates the construction of a new social representation that, if successful, can support a collective self that acknowledges past transgressions in a manner that is neither defensive nor crippling; one that promotes positive social identity (e.g., Vignoles et al., 2006) predicated on the triumph over past failings. On this

basis, the present article considers alternative ways to remember collective trauma that can break out of compulsive reenactments of the past, or defensive dynamics; ways that may reconcile the *meaning wars* between groups with a convoluted history and reduce intergroup tension and hostility.

FROM DISINTEGRATION TO NEWFOUND MEANING

Collective trauma is devastating for individuals and for groups; it constitutes a cataclysmic event that affects not only direct victims, but society as a whole. Just as trauma at the individual level shatters assumptive worldviews about oneself and one's position in the world (Janoff-Bulman, 1992), so does collective trauma transform the way survivors perceive the world and understand the relationship between their group and other groups, even those unrelated to the initial victimization (Alexander et al., 2004; Vollhardt, 2012). Trauma can disrupt people's global sense of meaning by exposing them to the darker sides of human nature (Park, 2013). Establishing meaning, therefore, is particularly important when individuals (or groups) encounter traumatic life experiences (Park, 2013). Sociologist Kai Erikson eloquently describes the similarities and differences between individual and collective trauma and their impact on the self:

> "*by individual trauma I mean a blow to the psyche that breaks through one's defenses so suddenly and with such brutal force that one cannot react to it effectively. . .by collective trauma, on the other hand, I mean a blow to the basic tissues of social life that damages the bonds attaching people together and impairs the prevailing sense of communality. The collective trauma works its way slowly and even insidiously into the awareness of those who suffer from it, so it. . .[is] a gradual realization that the community no longer exists as an effective source of support and that an important part of the self has disappeared. . . 'We' no longer exist as a connected pair or as linked cells in a larger communal body*" (Erikson, 1976, pp. 153–154).

Erikson's depiction of the disintegration of social support systems in the face of collective trauma clarifies the crisis of meaning that ensues and echoes Baumeister and Vohs' (2002, p. 608) contention that "the essence of meaning is connection." Collective trauma undermines a fundamental sense of security with long-standing effects among second and third generations of survivors. At the personal level, these individuals display significantly higher rates of psychological distress (Yehuda et al., 2002); at the social level second and third generation survivors display heightened individual and collective fear, feelings of vulnerability, injured national pride, humiliation (Lifton, 2005), a crisis of identity, and a predisposition to react with heightened vigilance to new threats, such that the pain of past generations is conflated with threats facing the current generation (Canetti et al., 2018).

The catastrophic image of the long-lasting effects of collective trauma portrayed by Erikson, albeit valid, represents only one side of the coin on how traumatic historical events impact individuals and groups. The current paper places the spotlight on another important aspect of collective trauma that has received less attention – the relationship between collective trauma and the construction of meaning. Although trauma is undoubtedly destructive, meaning is often unexpectedly found in calamity (Frankl, 1959/1976) and facilitated by processes of sense making (Davis et al., 1998). Trauma may contribute to the creation of a national narrative (Alexander et al., 2004), a sense of identity (Canetti et al., 2018), and cognitive working models that ostensibly function to ensure the safety and well-being of the group and provide it with values and guidelines for the future (Bar-Tal and Antebi, 1992; Hirschberger et al., 2017). Collective trauma may, therefore, facilitate the construction of the various elements of meaning and social identity: purpose, values, efficacy, and collective worth (Vignoles et al., 2006). These effects of trauma on the construction of collective meaning may, ironically, increase as time elapses from the traumatic event (Klar et al., 2013) because the focus of memory shifts from the painful loss of lives to the long-term lessons groups derive from the trauma.

The effects of collective trauma on the construction of meaning is not limited to the victim group that needs to reinvent itself and reconstruct all that was lost, but also to the perpetrator group that must redefine itself and construct a positive moral image of the group in light of the atrocities it committed (Shnabel and Nadler, 2008; Hirschberger et al., 2016b; Imhoff et al., 2017). The current paper traces the process of meaning-making for historical victims and perpetrators and suggests that although there are some pathological aspects to meaning borne out of trauma, these meaning structures ultimately contribute to group identification and cohesion, provide a sense of history and destiny, and propel groups to turn the calamity into a springboard for growth.

TRAUMA GENERATES A SEARCH FOR MEANING

Individuals and nations possess a collective memory (Halbwachs, 1980) of historical events, even those that took place long before they were born (Licata and Mercy, 2015). This collective memory does not constitute an accurate record of history, but rather is constructed by members of the group who function as 'lay historians' (Klein, 2013) in an attempt to inject meaning into history and provide a *usable past* (Wertsch, 2002; Licata and Mercy, 2015) that serves an important function in the present. One primary function of collective memories is to create and maintain social identity: "history provides us with narratives that tell us who we are, where we came from, and where we should be going. It defines a trajectory which helps construct the essence of a group's identity" (Liu and Hilton, 2005, p. 537). Collective memory not only promotes the construction of identity, but also the preservation of a positive collective identity (Tajfel and Turner, 1979) and a sense of worth (Vignoles et al., 2006). This can be achieved through social comparisons and devaluations of other groups, and also through the reconstruction of reality and memory as to uphold a positive image of the group.

Collective trauma may threaten collective identity; it may raise questions about the significance of the group, and about core

belief systems for both victims (e.g., "where was God when the trauma happened?"), and perpetrators ("How could my people commit such crimes?"); it may raise questions about the wisdom of continuing one's affiliation with a victimized group because being a member could be physically dangerous, and may also include feelings of humiliation and loss of agency (Shnabel and Nadler, 2008). It may also threaten affiliation with perpetrator groups as members inevitably contend with a burden of guilt. These processes may compromise group cohesion and lead to the disintegration of the group. Collective trauma, however, does not necessarily have a negative impact on group identity and cohesion and often bolsters affiliation with the group through a feeling of shared fate and destiny – an integration of the traumatic experience into one's identity and narrative (Gillies and Neimeyer, 2006). For instance, massacres and military defeats, as terrible as they may be, provide fertile ground for the production of cultural narratives and shared belief systems that infuse meaning and support social identity in the aftermath of calamity (Weber, 1946; Olick et al., 2011; László, 2013). Thus, historical trauma may be integrated into the social representation of both victim and perpetrator groups (i.e., "we are historical victims that continue to survive against all odds"; "it is our responsibility to promote values of acceptance and tolerance"), and then the trauma may have a solidifying and identity building effect as it becomes a central feature in collective memory and group narrative (Bar-Tal et al., 2009).

PART I: VICTIMS

Why Do Victims Want to Remember?

The historical memory for collective trauma may span millennia, with groups commemorating traumatic events that can be traced back to antiquity, and even to biblical times. Muslims remember their battle with the crusaders at the Horns of Hattin; Jews are commanded to never forget Amalek – the biblical people who threatened the Israelites. More recently, the Irish commemorate the rebellions against the British; Koreans carry with them the scars of Japanese oppressive rule; Bosnians can never erase the atrocities of Srebrenica; and the legacy of the Holocaust is to never forget. These memories of victimization that may convey an unflattering image of group weakness and powerlessness (Shnabel et al., 2009; Vollhardt, 2012) raise the question: why do these people and many others cling to their traumatic memory as a cherished possession? Why do they not want to move on and let bygones be bygones? In the following sections the manner by which the painful memory of trauma is adaptive to individuals and groups is presented layer by layer. In the first layer, the basic evolutionary level, the memory of trauma is shown to promote vigilance that may enhance actual group survival and restore a sense of efficacy. The memory of trauma, however, serves the needs of individuals and groups far beyond its contribution to survival; the memory of trauma and the existential threat that is inherent to it motivate a desire to construct meaning around the experience of extreme adversity. In this process of meaning-making, a transgenerational collective self is pieced together – a self-transcendent historical identity that provides a sense of continuity between past, present and future members of the group (Kahn et al., 2017). This transgenerational collective self promotes group cohesion, a sense of group importance and common destiny, and a strong commitment to group identity. This aspect of trauma reestablishes a sense of control, bolsters self/collective worth and prompts the search for meaning in suffering. To let go of the trauma, is therefore, highly aversive and costly; it is akin to abdicating collective meaning; and against this threat to meaning societies mobilize to keep the trauma alive as a lesson from the past to the future.

Traumatic Memory Is Adaptive

The 2004 Indian Ocean tsunami caused great devastation and a tragically high mortality rate – up to 90% of the population dead in some locations. In 1930, a tsunami of similar magnitude struck Papua New Guinea with only a fraction of that death toll – less than 1% of the population perished. According to a study on cultural responses to tsunamis (Mercer et al., 2012), this curious discrepancy in the lethality of two similar natural disasters can be attributed to a seemingly implausible cause: oral traditions. These traditions passed down from generation to generation over hundreds of years included, in the case of Papuan culture, the unequivocal instruction to run for the hills when the sea draws down. Indeed, Papuans who did not question this tradition, successfully escaped an almost certain death. An analysis of the communities that were most hard-hit in the 2004 tsunami reveal that these were mostly recent immigrants to coastal regions that had no collective memory about tsunamis, and no tradition on how to identify this threat and defend against it (Mercer et al., 2012). This comparison of two tsunamis provides a glimpse into how the memory of collective trauma (or the lack thereof) may directly influence group survival by promoting life-saving efficacy.

The collective memory of natural disasters and the collective memory of traumas intentionally caused by humans have much in common – they serve as guides for future generations on how to identify threat and how to respond to it effectively. However, whereas tsunamis will always be tsunamis with the lessons of the past forever applying to future generations, human societies change and evolve such that the villains of the past may have transformed and changed their relationship with the victim group. In this case, should the lessons of the past still inform future generations? From an evolutionary standpoint, exercising extra vigilance is warranted when it is not certain that the leopard has indeed changed its spots, or when this ostensible change is circumspect and may seem disingenuous. It makes good sense for victimized groups to keep their guard up, approach their past tormentors with some trepidation and hesitance, and ensure that future generations understand and remember the potential for danger.

Korean-Japanese relations, for instance, are still marked by Korean trepidation of their neighbor on the other side of the Tsushima Strait (Holmes, 2015). Although Japan has become a peaceful, even pacifist, country in the past 70 years since WWII, with one of the smallest military expenditures per GDP in the world, its record of aggression against Korea stretches back to

the 16th century. Koreans are, therefore, still weary of their former occupier, and keep their guard up to the possibility that Tokyo may someday revert back to its aggressive imperial past. This diffidence may not only reflect Korean frustration over the recent Japanese apology for sex slavery that many feel was disingenuous; it may reflect a gut instinct to steer clear of a group that caused them much harm in the past. This lack of historical closure that many Koreans feel with regards to Japan is often perceived as maladaptive because it stands in the way of intergroup harmony. But if the safety of the group is the ultimate goal, and intergroup relations are but a means toward this end, it makes clear sense to distrust and remain vigilant toward a former adversary.

Similarly, Germany has undergone significant transformation and a conscious effort to sever any continuity between Germany today and the Third Reich (Hein and Selden, 2000). Many of Germany's neighbors such as France (Hanke et al., 2013) and Poland (Imhoff et al., 2017) seem to recognize this transformation, and are able to separate the Germany of the past from that of the present. Israeli Jews, however, show a more ambivalent reaction, and a greater reluctance to close the book on the Holocaust and achieve closure; they are also more likely to conflate the past with the present, such that their attitudes toward contemporary Germany are contingent on their attributions for the past (Imhoff et al., 2017). Because the Holocaust is but the tragic climax of centuries of German and European anti-Semitism, many Jews are reluctant to let go of the past, and when engaging with contemporary Germans even on issues unrelated to the past, the Holocaust is often implicitly present (Imhoff, 2009).

The motivation to perceive continuity between the historical perpetrator group and current group members reflects ongoing caution toward a group that is still perceived as potentially dangerous. For instance Lebanese Maronite Christians who identify with their group perceived greater continuity among current and past members of their former enemies, Lebanese Muslims (Licata et al., 2012), indicating that they were motivated to view the current group as potentially having the same malevolent intents as the historical group.

These collective reactions to a history of trauma are similar in many respects to individual post-traumatic reactions. The experience of trauma at the individual level may lead to a post-traumatic reaction characterized by hypervigilance, re-experiencing the event, and avoidance of stimuli that are reminiscent of the event (Solomon and Mikulincer, 2006). Although such reactions may be debilitating, there are also adaptive elements to this extreme response that should not be ignored. A near-death experience often teaches people that greater vigilance and attention to threat are warranted to avoid the recurrence of such a life-threatening situation.

This dynamic of once bitten twice shy can be explained at the very basic evolutionary level as fear conditioning – an adaptive response to a threatening stimulus that is easily acquired, but is highly resistant to change (LeDoux, 1996). It can be inferred, therefore, that the same mechanisms that keep individuals out of harm's way, operate to safeguard group survival by maintaining heightened and prolonged vigilance toward out-groups that posed a threat to the group in the past.

From Adaptive Vigilance to Post-traumatic Worldviews

This relatively straightforward evolutionary explanation, however, does not suffice to explain the adaptive function of keeping the memory of trauma alive, because in some cases the historical perpetrator is no longer present. In these cases, an evolutionary explanation of vigilance in the face of a potentially dangerous adversary does not hold. One other way to explain the cultivation of an historical memory, that still remains within an evolutionary framework, is that vigilance born of trauma does not have to be directed toward a specific perpetrator group and can be generalized into a chronic and diffuse vigilance toward all other groups. Just as little Albert learned to generalize his fear to all furry objects in Watson and Rayner's (1920) cruel experiment, groups may learn that members of other groups harbor animosity toward them, and that the perpetrator only changes face, not harmful intent. This generalization of fear may reflect a harsh recognition that the group is, in fact, a target of hate by many other groups, and then an expectation for mistreatment by other group members seems reasonable.

For instance, the long history of persecution against the Jewish people has fostered a form of rejection sensitivity among Jews who often view the rest of the world as inherently hostile to them (Hirschberger et al., 2010). Today, as explicit anti-Semitism is considered unacceptable in many societies, but at the same time criticism of Israel's policies are on the rise, it becomes increasingly difficult to differentiate legitimate opposition to questionable policies from deep-seated hate cloaked in legitimate disguise. Research suggests that although a considerable amount of anti-Israeli sentiment in Germany can be directly attributed to anti-Semitism, the majority of Israel's critics harbor no anti-Semitic sentiments whatsoever (Kempf, 2011). One telltale sign of when virulent hatred underlies seemingly legitimate criticism is the tenor of that criticism – in a study of representative samples in 50 European countries, the use of extreme hyperbolic language against Israel was predictive of anti-Semitic motivation (Kaplan and Small, 2006). In signal detection terms (Macmillan et al., 2002), conflating well-meant criticism with hate (a false positive) over failing to spot hate when it is present (a miss) may have benefits for group survival that outweigh the costs of this paranoid outlook.

This seemingly adaptive caution, however, may develop into a post-traumatic worldview that is characterized by extreme vigilance, compulsive attention to threat that may be accompanied with inattentional blindness to positive signals from other groups, and the sense that the group is alone in this world and must fend for itself (Hirschberger et al., 2017). At the individual level, this perception of the world may cultivate anxiety and compromise achievement (Mendoza-Denton et al., 2002); at the collective level, the chronic distrust of others might foster extreme self-reliance and an aggressive stance toward any threat, big or small. If existence is capricious and the group stands alone against the entire world then any threat must be considered an

existential threat as there is no margin for error and no tolerance for incorrect rejections of a threat that may turn out to be real; responses must be swift and powerful, and because life itself is at stake, the moral justification for action is incontrovertible (Hirschberger et al., 2017). This post-traumatic worldview may no longer serve the evolutionary adaptive function of protecting the survival of the group and may, ironically, compromise the safety of group members by favoring aggressive policies that may not always be required, and that may propel the group into unnecessary conflict. Why then do group members cling to seemingly detrimental worldviews that may not serve their best interests?

Trauma Is of Death, and Death Creates Meaning

Although the colloquial use of the term *trauma* often refers to relatively benign events ("my visit to the dentist was traumatic"), the psychological definition of trauma includes the encounter with death, or extreme death anxiety, as a central component of this psychological phenomenon (Galea et al., 2003; Smelser, 2004). It is prudent, therefore, to understand the role of death in collective trauma and its relationship to the construction of meaning if we are to disambiguate the motivations underlying the resolve to perpetuate the memory of collective trauma, in spite of the detrimental effects this memory may have.

In the *Birth and Death of Meaning*, cultural anthropologist Ernest Becker asserts that: "...society is responsible, largely, for shaping people, for giving them opportunities for unfolding more freely and more unafraid. But this unfolding is confused and complicated by man's basic animal fears: by his deep and indelible anxieties about his own impotence and death, and his fear of being overwhelmed and sucked up into the world and into others. All this gives his life a quality of drivenness, of underlying desperation, an obsession with the meaning of it and with his own significance as a creature" (Becker, 1975).

Becker (1973, 1975) further asserts that humans are a social animal, not just because of their evolutionary nature, but because of their fundamental need to seek meaning and significance. At the core of this quest for meaning resides death as a fundamental human problem. Unlike other mortal beings that live in a perpetual present, oblivious to their ultimate fate, humans are bestowed with a complex cognitive system that generates self-awareness; it enables us to remember our past, imagine our future, and project our self in our mind over time and space to wherever we may desire to be. This remarkable ability comes with a somewhat disconcerting side effect – the poignant awareness of the limited, transient nature of existence. According to terror management theory (TMT: e.g., Pyszczynski et al., 2015), the awareness of death in an animal instinctively motivated by self-preservation creates an impossible tension between the desire to live, and the ultimate recognition that death is inevitable, and that attempts to overcome this fate are doomed to fail. To deal with this irresolvable anxiety, humans have developed cultural worldviews – existential illusions (Greenberg, 2012) that give life meaning, significance and purpose. These worldviews cannot solve the problem of death, but they provide the comforting illusion that part of the self will persevere and survive physical death through cultural rites, symbols, and belief systems. This sense of *symbolic immortality* (Lifton, 1973) provides a semblance of continuity that the physical self fails to provide, and by doing so not only alleviates individual existential concerns, but embeds the individual into a symbolic collective entity that existed before the individual was born and will likely continue to exist long after she or he expire. Adherence to, and identification with this symbolic collective entity is, therefore, vital to the management of the terror of death, to the extent that the memory of the collective becomes one's own memory; the aspirations of the collective become one's own aspirations; and the pains and woes of this collective are experienced as genuine personal suffering.

From an existentialist perspective, therefore, the same forces that threaten to break a group may, ironically be elemental in making a group. Specifically, the memory of collective trauma that amplifies a sense of individual and collective existential threat prompts the search for collective meaning through adherence and identification with the group (Hirschberger et al., 2016a). This process of identification necessarily involves the construal of the group as special and unique in the world to the point that it is worthwhile and honorable to suffer and even die for the group, as proclaimed in the ancient Latin adage: *dulce et decorum est pro patria mori* (it is sweet and honorable to die for one's country). In this process, the history of the group, and its traumatic past in particular become an indispensable vehicle for injecting meaning into the present struggles and confrontations of the group. The attempt to insert meaning into tragedy, and turn an otherwise pointless death into an act of heroism that corresponds with the collective memory of violence against the group, culminates at the point where the death of group members is, ironically, transformed into a symbol of group continuity and group immortality.

Suicidal terrorism, for example, is a form of wanton violence against innocent civilians wherein the terrorist sacrifices his or her own life in the process of killing random others. Some of the explanations for this seemingly irrational and senseless act suggest that a quest for meaning underlies the motivation of the suicide bomber (Kruglanski et al., 2009). By self-sacrificing for the group, the terrorist is seen as a martyr, and is transformed in the eyes of others from another unremarkable individual, part of an indistinguishable mass, into an immortal hero placed on a pedestal. This ultimate sacrifice for the group against the supposed enemies of the group not only elevates the status of the suicide bomber and grants him or her symbolic immortality at the expense of physical mortality; it connects the act to historical confrontations between the group and other groups and renders one comparable to legendary historical figures (Acosta, 2016). By doing so, the death of the young suicide bomber is transformed from an individual tragedy to a symbol of the group's immortality, and reaffirms the connection between the sacrifices made by historical heroes and present-day martyrs.

Wars, massacres and genocide confront people with the painful realization that individual lives are extremely fragile and vulnerable, and that during violent times the value of human life is often reduced to nothing. It is at these times, in particular, that

the collective self becomes invaluable; it substitutes the frustrated need for individual life with the promise that the collective will endure and survive over time. As French sociologist, Auguste Comte asserted: "The only real life is the collective life of the race [group]; individual life has no meaning except as an abstraction" (Gane, 2006). When people are confronted with massive death and with their inability to do much about it, they search for meaning and find comfort in the group – a collective symbolic structure that is greater and more enduring than the physical self (Becker, 1973), a structure that satisfies the basic elements of meaning and identity – values, efficacy, purpose and worth (Vignoles et al., 2006).

Trauma Motivates Self-Continuity

Existential threat prompts a motivation for self-continuity and symbolic immortality through social identity (e.g., Castano et al., 2002), but what is the nature of this continuous self, and how does it serve the purpose of infusing tragedy with meaning? In recent years, social psychological theory and research have recognized the importance of the temporal dimension in social identification, and there is growing interest in the role history plays in formulating group identity (e.g., Reicher and Hopkins, 2001). Social representations theory (Moscovici, 1988; Liu and Hilton, 2005), for instance, suggests that the way people construe and explain historical events may have a marked impact on how they relate to the present, and what they expect from the future. Other accounts, suggest that the social information traveling from the past to the present comprises two main components: perceived cultural continuity – the extent to which group values and norms are transmitted from one generation to the next, and perceived historical continuity – the extent to which events in the group's past are seen as causally interconnected and are incorporated into the group's current identity (Sani et al., 2007, 2009).

A related conceptualization of group continuity over time makes the distinction between perceiving the group as an intra-generational entity which includes only living group members, and a *trans*-generational entity that includes all members of the group: past, present, and future (Kahn et al., 2017). A series of correlational and experimental studies conducted on Israelis, Palestinians, and Swedes demonstrates that individuals who perceive the group as *trans*-generational are more tolerant of in-group casualties that are deemed necessary to promote the group's interests. Collective meaning, in this case, trumps the value of individual lives (Kahn et al., 2017).

This research on *trans*-generational conceptualizations of the group, highlights the distinction between the physical lives of group members and the existence of the symbolic collective in a manner that is complimentary of the existential explanations presented earlier. Namely, individuals who include past and future group members in their definition of the group are more likely to find the lives of present group members dispensable if this sacrifice is believed to promote group continuity. Collective trauma, therefore, may not only increase the desire to uphold a symbolic continuous collective self; it may shift concern from the effects of the trauma on individual group members to the implications the trauma may have on the future of the group.

The research on historical continuity and *trans*-generational identification add another layer of understanding to the role of trauma in the construction of collective meaning. If the existential anxiety emanating from trauma is a driving force behind the construction of a symbolic continuous collective self, to the extent that individual life is dispensable for the sake of group immortality (Pyszczynski et al., 2006; Routledge and Arndt, 2008), the successful construction of a *trans*-generational social identity is the pinnacle of this terror management; it enables individuals to overcome the instinctive terror that comes with exposure to the death and suffering of other group members, and instead assumes a bird's-eye view that disregards current sacrifices, transcends the present, and envisions only the benefits the group may reap in the future (Kahn et al., 2017). Napoleon must have been in this *trans*-generational mindset when he contended that "death is nothing, but to live defeated and inglorious is to die daily."

Meaning Is Not Monolithic: Social Representations of Trauma

At this point of the analysis of collective trauma and meaning, we have seen how trauma creates meaning for victim groups; it alleviates existential threat, induces a search for collective meaning, operates to embed the individual in a social group that transcends physical existence, promotes a continuous historical self spanning centuries and millennia that is valued above individual life, and increases group identification and group cohesion. Societies with a history of trauma are in a constant process of constructing and reconstructing the meaning of the trauma, not so much in an attempt to understand the past, but because of a pressing need to make sense of the present. Because the present is active in shaping the memory of the past, when present conditions change the motivation to remember the past in a certain way may change as well (Rimé et al., 2015). This reconstruction of meaning constitutes weaving once again the fabric of essential connection (Baumeister and Vohs, 2002); of finding purpose, values and worth and a sense of efficacy to make a difference. These conclusions, however, assume a monolithic relationship between trauma, memory and meaning such that all group members are expected to derive the same sense of meaning from the same collective trauma. But, people understand history in different ways, and what may induce guilt in some may foster pride in others depending on how they represent the past, and on the attributions they make for their group's wrongdoings (Doosje and Branscombe, 2003; Imhoff et al., 2017). For some, the history of genocide in Europe instills a sense of guilt and a desire to compensate for past wrongdoings by welcoming current immigration to Europe (Rees et al., 2013); for others, the same history may imply the danger of mixing with other cultures, and the need to safeguard Western civilization from unwelcome influences.

Similarly, the dictum 'never again' referring to the Holocaust is understood by some Israeli Jews as a call to arms to ensure that the Jewish people will never face the threat of annihilation again. For others, this same history delivers the moral imperative that Jews, having suffered the consequences of extreme racial

hatred, should be at the forefront of the struggle against all forms of prejudice and discrimination, and should be especially cautious to not victimize others (Bauer, 1979; Klar et al., 2013). Thus, there appear to be individual differences in the way group members remember collective trauma and in the meaning they derive from it. Social representations theory provides a framework to understand variations in the understanding of history and how these variations impact the construction of meaning.

The study of social representations of history indicates a growing understanding that the collective representation of history does not necessarily reflect the historical truth, but rather is a combination of historical facts with shared myths and beliefs that are essential in forming and maintaining group identity (e.g., Reicher and Hopkins, 2001; Liu and Hilton, 2005). Social representations are not only based on how a group construes its' past, but also on how other groups perceive it. Discrepancies between in-group and out-group perceptions of a group's history, therefore, may be a source of intergroup tension.

Discrepancies may exist not only between opposing groups, but between members of the same group. Moscovici (1988) makes a distinction between hegemonic representations that are shared by most of the members of a political party, or a nation; emancipated representations – variations on hegemonic representations that are tolerated and not contentious; and polemic representations that are related to social conflicts and controversies in a society.

This distinction between consensual and non-consensual social representations is fundamental to understanding how people make sense of history, and how they understand the role played by their group and other groups. The acts of perpetrators, for instance, are often difficult to understand and both scholars and laypeople make attributions about why perpetrators acted the way they did. The roots of German behavior in WWII are a case example of polemic representations that have been discussed since the early 1940's. Some, attributing an internal essence have described Germans as an "aggressor throughout the ages" (Hearnshaw, 1940), and as having a set of permanent characteristics that underlie their aggression: "if the criteria of a trait are permanence and lack of specificity we may rightly call aggressiveness a trait of these individuals" (Schreier, 1943, p. 211). Contemporary essentialist accounts focus on fixed worldviews and belief systems that are claimed to be uniquely characteristic of German society (Dawidowicz, 1975; Goldhagen, 1996; Imhoff et al., 2017).

Others reject the notion of an internal evil essence underlying evil acts and instead attribute wrongdoings to external forces working on the perpetrator group such as coercion by a powerful and ruthless regime. In the case of Germany, Nazi terror and fear among ordinary Germans could be offered as an alternative attribution for the horrors committed by this group (Imhoff et al., 2017). Another attribution that places the onus on the situation and not the group suggests that historical crimes are the end result of extremely harsh social and economic conditions that facilitated the rise of aggressive dictators (Imhoff et al., 2017). Historian Christopher Browning invokes the social psychological processes of conformity, compliance, and pluralistic ignorance to explain the transformation of ordinary men to mass murderers (Browning, 1992).

These different attributions underlie different representations of history, and these different representations have a profound influence on the meaning derived from the trauma. Attributing perpetrators' behaviors to an internal, evil essence highlights the moral distinction between victim and perpetrator, and consolidates the morally superior position of the victim group; it also allows victims to avoid the uncomfortable question of whether they would have behaved similarly under similar conditions. For perpetrator groups, however, this attribution is extremely threatening; it leaves the group forever guilty of the past, with each generation carrying the burden of their ancestors' crimes; it also forestalls any process of change, as changing the inner essence of the group is near impossible. To reconstruct a meaningful and positive group identity in the aftermath of group wrongdoings, members of perpetrator groups are motivated to attribute historical crimes to external, uncontrollable circumstances (Imhoff et al., 2017), a process that corresponds to the ultimate attribution error (Pettigrew, 1979) – a group level attribution error wherein people tend to attribute negative in-group behavior to external causes. This absolves them from the burden of guilt; allows them to draw a clear distinction between current group members and past members; and most importantly enables them to formulate a social representation of the group that isolates the dark episode as an uncharacteristic failing. In the words of Alexander Gauland, Germany's far-right AfD leader, "Hitler and the Nazis are just bird shit on the 1000 years old successful German history."

Social representations of history, therefore, are not merely attempts to understand what happened, but are building blocks in the construction of social identity. The intergroup animosity that existed during the trauma is often replaced with memory wars over the attributions made for the trauma and the significance of the trauma for the image of both victim and perpetrator groups. These tacit memory wars that take place between victim and perpetrator groups and within each one of these groups constitute an ongoing struggle with a troubling history and the inter- and intra-group negotiation of collective meaning.

PART II: PERPETRATORS

Trauma Threatens Meaning for Perpetrators

The manner by which an historical trauma is represented in collective memory may present an *identity threat* (Branscombe et al., 1999) to members of perpetrator groups, and may constitute a moral injury associated with loss of meaning (Litz et al., 2009). Reminding people of the responsibility of their group for past misdeeds leads to derogation (Castano and Giner-Sorolla, 2006) and to negative attitudes toward the victim group; it leads to a defensive attempt to protect the group by minimizing the historical crime (Doosje and Branscombe, 2003), distorting the memory of the event (Frijda, 1997; Dresler-Hawke, 2005; Sahdra and Ross, 2007), and justifying in-group behavior (Staub, 2006). Members of perpetrator groups often display 'blind spots' in their

memory of the event in order to eliminate inner conflict (Frijda, 1997, p. 109; Dalton and Huang, 2014), or deny the ongoing relevance of the past by demanding historical closure on this chapter in history (Hanke et al., 2013; Imhoff et al., 2017).

The threat posed by a history of perpetration to a group's moral image is particularly poignant for people who highly identify with their group (Ellemers et al., 2002). For them, defensive representations of history (Hirschberger et al., 2016b) are necessary to restore a positive social identity which reflects on their self-concept (Tajfel and Turner, 1979), and they are highly motivated to believe that their group is moral and good (Leach et al., 2007). At medium levels of group identification, a certain level of collective guilt seems tolerable, but high identifiers are averse to feeling guilty (Klein et al., 2011) and when reminded of their groups' misdoings react with defensive thoughts and responses to the reprimanding source (de Hoog, 2013), feel less collective guilt than low identifiers (Doosje et al., 1998), and also increase their opposition to the out-group (Smeekes and Verkuyten, 2013).

Denying the Trauma

The most extreme form of defense against the threat posed by collective trauma to the moral image of perpetrators is to deny that the traumatic event ever took place. If the trauma never happened, not only is the alleged perpetrator innocent of any wrongdoing, there is a complete reversal in the perpetrator-victim relationship such that the supposed victim is in fact the aggressor who is casting false allegations against others, tarnishing their reputation, and receiving undeserved reparations for harm that was never committed. In this case, the crisis to meaning facing the perpetrator group turns into an opportunity to fortify the group's moral standing. This type of victim blaming that is common in sexual crimes (Campbell and Raja, 1999), is more difficult to sustain in cases of collective trauma because of the number of witnesses and the quantity of physical evidence that is hard to discount. Nevertheless, as time passes from the collective trauma, and the direct witnesses are gone, it becomes more challenging to confront such historical revisionism (Lipstadt, 2012).

Reconstructing the Trauma

In the aftermath of collective trauma, discerning victims from perpetrators, and willing collaborators from collaborators at gunpoint, is often not clear cut. This ambiguity provides ample room for the reconstruction of history and the creation of a collective memory that is favorable to the group. The role played by Hungary and Poland in WWII – nations that stood on both sides of the victim-perpetrator divide – are case examples of how groups may construct a selective account of history that contains only favorable information about the group, while disregarding and distorting information that may compromise its positive image.

Whereas there is no doubt that Poles were the victims of the Nazis with three million ethnic Poles murdered during WWII, information has surfaced, in recent years, revealing horrific acts of mass murder perpetrated by Poles on their Jewish neighbors at their own volition, and not under Nazi coercion (e.g., Gross, 2001; Grabowski et al., 2013). These findings undermine the prevalent narrative of Poles as mere bystanders or victims, threaten the moral image of the group, and fuel vibrant debates in Poland about truth and memory (Bilewicz et al., 2014). Further, the attempt to defend an untarnished image of victimhood has stimulated victimhood-related anti-Semitism (Bilewicz and Stefaniak, 2013). Recently, the Polish Senate approved a controversial bill making it illegal to accuse the polish people or state of complicity in the Holocaust (John, 2018) indicating how memory wars are, not mere intellectual debates over history, but desperate attempts to salvage the image of the group and the meaning it provides in the face of a tumultuous past.

Similarly, while there is little question that many Hungarians were victims during WWII (such as members of left-wing movements and other dissidents), the historical record points to the uncomfortable fact of official and widespread Hungarian participation in the Final Solution (Stauber, 2010). Unlike Poland, however, that never officially collaborated with the Nazis, the Hungarian fascist Arrow Cross regime was an official ally of Nazi Germany (Deak, 1979). Nevertheless, many Hungarians today prefer to overlook the official collaboration of the Hungarian government, and maintain instead that Hungarians were forced to collaborate with the Nazis against their will, or were even victims of the Nazis. This defensive strategy dubbed by historians "an assault on historical memory" (Braham, 1999), is associated with both high nationalism and high antisemitism (Hirschberger et al., 2016b), indicating that the motivation to assume the coveted victim status includes competitive victimhood dynamics (Noor et al., 2012). Groups with a history of perpetration, however, do not always attempt to escape guilt, but either develop injunctive norms that suggest that they should not feel guilty (Bonnot and Krauth-Gruber, 2018), or some members of the group, such as older generations, protect themselves from negative feelings about the in-group by altering collective memory (Licata and Klein, 2010).

The debate over the role of Poland and Hungary in the Holocaust is a veritable struggle to salvage group meaning that is as poignant today as it ever was. When former FBI Director James B. Comey reflected on Hungary and Poland's role in the Holocaust at the 2015 annual dinner of the United States Holocaust Museum, a diplomatic storm ensued with a summoning of American ambassadors, angry rejections of the allegations, and a demand for an apology. These incensed reactions over the memory of a distant past are telling of the powerful relations between trauma, memory, and current group meaning.

Closing the Door on Trauma

Unlike third party collaborators that enjoy some degree of freedom in constructing a positive collective memory of the past that is not blatantly false, the direct perpetrators of trauma have no such luxury. They must either contend with their past, deny it, or alternatively, they may simply wish to close the door on history and never look back. Historical closure may convey benefits for both victims and perpetrators when closure is part of a reconciliation process (Hanke et al., 2013). In this case, closure

may indicate a symbolic departure from the past that entails the construction of consensual memory about the conflict. When the motivation for closure stems only from the perpetrator group, however, it may reflect fatigue with the burden of blame, and may be associated with hostility toward the victim group (Imhoff et al., 2010).

Many Germans, for example, feel that they should no longer suffer for the sins of their ancestors, and resent the expectation that they should feel guilty over the Holocaust (Ahlheim and Heger, 2002; Imhoff et al., 2010). Many Jews, on the other hand, feel that the Holocaust cannot be forgiven or forgotten and expect Germans to recognize their collective responsibility (Cherfas et al., 2006). Victims of other traumas also display a greater need to remember, are more reluctant to forgive and may harbor lingering antipathies toward their former nemesis, even generations later (e.g., Olick and Levy, 1997; Pennebaker et al., 1997; Paez and Liu, 2011; Hanke et al., 2013).

These differences in temporal perspectives between perpetrators that are motivated to look forward and turn their back to the past (Hanke et al., 2013; Imhoff et al., 2017), and victims that tend to place much weight on the past as a source of identity (Kahn et al., 2017), and as a prism through which to understand the present (Hirschberger et al., 2016a, 2017 Canetti et al., 2018) reflect another dimension in the memory war between victims and perpetrators. For one side the past poses a formidable threat to meaning, and for the other, the very essence of meaning stems from the same traumatic past. In identity process terms (Vignoles et al., 2006), for perpetrator groups that dissociate from the past, the need for self-esteem trumps continuity (i.e., to feel good about the group they are motivated to sever ties with the past), but for victim groups, self-esteem is inextricably tied to continuity. An interesting study conducted in the context of the Rwandan genocide indicates that not all members of the victim group share the same motivation with regards to the past, and that direct survivors of violence experience more difficulty moving on and reconciling with the other group than in-group members that were not direct survivors (Kanazayire et al., 2014). Thus, the different lessons learned from the past are not only between victim and perpetrator groups, but within each group as well.

Acknowledging Responsibility

One of the most difficult decisions perpetrator groups face is whether to accept responsibility for past transgressions and apologize for the harm they have done. Acknowledging responsibility may be devastating for a group's moral image and for its sense of meaning and significance. It is no wonder, then, that many groups are reluctant to admit their faults and moral failures. This is true for Turkey and the Armenian genocide; the Japanese occupation of Manchuria and Korea; and the Palestinian Nakba during Israel's war of independence. In all of these cases, and many others, acknowledging responsibility is costly as it requires change in the national narrative; it requires an incorporation of the victim's narrative and the recognition that victorious moments for the group (such as achieving independence) are often accompanied by harsh transgressions toward other groups that may cast a dark shadow on these celebrated moments (Bar-Tal and Salomon, 2006; Hammack, 2011).

The literature on in-group responsibility for historical crimes reveals a complex picture with motivations to both defend the in-group and repair relationships with the out-group (Gausel et al., 2012). Members of perpetrator groups who do acknowledge the past crimes of their groups tend to have more positive attitudes toward the victim group (Čehajić-Clancy et al., 2011; Hirschberger et al., 2016b), more contact with victim group members, and a heightened ability to take the perspective of the victims (Čehajić and Brown, 2010).

There is a price, however, to such acceptance of the group's past. Acknowledgment of in-group culpability creates dissonance between the motivation to believe that the group is good and its' past misdeeds. As a result, the wrongdoings of a perpetrator group might lead members to disassociate themselves from the actors of the crime (Marques et al., 1988; Branscombe et al., 1993). The dissonance between the desire to view the group in a positive light and the fact of its dark history can either be resolved by assuming a defensive representation of history that vindicates the group (and secures an exclusive victim consciousness as described by Vollhardt, 2012, or feelings of competitive victimhood as in Noor et al., 2012), or alternatively by distancing from the group and defending the self from the association with a group with a negative reputation.

Although acknowledgment of responsibility for past crimes seems incompatible with current in-group identification for members of perpetrator groups (Čehajić and Brown, 2010; Hirschberger et al., 2016b), some historical perpetrators have struggled to create new meaning for their group while acknowledging, not denying the dark past. In Germany, for instance, the term *Vergangenheitsbewältigung* means the struggle to overcome the negatives of the past by raising uncomfortable questions about collective culpability and group responsibility. German churches have led way in this process and have developed a post-war theology of repentance. Similarly, the Holocaust is part of the school curriculum from elementary school onward. The current prevailing liberal attitude in Germany that favors multiculturalism and opposes militarism of any form can be understood as a new cultural identity that uses the difficult past constructively as the backdrop of its current positive image. This reconstruction of meaning through acknowledgment of past transgressions has, thus far, received only some empirical attention (e.g., Rensmann, 2004).

CONCLUSION

Collective trauma is a devastating event in a group's history that has far-reaching effects and profoundly influences both perpetrator and victim groups many years after the events have ended. Until recently, the psychological literature has focused almost exclusively on psychopathology and health-related

consequences of collective trauma (e.g., Yehuda et al., 2002). But today, there is a burgeoning interest in understanding the social and political implications of perpetration and victimization as well (Vollhardt, 2012). This literature has already yielded several important insights: for example, it has demonstrated the relationship between collective victim beliefs and the justification and legitimization of current political violence (Maoz and Eidelson, 2007; Wohl and Branscombe, 2008; Vollhardt, 2012), and has also delineated the experience of collective victimhood, the material gains, and competition over these gains that are associated with it (Noor et al., 2012).

The current paper offers another perspective that is based neither on pathology nor on the belligerent consequences of trauma. Instead, it views collective trauma as a genuine experience with real consequences for subsequent generations. The preponderance of literature on historical victimization is situated in the intergroup relations literature (Noor et al., 2017), and is influenced by the goals and the central assumptions of this literature. Because one of the core goals of intergroup relations research is to understand and promote conflict resolution and reconciliation, the long-term effects of collective trauma are often evaluated by this criteria. Accordingly, historical victimization is typically understood as a barrier to peacemaking and a distorted lens (Schori-Eyal et al., 2017). In this paper I contend that the memory of victimization has both adaptive and maladaptive manifestations. Although members of victim groups may be less trusting of adversaries and more reluctant to compromise and make peace, this reaction may, at times, protect the group from duplicitous gestures of peace from disingenuous adversaries. Although the memory of trauma may foster a paranoid and paralyzing post-traumatic outlook, it may also spur growth through the meaning derived from the trauma. A meaning that emphasizes the resilience of the group and its ability to rehabilitate and change in the aftermath of calamity. These consequences are especially pertinent as these new generations of victim and perpetrator descendants attempt to construct social meaning that can explain the past, provide a roadmap to navigate present challenges, and prepare the group for the future.

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A Bioecological Model of Mass Trauma: Individual, Community, and Societal Effects

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Abstract

Biopsychosocial consequences of catastrophic events create an ongoing need for research that examines the effects of mass traumas, developing psychosocial interventions, and advocacy to address the needs of affected individuals, systems, and communities. Because it is neither possible nor necessarily desirable to intervene with all touched by disasters at an individual level, a systems approach that allows conceptualization and response at the individual, family, community, and societal levels seems optimal. Many of the models commonly used in counseling psychology to explain coping with difficult events focus on individual effects and do not adequately capture the complex, multisystemic effects of large-scale catastrophic events and disasters. A bioecological model of mass trauma, which provides a conceptual framework for understanding the effects, intervening in the aftermath, addressing prevention, and researching aspects of large-scale disasters, catastrophes, and mass traumas, is presented. Relevant literature and illustrative examples from three categories of mass traumas or catastrophic events (disasters, war, and terrorism or violence) that currently contribute

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to a persistent atmosphere of stress for many are reviewed using the bioecological model. Recommendations for future research are provided.

Keywords

disaster, trauma, bioecological, posttraumatic growth, terrorism

Humans have encountered traumatic events and catastrophes since the beginning of time. Sudden, unexpected, and uncontrollable catastrophic events often contribute to chronic stress and distress and can even lead to immediate or eventual mortality. The direct effects of such events (e.g., mortality, injury) are relatively easy to identify. The more indirect effects (e.g., chronic stress, ineffective coping, loss of social networks, feelings of injustice, and physical illness secondary to stress reactions) are more difficult to assess and are often underestimated (Parker, Barnett, Everly, & Links, 2006). Stress results from both primary and secondary exposure.

Because it is neither possible nor necessarily desirable to intervene with all touched by disasters at an individual level, a comprehensive systems approach that allows conceptualization and response at the individual, family, community, and societal levels seems optimal. Therefore, we believe that an ecosystemic model more accurately provides a conceptual framework that can account for the complexity of trauma. One of the best-known ecosystemic models was originally proposed by Bronfenbrenner (1979) and later expanded to include bioecological elements (Bronfenbrenner & Ceci, 1994). Their expanded model provides an integrated conceptual structure for understanding the effects, intervening in the aftermath, addressing prevention, and researching aspects of large-scale disasters and catastrophes. Another reason we selected a bioecological perspective was that it fits well with the core values of counseling psychology and provides a framework that utilizes our unique skills and perspectives. Specifically, counseling psychology's core values focus on hygieology, or promoting healthy development across the life span, rather than psychopathology. We also strive to facilitate vocational adjustment, promote social justice, and emphasize multicultural aspects of experiences. These emphases contrast sharply with the bulk of the psychological literature on mass trauma, which focuses on individual effects such as stress and other mental health reactions (e.g., Srinivasa, 2007) or on family disruptions (e.g., Wieling & Mittal, 2008) and has ignored other effects such as vocational disruptions and multicultural and social justice factors in relation to individual, community, and systems outcomes.

Using a bioecological model, we reviewed relevant literature and provide illustrative examples for three categories of mass trauma, exposure events (natural and technological disasters, war, and community violence or terrorism). Most days some aspect of these events affects individuals and communities directly or indirectly and dominates the news, creating a persistent environment of stress for many. A common theme woven through these traumatic events is that traditional resources of the individual, family, and community are either lost or severely compromised. Stressors created by exposure to one mass trauma (e.g., fear, loss of employment, fewer community resources) event may have a "ripple" effect and affect subsequent resources available to manage future exposure to mass traumatic events. Or one type of event (e.g., terrorism) might lead directly or indirectly to another mass trauma event such as war. Our goal was to identify the biopsychosocial effects that extend beyond initial injury and mortality. We focused our literature review on aspects and consequences of mass trauma that are especially relevant to the values, tenets, and skills of counseling psychologists. Specifically, we examined what effect these events have on survivors' individual psychological resources and well being as well as the way trauma influences key relationships within family, community, and societal networks. Throughout our review we examine the role of multicultural variables and social justice in mass traumas and their eventual effects. Then, we examine the literature on posttraumatic growth to see if under certain circumstances exposure to mass trauma events might provide opportunities for posttraumatic growth. These events in some instances might promote or support resilience. This emphasis on posttraumatic growth is especially relevant for counseling psychologists given that historically most research has focused on the negative or deleterious effects of traumatic events. Finally, we conclude with themes relevant to counseling psychology that emerged from this literature and discuss how these translate into areas for future research. We first describe our bioecological model of mass trauma.

Bioecological Model of Mass Trauma

Bronfenbrenner (1979) initially proposed a model of human development in which an individual is significantly affected by interactions among a number of nested systems. These nested systems form the social context that determines the impact of life events on the individual as well as his or her response to events. Disasters and community-based catastrophes are merely one type of life event that can be understood using an ecological model. Bronfenbrenner and Ceci (1994) expanded the original model adding a *bio*ecological element.

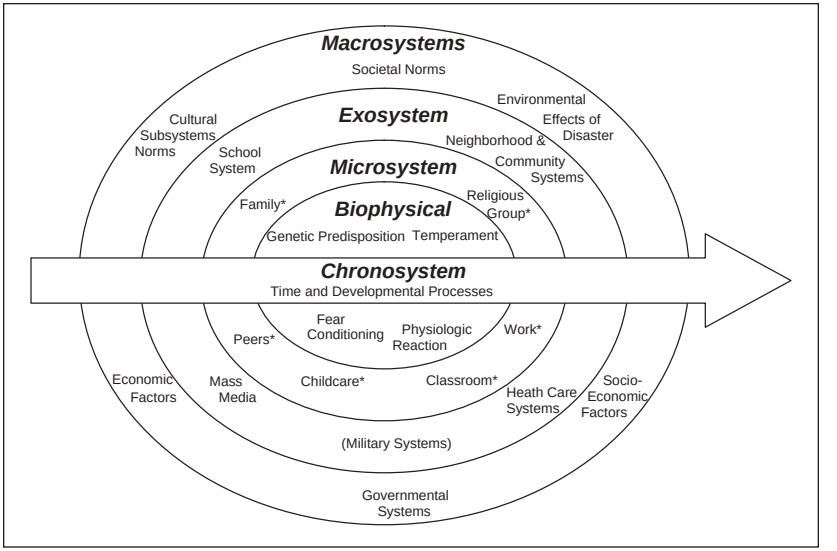

Figure 1. Bioecological model of mass trauma
Mesosystems are the connections between systems, for example, the relationship between family and school.

In this model life transitions and the life course are referred to as chronosystems, and there is an added focus on biomedical factors such as temperament and emotional reactivity. We applied a counseling psychology perspective of this model to large-scale disasters and community-wide catastrophes. Figure 1 displays the hierarchical nature of the nested systems in the bioecological model with the chronosystem transcending the levels across time and development.

Biophysical

This integrative model starts with the biophysical underpinnings of the trauma response. This is consistent with the current concept of interpersonal neurobiology, an interdisciplinary approach where the biological, psychological, and social aspects of human experience are woven into a coherent whole whereby each is understood separately and in connection to each other. Interpersonal neurobiology serves as the fundamental underpinning of all human experience, including trauma (D. Siegel, 2010). Exposure to a

traumatic life event is the genesis of a trauma response. A physical or emotional exposure can trigger a biophysical stress reaction (Pfefferbaum, 1997). Biophysical factors compose the innermost ring of the bioecological model of mass trauma (see Figure 1). Modern stress reaction theory originated with Selye's (1952) "fight or flight" response described by the characteristic behavioral and physiological responses displayed by humans to environmental stressors. Threatening situations such as those encountered in catastrophic events precipitate neurochemical changes in the body that trigger a stress response, including arousal and vigilance (Cohen, Perel, DeBellis, Friedman, & Putnam, 2002). Automatic psychological and physiological reactions to environmental stressors seem to precipitate a "fear conditioning" response (LeDoux, 1996) that is minimally influenced by higher cortical functions (van der Kolk, 2003). These responses appear to be classically conditioned fear reactions to stimuli associated with the trauma (Foa, Zinbarg, & Rothbaum, 1992) and may underlie the reexperiencing symptom cluster of trauma and posttraumatic stress disorder (PTSD), especially nightmares and intrusive memories (Cohen et al., 2002).

The diathesis-stress perspective further influences current biological models of trauma (Flouri, 2005). This perspective suggests certain individuals are predisposed via genetic predisposition or temperament to develop PTSD symptoms after exposure to a disaster or catastrophic event. Although there is an apparent predisposition to stress (Pfefferbaum, 1997), the heritability of PTSD is not yet clear, and estimates suggest that genetics may account for 13.6% (Chantarujikapong et al., 2001) to 30.0% (True & Lyons, 1999) of the variability in PTSD symptomatology. Sack, Clarke, and Seeley (1995) found that children with a parent diagnosed with PTSD were 5 times more likely to develop PTSD themselves. However, the specific genetic and environmental components reflected in this increased vulnerability were unclear.

Although these biophysical elements of trauma response are well documented and important, they must be understood in terms of the social context within which they occur *and* as they unfold across the life span. The additional systems of the bioecological model provide the conceptual framework for those context and developmental variables in trauma response and recovery and are described in the next sections with brief examples to illustrate each system.

Microsystems

Microsystems form the next level of the nested systems (see Figure 1) and include those systems that most directly and immediately shape human

development and responses to life events. Traditional developmental models have focused on the family, friends, neighborhood, and religious groups as core microsystems. For children, the microsystems also include peer groups, day care settings, and school. For adults, the microsystems include the work setting and coworkers. The family is consistently identified as a crucial microsystemic factor affecting trauma response, especially in vulnerable populations (Pfefferbaum, 1997; Pynoos, 1994; L. J. Siegel, 1998; Srinivasa, 2007). Symptom contagion may also occur within peer groups in trauma responses for children, teens, and adults (e.g., Tyano, Iancu, & Solomon, 1996).

Exosystems

The next level (see Figure 1) is the exosystem, which includes those environments that are external to the individual but still influence the person. Exosystems include the more immediate networks or systems that indirectly affect the individual such as neighborhood and community systems, health care systems, school systems, and the mass media. The military system is a salient microsystem for a subset of individuals (e.g., military personnel and their families). The inadequacy of these exosystems in responding to mass trauma has been highlighted in our nation's lack of preparedness in dealing with recent such traumas. However, schools and health care systems, in particular, appear to have heeded the "wake-up" call to improve their role in disaster response (Cook-Cottone, 2004). Although there is a burgeoning body of literature on emergency preparedness to manage mass casualties in the school and health care systems, it is based largely on anecdotal response to previous disasters (Cohen, 2004).

Macrosystems

Microsystems and exosystems operate within the context of the broadest ecosystemic level or the macrosystem. The macrosystem is the larger cultural context (see Figure 1) and includes societal norms, sociopolitical factors, cultural subsystem norms, governmental systems, economic factors, and the environmental effects of the disaster. Social class, race, ethnicity, and gender have all been found to correlate with trauma response (McCann & Pearlmen, 1990). The more widespread and significant the devastation from the disaster or catastrophic event, the greater the impact will be on the community. Societal and cultural subsystem norms can either mitigate or hinder adaptive coping and response (de Silva, 1999).

Mesosystems

Originally, mesosystems emphasized the bidirectional influence among the various microsystems (Bronfenbrenner, 1986). They were connections among the different contexts within which any given individual functions. These interactions include aspects such as the relationship of family and school experiences, family and peer relationships, and family and neighbor relationships. In a later revision of his model (Bronfenbrenner & Ceci, 1994), the mesosystem was expanded to include the bidirectional influence successive layers of systems have on one another and the interactions among the hierarchical systemic levels (see Figure 1).

Effects of catastrophes extend beyond the immediate impact on the individual by directly and indirectly affecting social and societal networks. The bidirectional influence of disasters represents the mesosystemic influence of these events. That is, not only do they directly affect the individuals in a community, but also the compounded impact on those individuals reciprocally influences broader social and community systems. For example, existing social services may become strained, social support networks may become fractured as survivors are displaced, and work settings may become inefficient as employees are absent or incapacitated (Erikson, 1994).

Chronosystem and Developmental Processes

Life transitions and life course are referred to as chronosystems in the most recent model (Bronfenbrenner & Ceci, 1994). Chronosystems are those changes that occur over time in a person (developmental processes) that are the result of changes in the environment (see Figure 1). Bronfenbrenner and Ceci's (1994) expanded model includes a bioecological developmental component as well in which they describe proximal processes as the building blocks of human development. Proximal processes are those enduring forms of interaction with the environment that form the basis for all growth and development. Examples include parent–child relationships, peer relationships, play and leisure activities, and school or work. Adaptation to a traumatic life event is expressed through these proximal processes.

Life transitions include both normative and nonnormative events (e.g., disasters). These life events not only directly influence the person but also indirectly influence her or him via the effect they have on family processes and the community in which the events occur. That is, these chronosystem changes occur within multiple ecological contexts, and these contexts

include all the original levels of Bronfenbrenner's (1986) nested systems: microsystems, exosystems, macrosystems, and mesosystems. Therefore, reaction of an individual to a disaster can be fully understood only in the context of both these developmental processes *and* the ecosystems within which she or he functions. For example, mass traumas can lead to environmental changes that affect schools, jobs, and neighborhoods, which in turn affect individuals and families across time.

Furthermore, expression of traits is reciprocally influenced by internal and external developmental processes. In the case of trauma, internal processes are composed of physical, emotional, and cognitive reactions to traumatic events. There appear to be critical life stages in terms of impact in that trauma experienced before the age of 11 results in 3 times greater risk of later PTSD (S. Davidson & Smith, 1990), and the separation of parents before the age of 10 increases vulnerability to subsequent PTSD with later stressors (J. R. Davidson, Hughes, Blazer, & George, 1991).

Application of the Bioecological Model to Three Types of Mass Trauma

Next, we examine three types of mass catastrophes or disasters: natural and technological disasters, war, and terrorism or violence. For each, the bioecological model of mass trauma serves as a guide in selecting literature relevant to counseling psychology to illustrate aspects of the model and to provide examples demonstrating core tenets or values of the field including multiculturalism, vocational issues, a strength-based perspective, and social justice.

Natural and Technological Disasters

We appear to have entered an era in which global disaster response has become the norm (McGuinness, Coady, Perez, Williams, & McIntyre, 2008). Recent global natural disasters including earthquakes, hurricanes, tsunamis, floods, and tornadoes received widespread media coverage, as have technological disasters such as the recent Gulf of Mexico oil spill. We as counseling psychologists experience a pull to offer our expertise and knowledge in response. A wealth of research exists about the impact of disasters on subsequent psychological functioning and on variables affecting both individual and community response to disasters. The bioecological model provides a useful conceptual tool for organizing contemporary research on disasters.

Biophysical. Personal variables can interact with exposure to a disaster to result in varying responses. For example, women experienced more

depressive symptoms after a hurricane than their male counterparts, and social networks seemed to mitigate the adverse impact of psychological distress for women (Haines, Beggs, & Hurlbert, 2008). Prior life experiences such as experience of an earlier trauma exacerbated symptom development in adolescents after hurricane exposure (Garrison et al., 1995). Being female, having learning and psychological difficulties in childhood, exposure to violence in the home, subjective appraisal of life threat, level of anxiety, and adjustment in the postdisaster period along with subsequent social support and traumatic life events led to PTSD in young adults exposed to a shipping disaster as teens as many as 8 years postdisaster (Udwin, Boyle, Yule, Bolton, & O'Ryan, 2000). The strongest predictors of PTSD were predisaster vulnerability in the forms of social, physical, and psychological difficulty 5 months following the disaster. Similarly, children with high versus low levels of trait anxiety were more adversely affected by the Three Mile Island technological disaster (Handford et al., 1986). Mills, Edmondson, and Parks (2007) found that 62% of adults living in a shelter several weeks following Hurricane Katrina met criteria for acute stress disorder. Furthermore, increased life threat, decreased sense of personal control, and experiencing an injury during the hurricane were predictive of higher levels of distress. Similar to the Udwin et al. findings, being female, being Black, and having a prior history of psychological problems were related to greater symptom severity.

Research suggests that the adverse impact of a disaster can be mitigated by trauma and grief focused interventions. Early adolescents with earthquake exposure experienced a reduction in PTSD symptoms and comorbid depression after receiving treatment (Goenjian, et.al., 1997). Furthermore, children and teens with positive competency beliefs, cognitive understanding, and social support demonstrated a capacity for posttraumatic growth following a natural disaster (Cryder, Kilmer, Tedeschi, & Calhoun, 2006).

Microsystems. The majority of existing research at the microsystems level focuses on how family factors influence trauma recovery. Some of those factors were reflected in the Udwin et al. (2000) longitudinal study described above. Goodman and West-Olatunji (2008) even proposed a transgenerational trauma model for response to disasters. Interestingly, these family factors (i.e., separation from parents immediately after a natural disaster, ongoing maternal preoccupation with the event and altered family function postdisaster) were more predictive of children's symptom development than exposure or loss (McFarlane, 1987). Similarly, elementary-school-aged children reporting high parental conflict postdisaster (in this case Hurricane Andrew) endorsed more PTSD symptoms than those describing low parental conflict

(Wasserstein & LaGreca, 1998). A more recent study with post-Katrina teens revealed that although these adolescents reported more distress and internalizing symptoms in addition to poorer self esteem as compared to nonexposed peers, their families mobilized extrafamilial and community support to cope with the increased familial stress (Vigil & Geary, 2008).

Exosystems. There is some literature to support the impact of disasters within the various described exosystems. Mass media clearly play a role in reaction to mass trauma. Even the mere prediction of a potential disaster (i.e., New Madrid earthquake) without actual exposure led to mild PTSD symptoms (Kiser, Heston, Hickerson, & Millsap, 1993), and media exposure appears to have a stronger effect in younger children (3rd graders) versus older youth (10th graders). For these reasons, minimizing media exposure to both potential and actual disasters may be important, especially with young children who may not have the emotional and cognitive resources to cope with the accompanying thoughts, feelings, and images.

Neighborhood and community systems play a significant role in postdisaster recovery. Roughly 1 in 10 worldwide disaster victims reported psychosocial resource loss that resulted in deficits in social support, social embeddedness, self-efficacy, optimism, and perceived control, factors that mediate the adverse impact of trauma and thus become risk factors for negative coping and outcomes (Norris, Foster, & Weisshar, 2002). Social support is one of the most consistently identified protective factors when coping with mass trauma. For example, social support appeared to reduce PTSD symptoms in elementary-school-aged children at several points (3, 7, and 10 months) post–Hurricane Andrew (La Greca, Silverman, Vernberg, & Prinstein, 1996). Social systems likely promote an individual's capacity to process and integrate experiences of postdisaster trauma by providing a safe context within which to experience thoughts and feelings associated with the mass trauma exposure (Pynoos et al., 1993b). Again there is evidence that community-based intervention can reduce PTSD symptomatology in elementary-school-aged children following natural disaster (i.e., an earthquake in Italy). However, when the breadth of destruction in certain communities resulted in a longer amount of time to reorganize and develop supportive interventions, subsequently there were greater amounts of symptomatology in at-risk children (Galante & Foa, 1986).

School systems are another important exosystem that can promote resiliency and coping in the aftermath of both natural and technological disasters. Following a technological (shipping) disaster, participation in a school-based intervention was associated with less severity and duration of PTSD symptoms in young adults (Udwin et al., 2000). Moderating variables included

adaptive predisaster social, learning, and psychological functioning as well as a lack of depressive symptoms immediately after the disaster. Similarly, school systems often served as a "home base" to foster broad community engagement for disaster responses to Katrina (Dean et al., 2008). In response to Katrina, school professionals often found themselves stretching beyond their prior areas of expertise to facilitate coordinated, community-based interventions and provide direct mental health services to adults and children.

Health care systems are often thought of as the "first line" in disaster response. Currier, King, Wofford, Daniel, and deShazo (2006) reviewed administrative and clinical records after Hurricane Katrina to assess medical facility responsiveness. They noted significant problems and issues needing to be addressed to improve quality of care in the wake of future disasters. One issue was that Red Cross regulations prevented volunteers from providing medical care other than first aid. In a situation with mass casualties there were not enough trained medical personnel to provide adequate coverage. These authors felt there were certain supportive functions their volunteers could have provided but were not allowed. Furthermore, most patients seen at medical facilities along the evacuation route had multiple medical problems, lacked insurance coverage, and had limited ability to access and purchase needed medications. For these reasons, the greatest issue was management of chronic illnesses in evacuees. There were also many difficulties with coordination of care when evacuees were living in shelter situations.

Macrosystems. Recall that macrosystems include the environmental effects of disaster, societal norms, cultural subsystem norms, economic factors, governmental systems, and sociopolitical factors. The severity of survivors' psychological reaction to trauma is affected by degree of exposure as well as intensity and level of destruction in both natural (e.g., Goenjian, Najarian, & Pynoos, 1994) and technological disastsrs (e.g., Handford et al., 1986). For example, proximity to a natural disaster (Armenian earthquake) and amount of devastation to the community were the strongest predictors of PTSD symptomatology in children (Pynoos et al., 1993a), and these effects persisted for years following the disaster (Bland, O'Leary, Farinaro, Jossa, & Trevisan, 1996). Similar effects related to proximity of the event and amount of devastation to home, belongings, and community were found in adults following an Oklahoma tornado (Middleton, Willner, & Simmons, 2002).

The effect of cultural subsystem norms on response to trauma is less clear. Research has yielded contradictory results in terms of racial differences in response to trauma (de Silva, 1999). It is likely that the cultural subsystem norms interact with a host of other factors to influence the trauma response of

any given individual. For example, elementary-school-aged children who reported high parental conflict postdisaster (Hurricane Andrew) endorsed more PTSD symptoms than those describing low parental conflict. In this study, there was also an *interaction between ethnicity and conflict* with Hispanic children in high-conflict households showing the greatest PTSD symptomatology. Interestingly, there was no interaction between ethnicity and parental conflict in generalized anxiety symptoms (Wasserstein & LaGreca, 1998). These authors believed the differences in PTSD symptomatology may have resulted from Hispanic family norms. Specifically, Hispanic families traditionally rely on multigenerational support more than community-based support. The Black and Caucasian families in the study may have had the support of broader community systems, which moderated the impact of parental conflict.

Another study of teens after Hurricane Andrew highlights the complexity of this issue (Garrison et al., 1995). PTSD symptomatology varied by ethnic group. Hispanic teens displayed the highest incidence of PTSD symptoms, followed by Black and non-Hispanic minorities. White teens demonstrated the lowest incidence of PTSD symptoms. However, no significant difference was found across ethnic teenagers. Overall, there were more similarities than differences in PTSD symptomatology and frequency of symptoms increased significantly with age as opposed to ethnic minority status. Furthermore, in that study parental exposure to the disaster and parental symptomatology were not associated with PTSD in the teens. "Undesirable" life events post-disaster, such as moving and changing schools, seemed to be the critical variable in predicting greater PTSD symptoms. Alternatively, in a study of students exposed to Hurricane Hugo, Black adolescents reported lower symptoms of PTSD than Caucasian teens (Hardin, Weinrich, Weinrich, Hardin, & Garrison, 1994). These results were surprising given that the Black youth reported higher levels of exposure to the hurricane per se, community violence prior to the disaster, and additional nonviolent stressors. Surveying adult responses to Hurricane Katrina, both race (African American) and lower socioeconomic status were related to psychological distress, although it is likely that exposure to the event was significantly greater for these individuals (Elliott & Pais, 2006). These studies highlight the complexity of the nature of cultural subsystem reactions to disasters.

In the absence of a clear understanding of the complex interplay of culture and individual response to disaster, Dean et al. (2008) highlighted the need to actively work to respect the complex and diverse cultural issues of students and families in their school-based response to Hurricane Katrina. Dass-Brailsford (2008) noted the need for not only multicultural competence in

disaster response but also an awareness of language barriers (including nonverbal and physical forms of communication). Kinship bonds resulting from racial and cultural affiliation often become more important during traumatic times and relocation may heighten adherence to these religious and subculture norms. These norms also can be a positive lens through which survivors understand and make meaning of the traumatic event. Adaptive recovery is enhanced when counselors working with survivors access these norms via culturally sensitive language and communication styles. Acknowledgment of the collective worldview of many subcultures is often an important component of understanding their experience.

Historically, most disaster research focused on identifying individual, family, and cultural subsystem responses to trauma and looked at broader community systems only as mechanisms for postdisaster service delivery. McGuinness et al. (2008) recommend that in a new era of global disaster response psychologists need to be prepared to provide macrosystem and organizational consultations postdisaster to facilitate the restoration of infrastructure as well as to support implementation of broad-based, community-wide services. He and his colleagues suggested psychologists need to define new roles within governmental systems and serve as advocates for social change. Specific macrosystem-level interventions and population-based initiatives would include promotion of federal–state agency interface, state-level interagency collaboration, and evidence-based disaster responses. However, it is important to recognize that existing sociopolitical and economic difficulties can be exacerbated by the disaster. Subcultures that have a history of institutional and cultural mistrust may be reluctant to access community- and government-provided support postdisaster (Dass-Brailsford, 2008).

Mesosystems. To date there is minimal research addressing mesosystem factors in disasters, and existing studies have focused primarily on school systems. Dean et al. (2008) described several mesosystem issues in their school-based response to Hurricane Katrina. Specifically, the fact that caregivers and school personnel themselves were often struggling with postdisaster coping may have limited their efficacy in response to students and families. Mechanisms for collaboration within and across levels of systems are needed.

Chronosystem and developmental processes. Research on age at time of exposure reveals that trauma exposure affects children regardless of age. Children as young as preschool age who were exposed to a flood had more subsequent emotional and special educational needs than those in the same school who did not experience the flood. The flood exposure effect was a stronger predictor of later emotional and academic deficits than level of poverty (Burke, Borus, Burns, Millstein, & Beasley, 1982). More recent studies of

children and teens exposed to natural disasters indicated that delayed evacuation, fear for one's own or another's life, and feeling extreme panic and fear were significantly correlated with PTSD symptomatology both 2 and 9 months after the disaster (Thienkrua et al., 2006). In addition, older age at time of exposure and fear for one's own or a family member's life correlated significantly with depression. Vulnerable teens exposed to Hurricane Katrina may be at greater risk for development of substance abuse postdisaster given increased life stress and family disorganization that co-occurred with this disaster (Rowe & Liddle, 2008). Similarly, the Mills et al. (2007) study conducted on adults post-Katrina (described in the biophysical section) projected that about 40% of their shelter sample who displayed levels of acute distress would eventually meet PTSD criteria 2 years postdisaster.

Afghanistan and Iraq Wars

In a recent speech, Defense Secretary Robert M. Gates described the United States as being in "an era of persistent conflict" resulting in soldiers becoming physically, socially, and culturally insolated from the rest of the country because the all-volunteer force represents such a small proportion of the population (Gerhart, 2010, p. A3). He further notes that most Americans view the wars as an abstraction that does not affect them personally, which further contributes to the isolation that military members, their families, and their communities experience. Because many counseling psychologists work in Veterans Administration medical centers and see individuals affected by war on their campuses, in their community, and in private practices, understanding the widespread effects of persistent war on individuals and their systems is critical.

Biophysical. This component of the model is evident in the fear and stress reactions and physiological responses found in military members and their families. Negative outcomes for deployed service members have been well documented, with the greatest emphasis on stress-related effects on the mental health of veterans. In a recent RAND Corporation study, Tanielian et al. (2008) showed that one in five service members returning from Iraq or Afghanistan reported symptoms of PTSD or depression. This represents more than 300,000 of the approximately 1.5 million service members who have returned over a 5-year time period. Depression and PTSD rates are higher in reservists versus active-duty troops (25% vs. 17%). Although much of the research focus has been on PTSD, recent studies show that a significant proportion of individuals exposed develop a range of stress-related disorders

beyond PTSD and that the level of exposure (dose response) contributes to a higher prevalence of distress (Srinivasa, 2007).

A new and enduring consequence of recent wars is the high rate of nonfatal traumatic brain injuries (TBIs), primarily because of the effects of roadside bombs. At least 30% of U.S. troops involved in active combat in Iraq and Afghanistan are estimated to have TBIs, which translates to hundreds of thousands individuals. Small portions of these injuries are caused by penetrating wounds and are therefore easy to diagnose. Most remain invisible but can lead to significant neurological and psychological effects including memory loss, short attention span, poor reasoning, headaches, confusion, anxiety, depression, irritability, rage, and impulse control (Glasser, 2007). TBIs in veterans are linked to impairment in personal functioning, leading to interpersonal and occupational difficulties that are discussed later (Glasser, 2007).

Although veterans from previous wars experienced stress reactions such as PTSD as well as depression and physical consequences following deployment, the rate is higher for the Iraq and Afghanistan Wars in terms of both psychological and physical effects ("War's New Wounds," 2007). Although there have been fewer fatalities, those who survived have experienced significantly more psychological and physical effects. One reason is that military personnel are experiencing higher levels of exposure because of more and lengthier deployments than in any other war in which the United States has been involved. For example, combat exposure may be the primary mediator of the impact of length of war deployment on substance abuse rates (Volkow, 2009). In addition, increased exposure translates into a large percentage of service people returning with significant, ongoing problems that affect their family members and community subsystems.

Microsystems. The effect of deployment on partners and other family members is significant, and multiple deployments have greatly increased this type of stress. About 40% of servicemen and servicewomen deployed to war zones are parents, with most having children younger than 12 years of age (Levin, 2008). Deployment can lead to temporary effects for children that include coping with an absent parent and adjusting to new roles and responsibilities as well as the stress of a returning parent (e.g., Mari, Roche, Sudhinaraset, & Blum, 2009). These effects are strongest when children have preexisting psychological issues or there are family risk factors such as violence or substance abuse (e.g., Lincoln, Swift, & Shorteno-Fraser, 2008) or when a parent returns with significant mental health or physical effects or when the family structure is altered as a result of the deployment. These examples show the interaction of biophysical factors with microsystem

factors. From a systems perspective, the number of persons affected by the wars in Afghanistan and Iraq far exceeds the approximately 300,000 service members believed to have PTSD and the hundreds of thousands returning with TBIs.

Microsystem effects include increasing rates of divorce, more behavioral problems in children, greater family violence, and other changes in family functioning. Youth who have at least one parent serving in the military report elevated levels of conduct problems based on clinical norms, although factors such as maternal support are protective (Morris & Age, 2009). Prevalence of reported family problems increases with length of deployment and when deployed family members return diagnosed with PTSD, TBIs, and/or other injuries (Doll & Bowley, 2008). Family adjustment problems and domestic violence are higher in families of veterans with mental health disorders (Sayers, Farrow, Ross, & Oslin, 2009). For example, the majority of the married or cohabiting veterans reported a problem in the past week including feeling like a guest in their home, their children or partner being afraid of them, and physical or verbal altercations.

Even among those U.S. Army officers and their families who are well prepared for the effects of deployment, are better educated, and receive higher pay for their work, higher levels of stress are reflected in divorce rates, which tripled between the years 2001 and 2004 (Doll & Bowley, 2008). This study found that about 20% of married service members currently said they were considering divorce or separation. Stress related to family and home was the most common reason soldiers sought psychological assistance in the war zone, and "failed relationships with spouses or intimate partners" is the highest risk factor for suicide (Levin, 2008, p. 1). Divorce rates for women service members are nearly triple those for men, although the reason for this has not been studied. Factors often cited as creating the greatest strains for relationships—between both partners and children—are extended and multiple deployments that lead to increased stress and mental health problems and family stressors with each deployment.

War injuries disrupt partner and parent–child relationships when a veteran is treated for an acute injury (Levin, 2007). However, little is known about the long-term effects on significant others when soldiers experience long-term and persistent effects from injuries such as amputations and TBIs that affect partner and parenting relationships. Extended and multiple deployments have also been linked to poorer work performance while in the military (Levin, 2008). Less is known about occupational outcomes for veterans once they leave the military.

Other factors that contribute to under- and unemployment include the high rates of PTSD and other psychological problems, TBIs, physical injuries such as amputations, hearing and vision loss, increased substance use, and homelessness (Doll & Bowley, 2008). Disruptions caused by involuntary conscription (recalling "inactive" service members to active duty) likely affect educational and career trajectories as well.

Exosystems. Military communities reflect the effects of wars on schools, neighborhoods, and health care. For example, Killeen, Texas, is home to Fort Hood, an army base. More than 90% of the students at the nearby high school have one or more family members in the military (Block, 2007). Children and teens in military communities may react to disruptions in schedules and in caregivers, may show signs of emotional distress and changes in behaviors, or may have difficulties in school when a parent is deployed (Waldrep, Cozza, & Chun, 2008). Yet active-duty families often live in military communities where more resources are available to address their needs. In contrast, because Reserve or National Guard members are typically activated from civilian jobs and from communities where relatively few others may be deployed, they and their families may find fewer resources to support them.

There is evidence the long durations of the recent wars paired with multiple deployments have intensified the typical effects that military communities experience (Gerhart, 2010). Current military families may struggle with balancing their perceptions of the value of the invasions with the sacrifices they have made. In contrast to other wars such as World War II where the majority of Americans had some involvement either at home or abroad, a small minority of Americans are currently involved in any manner, raising social justice issues in terms of who goes to war and the psychological, social, and economic factors and opportunity costs for military families.

Macrosystems. Enlistment rates provide one way to examine how military service may reflect societal norms, cultural norms, and socioeconomic factors. Department of Defense enlistment rates for various wars show that rates were highest for World War II, where about 12% of the population was in the military. In contrast, only about 0.5% of the population has enlisted for the all-volunteer military serving currently, which, according to Secretary of Defense Robert M. Gates, contributes to the increasing detachment of most Americans from the Iraq and Afghanistan Wars (Gerhart, 2010). This suggests that the vast majority of Americans have little connection to the wars in terms of the active involvement of a family member and subsequently few immediate effects on their families from a social and economic perspective.

Cultural, geographical, and demographic variables play a role in who enlists for the military. Enlistees are predominantly male high school graduates (most in the middle 50% of their high school class, with only about 11% having been in college) disproportionately from southern and rural areas. Research finds three factors associated with voluntary enlistment: lower socioeconomic status, living in an area with a high military presence, and having future (but not current) college aspirations (Kleykamp, 2006). Finally, a propensity to serve is a key factor in enlisting, as is viewing the military as a potential career versus as an occupational step to other careers (Woodruff, Kelty, & Segal, 2006). Propensity to serve is declining, and there are not enough "high-propensity" youth to meet needs (Woodruff et al., 2006). For example, African American enlistee numbers have plummeted in recent years (from 23% to 13%), attributable largely to negative attitudes toward the war and to military service. Resistance to volunteering during wartime is also seen in the Latino or Hispanic community. These findings have implications for counseling psychologists' research on vocational aspirations and opportunity costs.

Mesosystems. The effect of trauma on individuals reciprocally influences broader family, social, and community systems. For example, existing social services may become strained or ineffective, social support networks may be similarly stressed, and neighborhood, school, and work settings may become less effective in serving as buffers as employees and family members are absent or incapacitated (Erikson, 1994). Perhaps nowhere is this effect more pronounced than in Fort Hood, Texas, home of the nation's largest army base. In the past year, this base has experienced a mass shooting of 13 people by an army psychiatrist, the highest suicide rate among soldiers in the country, a rate that is nearly 4 times that of the civilian population and includes four suicides in a single recent weekend, and an increase in crime when brigades of soldiers return home (Gerhart, 2010). A growing concern is that characteristics and skills of soldiers that are functional in war may make them dysfunctional once home. Although Fort Hood and military centers have psychological supports in place, these appear to be failing many—in part because of stigma associated with seeking help, concerns about its effect on career advancement, and a lack of confidence that these services can help.

Chronosystem and developmental processes. Because the rate of diagnosed mental health problems increases dramatically with time since deployment, the influence of individual and environmental factors over time on returning military personnel is salient. A study of more than 88,000 service people returning from Iraq showed that mental health referrals increased more than 100% in just a 6-month time period because of stress-related mental health

problems and reports of conflicts with significant others (Milliken, Aucterlonie, & Hoge, 2007). One explanation was that number and length of deployments created unexpected and previously unseen effects. Another explanation is inadequate postwar mental health and health treatment as well as deficient military support to aid in work and other life-role adjustment (Priest & Hull, 2007). Finally, fighting two wars over 10 years is likely creating unprecedented stressors and effects.

Chronosystem effects also may result from deployment exposure. There is mounting evidence that the level of exposure (dose response based on number, frequency, and length of deployments with shorter leave times) relates to a higher prevalence of distress and that this distress often increases postdeployment (Srinivasa, 2007). Finally, studies of World War II veterans suggested that PTSD symptoms persist over many decades and can become exacerbated in the elderly because of life stressors such as retirement and poor health (Kaup, Ruskin, & Nyman, 1994).

Terrorism and Community Violence

Violence is a persistent and salient feature of the world community. War is probably the most extreme and obviously devastating form of violence; however, terrorism and community violence also generate mass trauma. The recent spate of shootings at schools and community institutions are other examples of violence that can result in mass trauma. When viewed with a bioecological lens, school violence affects not only the students and school personnel who directly experience the trauma but also multiple levels of systems where these individuals are embedded. Cicchetti and Lynch (1993) proposed an ecological/transactional model of the multisystemic and developmental effects of violence on child development that is similar to the bioecological model of mass trauma presented here. Community violence in the form of terrorism has been a fact of life for many years in other countries. But it was not until 9/11 that terrorism became a more salient aspect of daily life in the United States.

Biophysical. Prevalence rates of PTSD after the 9/11 attacks ranged from 7.5% to 40.0% depending on proximity to the disaster site, and depressive symptoms were present in up to 60.0% of those close to the city (Miller & Heldring, 2004). These rates are comparable to the 30.7% found in survivors of terrorist attacks in France over a period of 5 years (Verger et al., 2004) and the roughly 50.0% found following the 1995 Oklahoma City bombing in the United States (North et al., 1999). Intrusive thoughts and hyperarousal were the most commonly reported symptoms (Miller & Heldring, 2004). In a

longitudinal study of a national sample of Jews and Arabs exposed to repeated terrorist attacks (Hobfoll et al., 2009), only 22% reported having few or no trauma or depressive symptoms, 13% initially had symptoms that dissipated over time, 54% had chronic distress, and 10% had delayed stress reactions. Even preschool-aged children demonstrated emotional and behavioral reactions to the 9/11 terrorist attacks in the form of chronic sleep disruption, fear reactions, new fears, increased clinging, and separation anxiety that persisted for up to 8 months after the event (Klein, Devoe, Miranda-Julian, & Linas, 2009).

Gender, age, and ethnicity were not related to the development of posttraumatic symptoms following a sniper attack on an elementary school playground in California (Nader, Pynoos, Fairbanks, & Fredrick, 1990). Proximity and exposure to the shooting correlated most with a number of symptoms. However, Miller and Heldring's (2004) more recent review of the literature on the 9/11 attacks was more consistent with the general trauma literature. Their review suggested that gender, age, and ethnicity were important predictors of stress reactions. Most studies found higher prevalence rates of PTSD symptoms in women and girls as compared to males. School-aged children appeared to be at greater risk for PTSD symptomatology than adults, and non-White ethnic groups experienced greater psychological distress than Whites. Furthermore, both adults and youth in divorced or separated families had higher rates of stress symptoms as compared to those in married or coupled families. Their review revealed additional factors related to trauma response. Specifically, survivors experienced higher rates of stress-related medical leave as well as increased health problems and somatic complaints than the general population. Prior physical or psychological illness and general life stress were both related to symptom severity. Loss of friends, family, possessions, or job also was associated with more severe postattack symptoms.

Microsystems. Several microsystem factors have been explored in the context of terrorism or mass trauma as the result of community violence. Anxiety in the home environment was the best predictor of PTSD in Palestinian children living in East Jerusalem and the West Bank who were repeatedly exposed to terrorism (Khamis, 2005). Furthermore, there is some evidence that community violence results in a lack of trust in peer relationships in urban adolescent girls with compounded community trauma (Horowitz, Weine, & Jekel, 1995). In addition, inner-city youth with community violence exposure are more likely to exhibit aggressive behavior or depression within 1 year postexposure (Bell & Jenkins, 1993).

A post-9/11 longitudinal survey revealed that adaptive coping responses included seeking social support (Stein et al., 2004). Dass-Brailsford (2008) suggested agencies and professionals working with mass trauma survivors

may need to expand their definition of family, especially with certain minority groups, to include neighbors and friends. Almost three fourths of those surveyed reported turning to friends and family for advice in addition to engaging in risk-reduction strategies. For example, many were being cautious about situations such as flying and avoiding large public activities. These postterror behaviors have been termed the "new normal" (North & Pfefferbaum, 2002), in which initial shock and trauma subside but there remains a sense of persistent and widespread distress that adversely affects adaptive social functioning.

Exosystem. As with other forms of mass trauma the mass media play a significant role in terrorism and community violence. After 9/11, nearly half of the adults in a random survey indirectly exposed via the media reported one or more symptoms of PTSD in the days after the event and reported being worried about their own or their loved ones' safety. Just more than one third said their children had one or more stress symptoms. The majority, 84%, had talked to their children about the attacks, and one third restricted television viewing, particularly for children, because they believed viewing the events was traumatic (Schuster, et al., 2001). Elementary-school-aged children with media exposure (i.e., television, internet & print) were surveyed 1 month after the attack. More exposure, especially when it included images of death or injury in conjunction with fear a loved one might have died, resulted in greater PTSD symptoms. Older children and boys had greater media exposure and more trauma-specific PTSD symptoms. Interestingly, there was no benefit to seeing heroic or "positive" images (Saylor, Cowart, Lipovsky, Jackson, & Finch, 2003). Comer, Furr, Beidas, Weiner, and Kendall (2008) found parents could use modeling, media literacy, and reinforcement to minimize the impact of terror-trauma media on their children. High television exposure, without direct exposure to the Oklahoma City bombing, resulted in PTSD symptoms weeks after the bombing (Pfefferbaum, 2001) and 2 years later (Pfefferbaum et al., 2000). This media exposure effect was exacerbated by indirect interpersonal exposure such as having a friend who knew someone injured or killed.

Macrosystems. Exposure to terrorism and violence may have a reciprocal impact on societal and cultural subsystem norms. For example, urban teenage girls exposed to high and repetitive levels of community violence expressed "fatalistic" and "apocalyptic" perceptions of long-term prospects for a successful life and longevity for African Americans in general (Horowitz et al., 1995). These girls had prolonged and repeated exposure to multiple types of community-based violence (drive-by shootings and gang violence) that was akin to living in a war zone. It is noteworthy that repeatedly hearing about

violence without direct contact resulted in more PTSD symptomatology in these young women and higher feelings of vulnerability than exposure to an isolated traumatic incident. Similarly, Richman, Cloninger, and Rospenda (2008) found indirect exposure to the events of 9/11 exacerbated psychological distress, alcohol abuse, and negative terror belief or fears for those in Midwestern communities already experiencing macro-level stressors (i.e., job loss and poverty).

It appears the relationship between community cohesion and trauma reactions is influenced by level of exposure. High community cohesion appears to lead to more PTSD symptoms in communities with low to moderate exposure to the traumatic event, whereas high cohesion seems to mitigate PTSD in communities with high trauma exposure (Somer et al., 2008). These authors suggested high community cohesion with low to moderate exposure may precipitate a contagion-like effect in reaction to the trauma, whereas the increased support that accompanies cohesion in the high exposure group is a protective factor. This interpretation is consistent with the findings of Littleton, Axson, and Grills-Taquechel (2009) after the Virginia Tech shootings. These authors found that students with higher social support experienced greater resource gain following the trauma. Specifically, they were better able to access resources than those students with low social support.

Community-wide mistrust of government and management systems after 9/11 exacerbated issues with providing disaster relief in already disenfranchised (i.e., minority and immigrant) populations (Steury, Spencer, & Parkinson, 2004). As with other types of mass trauma, trust and communication must be developed with these groups before events occur to promote civic engagement in all social groups and to facilitate successful liaisons between these groups and governmental agencies or management systems. Nevertheless, 60% of a broad national sample reported social benefits including increased prosocial behavior, religiousness, and political engagement as a result of 9/11 (Poulin, Silver, Gil-Rivas, Holman, & McIntosh, 2009).

Mesosystem. There is little research specifically focusing on mesosystem factors, but a few examples of research related to these issues follow. There may be an interaction between teachers' PTSD symptomatology and the classroom behavior of their students following mass trauma. For example, after the Los Angeles riots, just fewer than half of school teachers reported moderate to severe symptoms of PTSD. Concurrently, the classroom behavior of children in this school system became more aggressive, noisy, and oppositional. There were more peer relationship problems following the riots as well (Stuber, Nader, & Pynoos, 1997). Although teacher symptomatology

was not the sole reason for these classroom behavior changes, it likely contributed to the difficulties.

More recently and broadly, Steury and colleagues (2004) suggested that we draw on concepts from social capital theory as a framework for intervention after terrorism, in this case 9/11. Social capital theory (Cullen & Whiteford, 2001, as cited in Steury et al., 2004) refers to the bonding that occurs between groups with common social frameworks, such as family, neighbors, friends, and demographic groups. These authors recommended that interventions following terrorism and violence utilize previously existing groups to promote recovery.

Chronosystems and developmental processes. One of the earliest studied school violence events was the Chowchilla school bus incident in California. Children and teens were kidnapped and buried alive in an underground trailer. Many children displayed regression in previously acquired developmental skills after exposure to this traumatic event (Terr, 1981).

Furthermore, there appeared to be developmental trends in the type of reaction to school shootings. Younger children displayed more avoidance symptoms and spontaneous intrusive memories and affect, whereas older children had more reexperiencing and arousal symptoms and stronger distress in reaction to specific triggers (Schwartz & Kowalski, 1991). When school shootings occur in communities that already experience high levels of violence, affected children and teens may experience what Horowitz and her colleagues (1995) refer to as "compounded community trauma." These vulnerable teens' exposure to mass trauma disrupts normal relationship development processes, as they are unable to experience the basic interpersonal trust necessary to develop meaningful and caring relationships. These teens also are at risk for high rates of teen pregnancy, and when they do have a child they describe their relationship with the baby as one that will provide safety, connection, and trust that is absent in their other relationships. This reaction has implications not only for these teens' interpersonal relationship development but also for their academic and vocational development.

Posttraumatic Growth or Benefit Finding After a Mass Trauma

Our review of the literature suggests much more is known about trauma exposure leading to posttraumatic stress than to posttraumatic growth (PTG). PTG, or benefit finding, represents one way to view positive coping and outcomes that may result from mass traumas and catastrophes. Few studies

exist that examine PTG in individuals exposed to the three broad mass traumas discussed in this article. These are discussed, followed by a brief overview of PTG, as it may be relevant to understanding growth following a mass catastrophe.

Several studies examined PTG following the September 11, 2001, attacks. A longitudinal, Internet-based study measured perceived PTG as well as trauma symptoms, cognitions, and coping strategies at two points in time following 9/11 (Butler et al., 2005). At Time 1 (about 9 weeks post-9/11), PTG was associated with higher trauma symptoms, more denial, and more positive changes in worldview. Although PTG was associated with higher trauma symptoms, this relationship was curvilinear, as those who reported intermediate levels of symptoms reported the highest levels of growth. At Time 2 (about 6 months post-9/11), PTG was highly correlated with levels at Time 1 but had declined over time. At Time 2, higher reported PTG was associated with decreases in trauma symptoms (from Time 1) and increases in positive worldview and positive reframing. Although this study used a convenience sample and covered only a 6-month time period, the results are interesting as they suggest that level of trauma symptoms reflected at the individual, biophysical level as well as cognitive and coping variables grounded in micro- and macrosystemic norms play important roles in benefit finding. For example, Koenig (2006) found support for the positive impact of religious organizations in providing emotional and spiritual care to facilitate social support and recovery postdisaster.

A longitudinal study of individuals working and living in Manhattan on 9/11 examined whether respondents reported benefit finding and, if so, what types of benefits were reported. Nearly half of respondents reported finding benefits from the event, with these benefits coded by raters into three broad categories: finding new meaning in life, serving others (usually through volunteer activities, although not always in areas related to 9/11), and reconnecting with significant others (Hoffman et al., 2004). It is noteworthy the majority of the respondents reported negative effects of 9/11 that persisted and were reflected across the chronosystems of time and development. The most common effects appear to be grounded in biophysical reactions and included negative sensory perceptions (auditory, visual, smell), intrusive thoughts or images of the actual event, fear of flying and of airplanes, and distrust of individuals who appeared to be Middle Eastern. These findings suggest that even with positive benefits, there are often negative effects and that finding benefit coexisted with high levels of distress in many of the participants.

Because findings have been inconsistent across various trauma contexts, Hobfoll and colleagues (2007) addressed the question of whether psychological distress arising from terror exposure was reduced or increased by PTG. They utilized samples from both New York City and Israel, and PTG was related to greater psychological distress as well as to more support for retaliatory violence. Positive benefit in PTG was found only when individuals were able to translate their cognitions into what the researchers termed action-focused growth. This suggests the importance of translating growth thoughts into actual growth to find benefit in certain mass trauma contexts. Micro-, exo-, and macrosystemic factors appear to all play a role in an individual's action potential. Again, certain family, religious, and cultural subsystem norms likely influence a person's ability to translate growth cognitions into action-focused growth, and this coping approach may be easier to do with some types of mass traumas than with others. For example, Steury et al. (2004) noted volunteerism posttrauma seems to mitigate adverse response to trauma, yet lower socioeconomic groups might not have the resources to engage in and benefit from these activities. These studies suggest PTG may result from the bidirectional impact of the individual on other systems—a mesosystem effect.

Although PTG and its correlates have been identified in adults, few studies have examined this construct in children and teens. PTG attributed to September 11 was examined among middle school adolescents residing in California (Milam, Ritt-Olson, Tan, Unger, & Nezami, 2005). About one third of the participants reported positive changes post-9/11 in macrosystemic factors such as life priorities, relationships, and spirituality. Factors positively related to PTG included optimism, religious identification, and discussion of the attacks, whereas alcohol use, depression, and anxiety were inversely associated with PTG.

Few studies have examined PTG in veterans. In a study of combat-exposed veterans, both overall PTG as well as several subcategories were examined (Maguen, Vogt, King, King, & Litz, 2006). A greater appreciation of life was predicted by higher military status, an exosystemic factor, and by greater perceived threat. Consistent with other literature on other mass traumas, PTG was predicted by microsystemic social support postdeployment.

Several broad questions might guide future research on PTG in persons exposed to mass traumas. First, does PTG reflect actual positive change or rather the illusion of gains or benefits (e.g., Frazier et al., 2009; Zoellner, Rabe, Karl, & Maercker, 2008)? For example, Frazier et al. (2009) found actual growth was related to decreased distress, whereas perceived growth

was linked to increased distress in an undergraduate population. However, a 2-month time span was utilized, and what is unknown is whether and under what circumstances illusory PTG may follow a trajectory where it may initially serve one function (e.g., denial to manage a threatening situation) but later lead to transformative change (e.g., Tedeschi, Calhoun, & Cann, 2007).

Another broad question is, what are the correlates of PTG? A meta-analytic review examining the role of optimism, social support, and coping strategies found that positive appraisal coping and religious coping produced the largest effect sizes; social support coping, optimism, and spirituality produced moderate effects; and acceptance coping showed the smallest effects (Prati & Pietrantoni, 2009). Other studies found that social support coping and gender (being female; e.g., Swickert & Hittner, 2009) and anger (Park, Aldwin, Fenster, & Snyder, 2008) correlated with higher levels of PTG whereas negative coping and depression correlated with stress rather than growth (Park et al., 2008). Similar findings, especially in terms of the relationship to seeking social support, were found in many of the studies cited in the current article.

Finally, researchers are seeking to identify moderators and mediators of constructive PTG. For example, seeking social support coping was found to be a partial mediator of the relationship between gender and PTG (Swickert & Hittner, 2009), age and gender were found to moderate certain types of coping such as religious coping (Prati & Pietrantoni, 2009), and PTSD severity was found to moderate PTG (Zoellner et al., 2008). This latter finding is noteworthy because other researchers have suggested PTG may be more likely to occur when trauma survivors show initial distress *and* attach lasting significance of the trauma for their lives. Many bioecological factors, including mesosystem variables, may contribute to both the initial distress and the enduring meaning of a mass trauma to individuals and their systems and therefore to the likelihood of utilizing PTG as a constructive and positive change.

Summary and Implications

The wide-ranging effect of major disasters and catastrophes underscores the need for knowledge about risk and recovery from trauma for individuals, systems, and communities. Merrill, Thomsen, Sinclair, Gold, and Milner (2001) described a three-generation view of sexual abuse research that parallels similar trends reflected in the mass trauma literature. The first generation of research identified the negative sequelae associated with trauma exposure including behavioral, psychological, and interpersonal difficulties. Although

this research identified individual factors associated with poor adjustment following trauma exposure, there was no way to identify a causal pathway between mass trauma exposure and these outcomes because of the methodologies used. Most existing research has focused narrowly on the effects of mass trauma on individuals at a single point in time after the traumatic event. This research has tended to use convenience samples following a specific catastrophic event, and the vast majority of the research has used a cross-sectional design that did not allow for identification of causal relationships between short- and long-term outcomes. Furthermore, the literature has typically focused narrowly on the more serious individual psychological consequences such as PTSD. In addition to PTSD, catastrophes are related to the development of mood disorders such as anxiety and depression. Although understanding deleterious psychological outcomes of disasters is important, research is needed to identify predictors of resilience to stressors as well as a better understanding of how biological, psychological, social, and environmental factors interact and mediate posttrauma outcomes.

The second generation of research worked to identify those factors affecting risk and resiliency in response to mass trauma. This generation began to expand beyond the biophysical level to include exploration of specific systemic factors that interacted with biophysical and psychological factors to affect trauma response. Although this generation of research has been useful in highlighting the complex nature of trauma response, it has not yet been able to capture the nature of the interaction among factors at the various systemic levels. The third generation of research should utilize process models in which causal pathways among the multisystemic factors affecting trauma response and trauma outcomes are identified and empirically assessed. We propose that the prior research conceptualized in terms of the bioecological model described herein serves as the theoretical basis for making predictions about causal pathways that then could be tested empirically. When viewed with a bioecological lens, several themes emerged from the literature on mass trauma and have implications for both research and practice. These themes are reviewed below, and suggestions for future research guided by the core values of counseling psychology are discussed within each section.

Biophysical

Exposure, physical and emotional, to a traumatic event and repeated exposure to multiple traumatic events emerged as a key factor in contributing to long-term and ongoing posttrauma symptomatology in the form of stress reactions, depression, and anxiety (Pfefferbaum, 1997). This outcome following

exposure was found across populations and types of mass trauma. Individual characteristics such as temperament, coping skills, and emotional regulation appear to play an important role in moderating the effect of mass trauma. Furthermore, there is limited research that evaluates aspects of an individual's pretrauma level of functioning that predict risk and resiliency following exposure. It is important to assess aspects of individual functioning that promote adaptive coping in the aftermath of mass trauma. There was very little research on why some individuals rebound following a traumatic event, and some even perceive themselves to have grown from the experience (i.e., Tedeschi et al., 2007). Research on the myriad other systemic variables may answer these questions about individual risk and resiliency.

Microsystems

Social support was the most consistently identified protective factor in terms of moderating response to trauma. Mass trauma affects most major aspects of social function including family, career, school, peer, and cultural networks. Yet these areas have received little research focus, with one exception, the family and child literature, although even this literature has tended to focus on family and to a lesser extent on school variables that are related to individual functioning following the traumatic event. By and large, other systems, for example the workplace, religious institutions, and community agencies, have not been examined in terms of their role in influencing outcomes following mass trauma.

Social advocacy, to promote and support microsystemic and macrosystemic interventions that foster social support, is needed. Furthermore, evidence-based research should guide and inform both prevention and intervention programming across the levels of systems. Recent guidelines for mass trauma intervention generated by a group of internationally recognized experts on trauma (Hobfoll et al., 2007) were an attempt to synthesize what is currently known in the mass trauma literature to inform "best practices." These authors noted there was not sufficient research yet to generate an evidence-based consensus for the guidelines. However, there were some basic trends in the literature that could be used to guide interventions at both individual and community levels, including fostering a sense of safety, calmness, self- and community-efficacy, connectedness, and hope. These trends need to be studied in more detail to operationalize how they might be applied to psychosocial interventions. For example, Landau, Mittal, and Wieling (2008) have developed a multisystemic model for intervention that they call the linking human systems approach. This approach uses an ecological perspective as the basis for a

comprehensive, multisystemic approach to intervention following mass trauma. Their research is an initial attempt to provide outcome research that is congruent with the strength-based approach of counseling psychology and is a good beginning toward evidence-based practice research using a bioecological model for intervention.

Finally, there is a dearth of research on the impact of mass trauma on work and career. The natural disaster and war literature demonstrates mass trauma can disrupt the development of a work identity and the trajectory of a career. Because school experiences are precursors to work experiences, the sections of this article on natural disasters and terrorism and violence presented many studies identifying the importance of schools during times of mass trauma and the negative effects when these systems were disrupted. Counseling psychologists should lead the way in exploring the effects of mass trauma on work environments and careers.

Exosystems

The literature clearly supports the impact of media exposure in mass trauma response both for those directly exposed to trauma and for secondary stress reactions in those exposed to the trauma only via the media. This phenomenon needs further research. In particular, developmental factors in media influence and factors moderating the negative impact of media across the life span should be investigated. Furthermore, counseling psychologists could serve as consultants and advocates to inform public policy in terms of guidelines for media exposure following traumatic events. Social advocacy is also needed to inform public health policy, especially in terms of promoting integrative systems of care among medical, school, community, and religious groups and governmental agencies. Another theme we identified was the disproportionate effect of these three types of traumas at the community level. Defining communities as either geographical or social entities, research is needed on how to make communities more resilient as individual benefits from interventions are difficult to maintain if the community is overstressed.

Macrosystems

Many studies have investigated the relationship between ethnic group and culture and response to mass trauma. However, the research to date has yielded no clear patterns (de Silva, 1999). This lack of consistency may be because most research to date has failed to distinguish emic versus etic multicultural factors. Most probably, cultural subsystem norms interact with

other factors to influence an individual's trauma response. Furthermore, although females (across developmental continuum) consistently demonstrate more psychopathology in response to trauma (Norris et al., 2002), the causative factors underlying these reactions are not clear. It is likely that as with culture, complex multisystemic influences are at play. Understanding the relationship of gender and culture in stress reactions following mass trauma requires complex conceptual process models such as the bioecological model proposed herein to identify and understand the myriad systemic factors that interact to form the basis of any given individual's response to mass trauma. Counseling psychologists could clearly lead the way in this research, and findings from the body of literature we generate could then be used to inform public policy in responses to mass trauma.

Another broad macrosystemic theme was that the resources individuals, systems, and communities have can mitigate exposure and response to mass trauma. Perhaps one of the most salient resources was socioeconomic status, which includes educational attainment, job skills, and financial assets (Steury et al., 2004). Socioeconomic status appears to often buffer the effects of mass trauma. For example, persons with more financial resources were more likely to evacuate during a weather-related disaster such as a hurricane, to have the resources to rebuild their lives, and to have access to resources such as psychotherapy and medical care after a mass trauma.

Mesosystems

The research to date on mesosystemic influences is extremely limited, and mesosystemic issues are described in a conceptual rather than empirical manner (i.e., Dean et al., 2008). There was only one study that appeared to examine mesosystemic relationships in trauma response following mass trauma (Stuber, et al., 1997). This study explored the association between teachers' PTSD symptomatology and classroom behavior of their students following mass trauma as well as peer relationship problems following the Los Angeles riots. The bioecological model highlights the fact that catastrophes have effects that extend beyond the immediate impact on the individual as they directly and indirectly affect social and societal networks.

It is in the area of mesosystems that counseling psychology could make significant contributions to the understanding of mass trauma response and recovery. The bioecological model provides a conceptual framework to guide this research by identifying mediating and moderating variables among the systems. For example, we could contribute our expertise in the area of work and career development to investigations of the interface between work or

school and family factors following traumatic events. Similarly, we could further understanding about how social and cultural subgroup factors interact with other systems to either facilitate or hinder trauma recovery. We could also work to ensure multicultural competence in first responders and other professionals or agencies that interact with individuals and groups following mass traumas.

Chronosystems and Developmental Processes

Chronosystem influences might better be viewed through the lens of recovery rather than of resilience shown at the time of the event. Thus, it may be important to identify those elements within each of the bioecological systems that promote recovery in the wake of mass trauma. Trauma recovery appears to be most affected by social support, especially in the immediate microsystems. Women, children, and minorities are typically more vulnerable populations, especially in the context of macrosystems, and adult males demonstrate better outcomes and recovery. Furthermore, there does seem to be emerging evidence for the construct of community resilience in avoiding or mitigating the effects of mass trauma. It will be important to investigate those meso- and exosystemic factors contributing to community resilience. A theme across all of these studies was that some mass catastrophes have such devastating effects that immediate and ongoing exposure to the disaster and its aftermath may tax even the most resilient individual and community. In those cases, it will be important to intervene also at macrosystemic levels over time to ameliorate the devastating effects of these types of mass trauma.

Longitudinal studies are needed to investigate the developmental processes that influence risk and resiliency. To date, most research has focused on risk factors. For example, chronosystem factors likely contribute to military personnel returning from Iraq actually getting worse over time once they return. Counseling psychology's core values suggest we emphasize resiliency and adaptive coping following mass trauma. Future chronosystem research might examine the relationship of PTG to resilience. Although many individuals report PTG when experiencing major crises, it is important to note it is not expected to occur whenever an individual experiences a bad event. Rather, it is hypothesized to occur when core beliefs are challenged. It can coexist with stress symptoms, making it difficult to discern beneficial growth over time, suggesting the importance of longitudinal studies to adequately study this construct (Tedeschi et al., 2007). Furthermore, there is great inconsistency in the manner in which this construct is measured, and the same is true for resiliency. An important question is whether people report

PTG as a means of coping when they lack the resilience to manage the psychosocial consequences of a mass trauma (see Westphal & Bonanno, 2007).

Furthermore, there is evidence of developmental differences in the types of coping methods utilized (Thienkrua et al., 2006). Research to better understand the interplay between developmental stage at time of exposure and subsequent coping would provide a developmental model for intervention. Finally, as previously stated in the biophysical section, the majority of the research indicates exposure is a primary determinant of adverse impact. Although we may not be able to control exposure, an increased understanding of the interaction of developmental stage at time of exposure as well as factors affecting risk and resiliency factors could be used to help mitigate the adverse impact of trauma exposure and promote healthy lifelong development.

In sum, much remains to be learned about the bioecological effects of large-scale disasters and catastrophes on individuals, systems, and communities. In moving beyond a focus on the individual, researchers face substantive and interesting challenges. The bioecological model of mass trauma can provide a framework for research and practice. Furthermore, it is congruent with core values of counseling psychology because it incorporates a developmental perspective, including career development, and an emphasis on maximizing growth potential by enhancing both individual and systemic strengths. Moreover, this model allows for an examination of multicultural variables. It can be used to promote not only posttraumatic growth and resiliency in the wake of mass trauma but also social justice by informing public policy.

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Social trauma and its association with posttraumatic stress disorder and social anxiety disorder

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ABSTRACT

The key characteristic of a traumatic event as defined by the Diagnostic and Mental Manual of Mental Disorders (DSM) seems to be a *threat to life*. However, evidence suggests that other types of threats may play a role in the development of PTSD and other disorders such as social anxiety disorder (SAD). One such threat is *social trauma,* which involves humiliation and rejection in social situations. In this study, we explored whether there were differences in the frequency, type and severity of social trauma endured by individuals with a primary diagnosis of SAD (n = 60) compared to a clinical control group of individuals with a primary diagnosis of obsessive compulsive disorder (OCD, n = 19) and a control group of individuals with no psychiatric disorders (n = 60). The results showed that most participants in this study had experienced social trauma. There were no clear differences in the types of experiences between the groups. However, one third of participants in the SAD group (but none in the other groups) met criteria for PTSD or suffered from clinically significant PTSD symptoms in response to their most significant social trauma. This group of SAD patients described more severe social trauma than other participants. This line of research could have implications for theoretical models of both PTSD and SAD, and for the treatment of individuals with SAD suffering from PTSD after social trauma.

1. Introduction

1.1. The Criterion A debate

Post-traumatic stress disorder (PTSD) has been conceptualized as a response to a traumatic stressor. The Diagnostic and Statistical Manual of Mental Disorder (DSM) has from the third edition and onward been focused on objective indicators of psychopathology in order to increase the reliability of diagnoses. This emphasis also affected the traumatic stressor criterion, by attempting to pre-define the kind of events that can lead to PTSD symptoms. In DSM-5, trauma is characterized as "exposure to actual or threatened death, serious injury, or sexual violence" (American Psychiatric Association, 2013, p. 271, Criterion A). A diagnosis of PTSD is made if Criterion A is met in addition to post-traumatic stress symptoms (PTSS) for more than one month, such as intrusion symptoms (e.g., memories of the event), avoidance of stimuli related to the event, negative alterations in cognitions and mood, and changes in arousal and reactivity (American Psychiatric Association, 2013, pp. 271–272).

The key characteristic of a traumatic event according to the DSM seems to be a *threat to life* (Weathers & Keane, 2007), although sexual violence does not necessarily fit this definition. There has, nevertheless, been a considerable debate, sometimes referred to as the *Criterion A debate*, in the literature on what constitutes a traumatic stressor that can lead to PTSD (Boals & Schuettler, 2009; Gold, Marx, Soler-Baillo, & Sloan, 2005; Long et al., 2008; Stein, Wilmot, & Solomon, 2016) and reaching a general consensus has proven difficult. There has been a number of studies that have found that individuals often report PTSS in response to events that are not life-threatening and do not meet Criterion A. A recent meta-analysis (Larsen & Pacella, 2016) revealed that the association between Criterion A events (as defined by DSM-III and DSM-IV) and PTSS resulted in only a slightly larger effect size than events that do not meet that criterion. Furthermore, a recent study of DSM-5 Criterion A events vs. events that do not meet that criterion showed a similar but non-significant effect size (Larsen & Berenbaum, 2017).

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The Criterion A debate remains unresolved, and we may need a different approach to reveal what makes an experience traumatic and likely to lead to PTSD. It is clear that certain types of experiences (e.g, rape compared to an avalanche) are more likely than others to result in PTSD symptoms (Friedman, Resick, Bryant, & Brewin, 2011). However, rather than emphasizing the types of events that count as trauma, a more constructive approach may be to consider the types of perceived *threat* that are related to reproductive success in the evolutionary history of our species (Stein & Nesse, 2011). This would also provide a stronger link to current theoretical models of PTSD (see especially Ehlers & Clark, 2000) that emphasize not the event itself but rather how the individual appraises the experience, and whether he or she does it in a way that leads to a sense of constant threat. Larsen and Berenbaum (2017) examined a number of predictors of PTSD symptoms and found only one consistent predictor: the individual´s assessment of life threat. Other studies have found similar results (see e.g., Pinto, Henriques, Jongenelen, Carvalho, & Maia, 2015): Perceived threat may be a much more likely causal factor in the development of PTSD than a pre-defined list of "traumatic" events. Threat to life is one, but there may be other types of threat that can result in a traumatic response. Furthermore, it is important to explore the extent to which different types of threat play a role in the development and maintenance of other disorders, such as social anxiety disorder.

1.2. Social anxiety disorder and social trauma

Social anxiety disorder (SAD) is characterized by a persistent fear of being humiliated or embarrassed in social situations (American Psychiatric Association, 2013). Most people with SAD report a single event or an ongoing social experience, which commonly revolve around humiliation, rejection and criticism, as having played a significant role in the onset of the disorder (Bandelow et al., 2004; Hackmann, Clark, & McManus, 2000), although not all studies have found that such conditional events are the most important factors in the onset of SAD (Harvey, Ehlers, & Clark, 2005; Hofmann, Ehlers, & Roth, 1995). Negative social events are usually not considered to be traumatic. However, research suggests that aversive social events are sometimes experienced as such. Erwin, Heimberg, Marx, and Franklin (2006) examined (with a clinical interview) PTSS in response to stressful social events among individuals with SAD and non-anxious controls. The results showed that all participants in the SAD group and 70% of the non-anxious group had experienced a socially stressful event. Most importantly, more than one-third of the participants with SAD (but none in the control group) met criteria for PTSD in response to the social event (which, however, did not meet Criterion A). Similarly, Carleton, Peluso, Collimore, and Asmundson (2011) compared patterns of social anxiety symptoms and PTSS relative to negative social events and Criterion A trauma. They found that one third of the participants reported a negative social event as being the most distressing event that they had ever experienced, despite most also having experienced Criterion A events. In addition, participants who had experienced negative social events had higher levels of PTSS and SAD symptoms. These findings suggest an important relationship between negative social experiences and both SAD and PTSD (Carleton et al., 2011). Everyone experiences some sort of aversive social experiences during their lifetime. Nevertheless, it may be that individuals that develop SAD have a psychological vulnerability (see e.g., Rodebaugh et al., 2017) to events that are not commonly considered traumatic. Even though negative social experiences are neither necessary nor sufficient for the onset of SAD, their role in the developmental process of SAD is reminiscent of the role of trauma in the development of PTSD.

1.3. Threat appraisal

Collimore, Carleton, Hofmann, and Asmundson (2010) called for research on disentangling temporal sequence between SAD, PTSD and traumatic experiences and whether there was a shared vulnerability (genetic and/or psychological) to both disorders, but their review, published a decade ago, has not sparked systematic research on these critical issues. The Criterion A debate has revolved around what kind of *events* have the potential of being traumatic and playing a role in the development of PTSD. We propose that one way of advancing the field may be to shift the focus away from pre-defined events, and instead focus on the types of perceived *threat* that can have the potential of leading to PTSD, but also to other disorders such as SAD. In that sense, there may be a group of individuals who do not have co-morbid PTSD and SAD (two separate conditions) but rather react to a social threat in such a way that they live life as if under constant social threat, with accompanying symptoms (such as intrusive memories, vigilance and avoidance of social situations) of both PTSD and SAD as *one* integrated condition.

We explored in this study whether there may exist at least two types of trauma*; threat to life* and *social threat*. The latter threat involves perceived rejection or humiliation and can only be understood from an evolutionary perspective (Bjornsson et al., 2016). Humans are social animals that have throughout their evolutionary history relied on their group for access to food, mating partners and security (Gilbert, 2002; Gilboa-Schechtman, Shachar, & Helpman, 2014). Being rejected from one's group may have been, from an evolutionary perspective, just as life-threatening as physical attacks (Bjornsson et al., 2016). However, there are likely to be different processes involved, and not necessarily the same emotion regulation processes (e.g., social trauma may be more likely to be associated with shame than threat to life). Research is needed on whether certain experiences can be considered socially traumatic in this sense, and whether they have a unique relationship to the development of not only PTSD but to SAD as well. We use the term social trauma in the same way as threat to life trauma, such that the individual experiences these types of threats, which have the potential of provoking (but do not necessarily cause) post-traumatic stress symptoms. It should be noted that the construct of social trauma is different from the notion of interpersonal trauma, which is often referred to in the literature (see e.g., Nishith, Mechanic, & Resick, 2000) since most traumatic experiences involve other people and the term "interpersonal trauma" does not reveal the type of threat involved. However, it is likely that the concept of social trauma can make sense of why certain interpersonal experiences are more potent than other experiences in causing PTSS. In addition, it is hoped that an emphasis on both life threat and social threat can result in integrating literatures that have the potential to cast light on how certain experiences become traumatic. Notable examples are the literature on bullying and peer victimization (see e.g., Kowalski, Guimetti, Schroeder, & Lattanner, 2014; McCabe, Miller, Laugesen, Antony, & Young, 2010) and the literature on adverse childhood experiences (ACE; Hughes et al., 2017; Petruccelli, Davis, & Berman, 2019). Research on ACEs investigates a rich array of experiences, such as physical violence, sexual violence, bullying and neglect, but may benefit from specifying further how different types of threat affect mental and physical health.

In order to assess whether social trauma has a special relationship with SAD and PTSD, we need to compare such trauma among individuals with SAD, with a control group of individuals with no psychiatric disorders, but also a clinical control group of individuals with a different psychiatric disorder (in this study, obsessive-compulsive disorder, OCD). The reason for including not only a control group but also a clinical control group was to assess whether social trauma and PTSD in response to social trauma is uniquely associated with SAD but not only psychopathology more generally. The reason for choosing OCD as a clinical control group is that OCD has been associated with threat to life trauma (Miller & Brock, 2017). We also need to assess this new construct (*social trauma*) with a clinical interview and to assess both PTSD and SAD symptoms and their age of onset with a diagnostic interview conducted with a trained assessor (as opposed to self-report measures that are common in this literature).

1.4. Aims of the study

The purpose of this study is to explore the construct of social trauma and whether it may be associated with the development and maintenance of both PTSD and SAD. The aims of the current study are fourfold. First, to examine the frequency of social trauma among individuals diagnosed with SAD as a primary diagnosis (the disorder that is most impairing and distressing), a clinical control group of individuals with OCD as a primary diagnosis and a control group of individuals with no psychiatric disorders. Second, to examine if the social trauma is different in the three groups with regard to types of experiences and their severity. Third, to assess PTSD and clinically significant PTSS in response to social trauma and, fourth, to examine if different types of experiences or severity are differentially related to PTSD.

2. Method

2.1. Participants

The sample consisted of 139 participants 18 years of age or older. Participants in this study consisted of three groups. The SAD group comprised 60 individuals in treatment or seeking treatment for social anxiety at the Icelandic Center for Treatment of Anxiety Disorders. The inclusion criterion for the SAD group was to be diagnosed with SAD as a primary diagnosis (defined as the disorder causing most impairment and distress). The diagnosis of OCD was an exclusion criterion for this group. The clinical control group consisted of 19 individuals with OCD as a primary diagnosis that were either in treatment or seeking treatment, who were recruited using advertisements on social media and on bulletin boards. An exclusion criterion for this group was the diagnosis of SAD. The control group consisted of 60 adults who were recruited using advertisements on social media and on bulletin boards. The inclusion criteria for the control group consisted of having no psychiatric diagnoses. Participants in the control group were screened via a brief phone interview in order to exclude those who suffered from psychiatric disorders. The National Bioethics Committee of Iceland approved the study, and all participants signed an informed consent. All participants received a 5000 ISK gift certificate for their participation in this study.

All participants were Icelandic and there were no significant differences in age or gender between the three groups (see Table 1). Participants in the SAD group were less likely to have completed junior college or more (45.0%) compared to the control group (80.0%) and the clinical control group (63.2%; $p < .001$). Participants in the SAD group were also significantly more likely to be single (50.0%; $p < .05$) compared to the control group (35.0%) and the clinical control group (31.6%). The patients with SAD and OCD met criteria for a number of other psychiatric disorders, as can be seen in Table 1.

We compared social anxiety symptoms, depression symptoms, quality of life and functional impairment in the three groups (see Table 1). Post hoc comparisons using the Bonferroni correction indicated statistically significant differences between the groups with regard to social anxiety symptoms (as measured by the LSAS and SPWSS, see below), depression symptoms (as measured by PHQ-9, see below), quality of life (as measured by QOLS, see below) and functional impairment (as measured by SDS, see below), as can be seen in Table 1. The mean scores on LSAS, SPWSS, PHQ-9 and SDS were significantly higher in the SAD and clinical control group, and mean scores on the QOLS were lower, than in the control group ($ps < .001$). Additionally, the mean scores on the LSAS and SPWSS were significantly higher in the SAD group, and QOLS mean scores lower, compared to the clinical control group ($ps < .001$) but the groups did not differ with regard to scores on SDS ($p = .273$).

2.2. Measures

Background information about the participants was collected with a demographics form that included questions about age, education, work and marital status.

The Imagery and Social Trauma Interview is a non-invasive semi-structured interview, based on earlier versions of imagery interviews (Hackmann et al., 2000; Lipton, Brewin, Linke, & Halperin, 2010) translated by the the first author and adapted to focus more specifically on reactions to intrusive images and social trauma. The interview is divided into two parts. The first part of the interview assesses the presence of intrusive images. The second part assesses social trauma and takes approximately 15-20 minutes to administer. For the purposes of the current study, only the second part is described. To assess whether the participant has ever endured a socially traumatic experience, the interviewer asks the participant if he or she has ever been humiliated or rejected by other people during their lifetime. If the participant endorses such an experience, he or she is asked to choose the worst one. The interviewer then asks about the experience in detail, including what happened, what the situation was, who were involved, whether it happened repeatedly and at what age it happened. Participants are asked how strongly they remember the experience (ranging from “very weak” to “very strong”) and then are asked to identify and rate the strength of current emotional responses (on a scale from zero to ten) to it, first in an open-ended format, and then by asking about various other emotions that were not listed by free recall. Next, the interviewer asks how distressing the experience was (ranging from “not at all distressing” to “extremely distressing”), and how much it interfered with work, school, daily activities and social life at the time it happened (ranging from “no interference” to “extreme interference”).

The Mini International Neuropsychiatric Interview (MINI) is a structured diagnostic interview that assesses Axis I psychiatric disorders according to the DSM-IV. It is used in this study to characterize the sample and to ensure that individuals in the control group had no diagnosable disorders. Inter-rater and test-retest reliability has been shown to be good, with kappa’s in the high to very high range. The MINI has strong reliability and validity in relation to the Structured Clinical Interview for the DSM-IV (SCID-IV). The majority of kappa values were .90 or higher, which indicates excellent inter-rater reliability ($\kappa s = .79–1.0$; Sheehan et al., 1997). An Icelandic version of the MINI was used in this study. The Icelandic version of the MINI has good convergent validity with self-report measures of depression and anxiety symptoms (Sigurðsson, 2008). The inter-rater reliability was high in this study: Percentage of agreement between raters in the control group was 100% for all disorders, and in the SAD group it ranged from 90.9% to 100%.

The Body Dysmorphic Disorder Diagnostic Module (BDD-DM; Phillips, 2005) is a brief semi-structured interview, designed to diagnose BDD (the MINI does not assess BDD). BDD-DM has been found to have good psychometric properties, including high inter-rater reliability ($\kappa = .96$; Phillips, 2005). Inter-rater reliability for the Icelandic version of BDD-DM used in this study was high, with 87.5% percentage agreement between raters in the control group for lifetime BDD and 100% for current BDD, and 100% for lifetime BDD and 90.9% for current BDD in the SAD group.

The Liebowitz Social Anxiety Scale (LSAS) is a brief semi-structured clinical interview that assesses anxiety and/or fear and avoidance in 24 social situations (Liebowitz, 2003). Participants are asked to rate their anxiety and/or fear and avoidance (on a four point Likert scale) during the previous week. The LSAS total score was used to assess the severity of social anxiety symptoms. The scale has been found to be sensitive to change following treatment and to have excellent internal consistency on different subscales (Cronbach’s alpha = .81–.92; Heimberg et al., 1999). The Icelandic version used here had good internal consistency for the SAD ($\alpha = .90$), clinical control group ($\alpha = .91$) and control group ($\alpha = .91$). Additionally, scores on the LSAS predicted a SAD

Table 1
. Background variables and clinical characteristics of the groups (N = 139).

Variables[a]	SAD group n = 60	Clinical control (OCD) group n = 19	Control group n = 60	Chi-Square- or F statistic
Demographic variables				
Age (M; SD)	29.0 (10.7)	30.7 (7.4)	31.6 (10.2)	F (2, 136) = 1.02
Gender (% female)	36 (60.0)	16 (84.2)	33 (55.0)	X^2 (2, 139) = 5.2
Nationality (% Icelandic)	60 (100)	19 (100)	60 (100)	-
Education (% Junior College or more)	27 (45.0)	12 (63.2)	48 (80.0)	X^2 (2,139) = 15.7**
Currently a student (%)	25 (44.6)[e]	10 (52.6)	23 (39.0)[c]	X^2 (2, 134) = 1.6
Married or living with a partner (%)	30 (50.0)	13 (68.4)	39 (65.0)	X^2 (2, 139) = 3.6*
Comorbidity[b]				
Major depressive disorder	22 (36.7)	6 (31.6)	-	-
Dysthymia	2 (3.3)	-		
Bipolar I disorder	1 (1.7)	-	-	-
Bipolar II disorder	3 (5.0)	2 (10.5)	-	-
Panic disorder with agoraphobia	5 (8.3)	1 (5.3)	-	-
Agoraphobia without panic	3 (5.0)	3 (15.8)	-	-
Social anxiety disorder	60 (100)	-	-	-
Obsessive compulsive disorder	-	19 (100)	-	-
Posttraumatic stress disorder (threat to life trauma)	3 (8.3)	3 (15.8)	-	-
Posttraumatic stress disorder (social trauma)	13 (21.7)	-	-	-
Alcohol dependence	7 (11.7)	2 (10.5)	-	-
Alcohol abuse	1 (1.7)	2 (10.5)	-	-
Drug dependence	2 (3.3)	-	-	-
Drug abuse	-	-	-	-
Bulimia	-	3 (15.8)	-	-
Anorexia nervosa	-	1 (5.3)		
Generalized anxiety disorder	7 (11.7)	4 (21.1)	-	-
Body dysmorphic disorder	9 (15.0)	1 (5.3)	-	-
Other clinical characteristics				
LSAS[f]	80.80 (18.30)	42.88 (19.67)[c]	12.62 (10.44)	F (2, 134) = 298.6 ***
SPWSS[g]	39.36 (7.86)[e]	19.29 (8.89)[c]	9.40 (4.93)	F (2, 130) = 123.0 ***
PHQ-9[h]	10.67 (6.17)[d]	10.18 (6.67)[c]	1.95 (2.00)	F (2, 131) = 52.6***
QOLS[i]	64.28 (12.01)[d]	78.12 (14.24)[c]	94.72 (9.49)	F (2, 131) = 106.9***
SDS[j]	181.46 (59.36)[d]	156.88 (79.61)[c]	14.36 (31.03)[c]	F (2, 130) = 158.3 ***

Note. *p < .05 **p < .01 ***p < .001 [a] Results in the table are presented as n (%) or mean (standard deviation). [b]The Mini International Neuropsychiatric Interview was used to assess all disorders except that body dysmorphic disorder (BDD) was assessed with the Body Dysmorphic Disorder Module. [c]One missing value. [d]Three missing values. [e]Four missing values. [f]LSAS = Liebowitz Social Anxiety Scale. [g]SPWSS = Social Phobia Weekly Summary Scale. [h]PHQ-9 = Patient Health Questionnaire-9. [i]QOLS = Quality of Life Scale. [j]SDS = Sheehan Disability Scale.

diagnosis on the Icelandic version of the MINI. Inter-rater reliability for the Icelandic version of LSAS was high (on both subscales i.e., the intraclass correlation coefficient [ICC] = 1.00 and .90 for anxiety and ICC = .91 and .94 for avoidance) and for the total score (i.e., i.e., the intraclass correlation coefficient was .98 and .92) for the control and SAD group, respectively.

The Social Phobia Weekly Summary scale (SPWSS) is a six-item weekly summary measure of social anxiety, social avoidance, self-focused versus external attention, anticipatory processing, and post event rumination. The SPWSS has been found to have good internal reliability (Cronbach's alpha = .81; Clark et al., 2006). The Icelandic version of the SPWSS used in this study had poor internal consistency in the control group (α = .57) but fair in the SAD group (α = .74) and the clinical control group (α = .73).

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item self-report measure of depression symptoms and the severity of those symptoms. Each item can be scored from 0 (i.e., not at all) to 3 (i.e., nearly every day). The PHQ-9 has excellent internal reliability (Cronbach´s alphas from .86–.89) and good test-retest reliability (r = .84) (Kroenke, Spitzer, & Williams, 2001). The Icelandic version of the PHQ-9 used in this study had good internal consistency in the SAD group (α = .87) and the clinical control group (α = .85), but fair in the control group (α = .66).

The Quality of Life Scale (QOLS) is a self-report measure (of 16 items) of quality of life on a seven point Likert scale ranging from 7 (delighted) to 1 (terrible). The domains that are assessed are the following: Social and community activities, material and physical wellbeing, relationships with other people, personal development and fulfilment, and recreation. The QOLS has good reliability and validity (Liedberg, Burckhardt, & Henriksson, 2005). The Icelandic version of the QOLS used in this study had fair internal consistency in the SAD group (α = .76) but good in the clinical control group (α = .87) and the control group (α = .86).

The Sheehan Disability Scale (SDS) is a brief self-report measure of functional impairment in three domains: Work/school, social and family life. The three domains are assessed on an 11-point Likert type scale ranging from 0 (not at all) to 10 (extremely). Scores on the SDS have been found to be highly correlated with both symptoms of SAD and MDD, in addition to high internal and test-retest reliability, and good construct validity (Leon, Olfson, Portera, Farber, & Sheehan, 1997). The Icelandic version of the SDS used here had fair internal consistency in the SAD group (α = .70), but good internal consistency in the clinical control group (α = .84) and control group (α = .81).

2.3. Procedure

Trained assessors conducted the interviews (i.e., the Imagery interview and Social Trauma Interview, MINI, BDD-DM and LSAS). Every assessment was documented on a laptop computer using the RedCap database, an encrypted, electronic software and stored on secure servers (Harris et al., 2009). The assessors were experienced psychologists or advanced graduate students in clinical psychology. The assessors received thorough training from the first author (a licensed clinical psychologist) in conducting the interviews. The training included sitting in on an assessment session, reviewing records of assessment sessions, reviewing administration manuals and completing mock interviews. All assessors received weekly group supervision with the first author in which each interview was discussed (often by listening to

segments of tape from assessments) with regard to issues like differential diagnoses on the MINI until consensus was reached.

Content analyses were conducted with the aim of identifying the main themes of the social trauma. These analyses were managed by the first author and two advanced graduate students in clinical psychology. All three assessors were blind to group assignment when conducting the content analyses. Adopting a methodology based on Joffe and Yardley (2004); see also Lipton et al., 2010; Purdon & Holdaway, 2006), we created separate themes for the content of the social trauma, prior to examining the data, by reviewing the existing literature on negative social events (with reference to, e.g., Brook & Schmidt, 2008; Carleton et al., 2011; Gold et al., 2005; Levinson, Langer, & Rodebaugh, 2013; Olweus, 1993; Rigby, 2002; Van Hooff, McFarlane, Baur, Abraham, & Barnes, 2009). The coders subsequently attempted to categorize the data, and some themes were modified when they were deemed not appropriate for this data set. If coders did not agree on the categorization of a single event or appraisal, further discussion was made until majority consensus was reached. If the event did not clearly fall into any category due to ambiguity or insufficient information, the event was rated as "uncodeable".

Final categories for the social trauma were the following: 1. Bullying (e.g. someone intentionally and repeatedly hurting the participant). The definition of bullying in this study included the three characteristics presented by Olweus (1993): intentional aggression; a power imbalance between the aggressor and victim; and repetition of the aggressive behavior; 2. Teasing (e.g. making a joke about the appearance of the participant); 3. Mental/physical and sexual violence/harassment (e.g. someone hitting and/or raping the participant with the intention of humiliating him/her); 4. Anxiety-provoking remark (e.g. someone saying that the participant is red in the face) which is a statement that appears to be innocent but neverthless is interpreted in a way that results in increased social anxiety and other emotions; 5. Being rejected by someone/not included (e.g. ending a relationship, excluding the participant from a group); 6. Social mishap (e.g. feeling like one messed up in a social situation); 7. Being an outsider (e.g. the experience of not belonging even if there is no clear evidence of exclusion).

Severity of the social trauma was also coded. Each rater categorized each experience with regard to severity of rejection and/or humiliation, taking into account whether it was an isolated event or repeated, and if the experience took place over a long period of time. Each member rated the severity of the social trauma on a five point Likert scale: 0 = No humiliation and rejection (e.g. innocent comment); 1 = Mild humiliation and rejection (e.g. teasing over a short period of time, mild traumatic remark, mild social mishap); 2 = Considerable humiliation and rejection (e.g. a negative comment such as "You are stupid"); 3 = Severe humiliation and rejection (e.g. repeated bullying over a long period but not of the most severe kind); 4 = Extreme humiliation and rejection (e.g. physical assault, severe bullying, or rape). In addition, the team rated whether the negative social experience involved one, two or a number of people.

2.4. Statistical Analyses

Deviations from normality and univariate outliers were screened for all variables of interest. Descriptive statistics were used to characterize the three groups in terms of background variables and clinical characteristics, in addition to social trauma (based on the content analyses described above). Background characteristics and clinical variables of the three groups were compared with chi-square tests of independence and one-way between-subject ANOVAs along with post-hoc comparisons using the Bonferroni correction. We conducted two logistic regression analyses to examine, first, the relationship between trauma severity and PTSD or clinically significant PTSS, and, second, between trauma severity and a diagnosis of SAD. An appropriate model was selected by comparing the model fit criteria (i.e., Akaike Information Criterion) between models but also by comparing significance tests results for main and interaction effects. In general, a model with a lower AIC is believed to be a better fit, and a two-point difference in AIC is considered meaningful.

3. Results

3.1. Frequency and characteristics of social trauma

Members of all three groups reported high rates of social trauma: 49 of the 60 (81.7%) participants in the SAD group, 15 out of 19 (78.9%) in the clinical control group and 38 of the 60 participants in the control group, (63.3%; X^2 [2, N = 139] = 5.51, p = .60). About 77% of individuals in the SAD group reported that the social trauma took place repeatedly compared to 87% for individuals in the clinical control group and 72% of individuals in the control group (X^2 [2, N = 80] = 1.03, p = .60). Most (77%) individuals in the SAD group said that the traumatic experience took place over a period of time (rather than being an isolated event) compared to 73% in the clinical control group and 67% in the control group (X^2 [2, N = 80] = 0.66, p = .72). Most participants reported a strong memory of the experience, with 63% in the SAD group, 67% in the clinical control group and 65% in the control group reporting either a considerably strong or very strong memory of the experience (X^2 [2, N = 102] = .09, p = .96).

The great majority (70.7%) of those who had experienced social trauma in the SAD group reported that the event happened before the age of onset of SAD (i.e., the age at which the social anxiety was starting to have a significant effect on the participant´s life), the mean age of onset was 14 years (SD = 5.4), and mean age of worst social trauma was at age 12.5 (SD = 6.3), however, there was not a statistical difference between those two time points, (t(40) = 1.77, p = .08). Participants in the SAD group (85.7%) and the clinical control group (66.7%) were more likely to report that their social trauma led to them becoming socially anxious (or more anxious in social situations) compared to the control group (23.7%; X^2 [2, N = 102] = 34.60, p < .001). There was a statistically significant difference between age of onset of SAD (M = 14.3 years, SD = 5.5) and the timing of the trauma (M = 12.6 years, SD = 6.7) for those in the SAD group who reported that their trauma had led them to becoming socially anxious (t (35) = 2.12, p < .05).

3.2. Type and severity of social trauma

Results of the content analyses of the social trauma reveal some differences between the groups (see Table 2), although few statistically significant differences were found. There were similar rates of *bullying* in the groups, but *teasing* was more common in the control group (28.9%) than the SAD group (10.2%; z = 2.4, p < .05). Mental/physical abuse and sexual violence/harassment and abuse was reported more frequently in the clinical control group (53.3%) than in the SAD group (22.4%; z = 2.3, p < .05) and control group (7.9%; z = 3.7, p < .001).

Participants described a variety of emotions that they experience now when they bring the social trauma to memory. The most frequently mentioned emotions (in order of frequency) for the SAD group were sadness (75.5%, and the strength of the emotion was M = 5.92 on a 10-point Likert scale, SD = 2.22), anger (75.5%, M = 5.62, SD = 2.29) and shame (73.5 %, M = 5.65, SD = 2.68), for the clinical control group the most frequently mentioned emotions were sadness (86.7%, M = 5.31, SD = 2.10), disgust towards others (80.0%, M = 5.92, SD = 2.71) and anger (80.0%, M = 5.58, SD = 2.99), and for the control group the most frequently mentioned emotions were anger (60.5%, M = 3.22, SD = 1.95), sadness (57.9%, M = 2.93, SD = 1.80), and shame (47.4%, M = 3.00, SD = 1.68). There were statistical differences in the strength of the following emotions: Sadness, shame, disgust towards others, anger, anxiety and fear were stronger in the SAD group than in the control group (ps < .05). Sadness, shame, anger, and

Table 2
Information about the social trauma in the three groups (n = 94).

Type of social trauma[a]	SAD group n = 49 Frequency (%)	Clinical control group n = 15	Control group n = 38
I. Bullying	20 (40.8)	4 (26.7)	11 (28.9)
II. Teasing	5 (10.2)	2 (13.3)	11 (28.9)
III. Mental abuse	7 (14.3)	3 (20.0)	3 (7.9)
IV. Physical abuse	1 (2.0)	3 (20.0)	-
V. Sexual abuse	3 (6.1)	2 (13.3)	-
VI. Anxiety-provoking remark	2 (4.1)	-	2 (5.3)
VII. Rejected by other people/not included	4 (8.2)	1 (6.7)	7 (18.4)
VIII. Social mishap	5 (10.2)	-	4 (10.5)
IX. Being an outsider	1 (2.0)	-	-
X. Uncodeable	1 (2.0)	-	-
Humiliation or rejection	**n = 48**	**n = 15**	**n = 38**
Mild	6 (12.5)	2 (13.3)	10 (26.3)
Considerable	11 (22.9)	4 (26.7)	13 (34.2)
Severe	21 (43.8)	6 (40.0)	12 (31.6)
Extreme	10 (20.8)	3 (20.0)	3 (7.8)
Individuals involved in the social trauma	**n = 48**	**n = 15**	**n = 38**
One or two	11 (22.9)	8 (53.3)	13 (34.2)
Three or more	37 (77.1)	7 (46.7)	25 (65.8)

Note. [a]Categories are mutually exclusive.

Table 3
Information about the social trauma among individuals with SAD and with/without social PTSD/PTSS (n = 48[a]).

Type of event	Social PTSD/PTSS	
	Yes (n = 16)	No (n = 33)
	Frequency (%)	
I. Bullying	7 (43.8)	13 (39.4)
II. Teasing	-	5 (15.2)
III. Mental abuse	3 (18.8)	4 (12.1)
IV. Physical abuse	-	1 (3.0)
V. Sexual violence/harassment	2 (12.5)	1 (3.0)
VI. Anxiety-provoking remark	-	2 (6.1)
VII. Rejected by other people/not included	2 (12.5)	2 (6.1)
VIII. Social mishap	2 (12.5)	3 (9.1)
IX. Being an outsider	-	1 (3.0)
X. Uncodeable	-	1 (3.0)
Severity	**n = 16**	**n = 32**
Mild	2 (12.5)	4 (12.5)
Considerable	1 (6.3)	10 (31.3)
Severe	8 (50.0)	13 (40.6)
Extreme	5 (31.3)	5 (15.6)
Individuals involved in the social trauma	**n = 16**	**n = 32**
One or two	4 (25.0)	7 (21.9)
Three or more	12 (75.0)	25 (78.1)

Note. One missing value.

anxiety were stronger in the clinical control group than in the control group (*ps* < .05). Strength of emotions did not differ between the SAD group and the clinical control group.

Almost everyone reported that they had experienced at least considerable distress in response to the social trauma at the time it happened (98% in the SAD group, 100% in the clinical control group and 87% in the control group, X^2 [2, N = 102] = 5.88, p = .05), however, 67% reported extreme distress in the SAD and clinical control groups, compared to 32% in the control group (X^2 [2, N = 102] = 12.17, p < .01). When they were asked about functional impairment associated with the social trauma at the time it happened, the great majority of individuals in the clinical groups reported at least considerable functional impairment (80% in both the SAD and the clinical control groups), compared to 42% in the control group (X^2 [2, N = 102] = 14.94, p = .01). Furthermore, 29% in the SAD group and 20% in the clinical control group reported extreme impairment, compared to only 8% in the control group (X^2 [2, N = 102] = 5.91, p < .05). Raters blind to group assignment conducted ratings of the severity of the social trauma (see Table 2). The groups differed with regard to severity of the social trauma (F (2, 98) = 3.4 p < .05). However, post hoc comparisons indicated that the only significant difference was trauma in the SAD group (M = 2.7, SD = 0.9) being rated higher in severity compared to trauma in the control group (M = 2.2, SD = 0.9; p < .05).

3.3. Frequency and characteristics of PTSD in response to social trauma

There were 16 (32.7%) individuals in the SAD group that met criteria for PTSD or clinically significant PTSS in response to the social trauma. Of those 16 individuals, 13 (81%) met full criteria for PTSD (meeting criteria for DSM-IV PTSD in response to social trauma) and three (19%) reported clinically significant PTSS; i.e., meeting Criteria B1 (having intrusive memories) at least two symptoms in Criterion C (persistent avoidance of stimuli associated with the event and numbing) and D (symptoms of increased arousal), meeting Criterion E (duration more than one month); and meeting Criterion F (symptoms causing clinically significant distress and/or impairment) for PTSD.

There were no clear differences in the types of experiences between individuals with SAD and PTSD/PTSS and individuals with SAD but no clinically significant PTSS associated with the experience (see Table 3), although it may be noted that certain experiences were not associated with post-traumatic symptoms, such as teasing, physical abuse, an anxiety-provoking remark and being an outsider. Individuals that reported PTSD/PTSS reported more and stronger emotions than the individuals without PTSD/PTSS, with the most frequent emotions for the PTSD/PTSS group being anxiety (93.8%, M = 7.90, SD = 2.14), shame (93.8%, M = 7.03, SD = 2.16), sadness (87.5%, M = 7.21, SD = 1.37), fear (87.5%, M = 7.32, SD = 1.92) and anger (87.5%, M = 6.29, SD = 1.82), and the most frequent emotions for the SAD group without PTSD/PTSS being anger (69.7%, M = 5.22, SD = 2.49), sadness (69.7%, M = 5.12, SD = 2.28), shame (63.6%, M = 4.67, SD = 2.61), anxiety (60.6%, M = 6.15, SD = 2.16) and disgust towards others (54.5%, M = 5.00, SD = 3.05). Sadness (t(35) = 3.09, p < .005), shame (t(34) = 2.87, p < .05), disgust towards others (t (25.8) = 3.05, p < .05), anxiety (t(33) = 2.38, p < .05), and fear (t(27) = 2.38, p < .05), were significantly stronger in the PTSD/PTSS group than in the group without PTSD/PTSS. Raters blind to group assignment rated the social trauma of individuals with PTSD/PTSS as being more severe (M = 3.0, SD = 0.9), on average, than the social trauma of individuals with SAD but without PTSD/PTSS (M = 2.43, SD = 0.9), and this difference was statistically significant (t (23.1) = 2.27, p < .05). Individuals in the SAD group with PTSD/PTSS also scored higher on all clinical variables compared to individuals in the SAD group without PTSD/PTSS, which indicates more depression and SAD symptoms in the PTSD/PTSS group, although statistically significant differences were only found on the PHQ-9 (p < .01) and SPWSS (p < .01; see Table 4).

A logistic regression analysis was conducted to predict PTSD/PTSS in response to social trauma using severity as a predictor. A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between those who suffered a social trauma and met criteria for PTSD/PTSS and those who did not meet criteria (chi square = 4.9, p < .05, df = 1). The coefficient on the severity variable had a Wald statistic equal to 4.4, p < .05. The odds ratio for severity was 1.96 (CI [1.0; 3.7]) which suggest that a unit increase on the severity scale increased the odds of receiving a diagnosis of PTSD/PTSS by 96%. Severity was also a significant predictor of receiving a SAD diagnosis in a logistic regression analysis. A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between the SAD group, the control group and the clinical control group (chi square = 4.2, p < .05, df = 1). The coefficient on the severity variable had a Wald statistic of 4.0, p < .05. The odds

Table 4
Comparison of depression and social anxiety symptoms, quality of life and impairment of functioning among individuals with SAD with or without PTSD/PTSS (n = 49) in response to social trauma.

	PTSD/PTSS[b]		
Instrument	Yes (n = 16) M (SD)	No (n = 33)	Independent two-tailed t-test
LSAS[c]	85.2 (15.9)	79.6 (18.7)	t (34) = 1.1, p = .28
PHQ-9[d]	15.3 (5.9)[a]	8.8 (5.2)[a]	t (24) = 3.6, p < .01
QOLS[e]	65.5 (13.6)[a]	62.8 (11.7)[a]	t (24) = 0.7, p = .50
SDS[f]	205.6 (40.4)[a]	180.2 (57.8)[a]	t (37) = 1.7, p = .09
SPWSS[g]	34.1 (6.3)[a]	27.1 (7.1)[a]	t (31) = 3.4, p < .01

Note. [a]One missing value. [b]PTSD/PTSS = Meeting full criteria for PTSD or having clinically significant PTSS symptoms in response to social trauma. [c]LSAS = Liebowitz Social Anxiety Scale. [d]PHQ-9 = Patient Health Questionnaire-9. [e]QOLS = Quality of Life Scale. [f]SDS = Sheehan Disability Scale. [g]SPWSS = Social Phobia Weekly Summary Scale.

ratio for severity was 1.55 with a (CI[1.0; 2.4]) suggesting that a unit increase on the severity scale increased the odds of receiving a diagnosis of SAD by 55%.

4. Discussion

Which kind of events can be defined *a priori* as being traumatic and as having the potential of leading to PTSD? We propose that rather than focusing on type of *events* (Criterion A debate) that it may be more fruitful to explore whether there are different types of perceived *threat* that play a role in the development of PTSD, but also other disorders such as SAD. We hypothesized that there are at least two types of traumatic threats, involving threat to life or social trauma, the latter involving humiliation or rejection. We explored the frequency, characteristics and severity of social trauma, reported by individuals with a primary diagnosis of SAD, individuals with a primary diagnosis of a OCD (the clinical control group), and a control group with no psychiatric disorders. Our aim was also to assess PTSD and clinically significant PTSS in response to social trauma.

4.1. Social trauma

Most participants in this study (ranging from 63% in the control group to 82% in the SAD group) reported social trauma. In other words, experiencing social trauma appears to be very common, similar to what has been found with threat to life trauma (Benjet et al., 2016). These results are in line with Erwin et al.'s study (2006) in which outpatients with SAD were compared to non-anxious controls, except that the authors of that study assessed social events (taken from the LSAS) that were stressful, but not necessarily experiences in which individuals experienced being humiliated or rejected (as in our study), which we deem necessary for being considered socially traumatic.

Previous studies of negative social events (see e.g., Boals & Schuettler, 2009; Carleton et al., 2011; Long et al., 2008) have mainly used self-report measures in which individuals choose pre-selected experiences. To our knowledge, the present study is the first in which individuals are asked an open-ended question about a socially traumatic experience characterized by humiliation or rejection. Raters blind to group assignment conducted content analyses of these answers and we then sought to determine if there were certain types of social trauma that were more common among those in the SAD group compared to the other groups. The results showed that *bullying* was common in all groups and was most frequent in the SAD group (40.8%), although rates of bullying did not differ significantly between groups. The clinical control group had more reports of mental/physical and/or sexual violence/harassment compared to the other groups. Individuals in the clinical groups were more likely to report extreme distress and greater functional impairment caused by the social trauma than individuals in the control group, and to report more emotions and stronger emotions when they brought the social trauma to conscious memory. When we analyzed independent ratings of severity of the experiences there was a significant difference in severity between the clinical groups and the control group. More specifically, severity of the social trauma predicted whether the individual was likely to be diagnosed with SAD in a logistic regression analysis. However, social trauma may be implicated in the development of other disorders as well, such as OCD, similar to what has been found in the literature with threat to life trauma (Cromer, Schmidt, & Murphy, 2007).

The findings in this study indicate that social trauma may be a major factor in the onset of SAD. The majority of participants in the SAD group (70%) reported that the social trauma happened before age of SAD onset, and almost all participants in the SAD group (85.7%) believed that the social trauma caused the onset of their social anxiety or contributed to it. These results are in line with other studies that have found negative social events to be a possible causal factor in the development of SAD (Bandelow et al., 2004; Carleton et al., 2011; Chartier, Walker, & Stein, 2001; Erwin et al., 2006; McCabe Miller, Laugesen, Antony, & Young 2010, Stein et al., 1996), in line with diatheses-stress (Rapee & Spence, 2004) and maintenance (e.g., Heimberg, Brozovich, & Rapee, 2012) models for SAD. What the current study adds to the previous literature is the hypothesis that a reaction to a socially traumatic experience may play a key role in the onset and later maintenance of the disorder for a large group of individuals with SAD.

It should be added that not all studies have found conditional events to be the most significant experiences in the onset of SAD. Hofmann et al. (1995), in a study of SAD individuals with speech fears, found that aversive speaking situations were ranked by 17% as being the most important reason for the onset of their social anxiety while 33% found panic attacks to be the most important reason. Harvey, Ehlers, & Clark, 2005 found that about 13% of individuals with SAD identified a traumatic event in a social situation as being the most important reason for the development of their social anxiety while 27% of them rated the lack of social skills as the most significant reason. These findings are not necessarily opposed to the findings in the current study and may be accounted for by different constructs across studies and the methods used to measure them. We asked individuals in a clinical interview an open-ended question about their most severe experience involving humiliation or rejection, in line with how we define the construct of social trauma. We then went on to ask them about their most severe social trauma and found that 77% of individuals with SAD reported that the experience took place over a period of time rather than being an isolated conditional event. The beliefs that individuals have about themselves likely determined how they responded to the social trauma, for example whether they believed that they had adequate skills to handle bullying.

4.2. Frequency and characteristics of PTSD in response to social trauma

Researchers have pointed out the high co-morbidity between PTSD and SAD (see e.g., McMillan & Asmundson, 2016), and revealed that co-morbid PTSD and SAD is related to decreased quality of life and greater suicidality (McMillan, Sareen, & Asmundson, 2014). The current study reveals at least one reason for this high co-morbidity. Sixteen individuals (27% of all SAD-participants but 32.7% of all those who reported social trauma) met criteria for PTSD (n = 13) or had clinically significant PTSS (n = 3) in response to social trauma. These rates of PTSD are similar to the only other study in which PTSD in response to a negative social event was assessed with a clinical interview, in which more than one-third of the participants with SAD met criteria for PTSD in response to a negative social event (Erwin et al., 2006). It can be estimated that about a third of individuals with SAD meet full criteria for PTSD or suffer from clinically significant PTSD symptoms in response to their social trauma, that in most cases will not be found to

meet Criterion A.

The results in this study showed that there were no clear differences in the types of social trauma that did or did not lead to PTSD/PTSS. *Bullying* was common among SAD individuals with or without PTSD or PTSS (43.8% vs. 39.4%), and *mental/physical and/or sexual violence/harassment* was also common in both groups (31.3% vs. 18.1%, respectively). It is worth noting that there were certain experiences (such as teasing, anxiety-provoking remarks and feeling like an outsider) that were not reported by the PTSD group and therefore may not be likely to lead to PTSD. Even though there were no clear differences in the types of experiences between the groups, the severity of the social trauma predicted who was likely to go on to develop PTSD/PTSS. In addition, symptoms of social anxiety (on the SPWSS but not the LSAS) and depression were more severe in the PTSD/PTSS group, and this group reported more emotions and stronger emotions in response to the social trauma. These results are partially in line with Carleton et al. (2011), in which participants reporting a negative social event also reported higher levels of PTSS and SAD symptoms along with higher levels of fear of negative evaluation and anxiety sensitivity.

We are accustomed to thinking of psychiatric disorders as separate, often belonging in different chapters of the DSM, as is the case with these two disorders. However, this may not be the most appropriate conceptualisation for a large group of individuals suffering from PTSD after social trauma. The results of the current study indicate that most of the individuals developed both PTSD and SAD in response to their most significant social trauma. They not only developed a clinically significant fear of negative evaluation, and increased avoidance of social situations. They also experience intrusive memories of the experience, often with intense distress and physiological symptoms, feelings of detachment, restricted range of affect, and a sense of a foreshortened future, and persistent symptoms of increased arousal, such as irritability or outburts of anger, difficulty concentrating, hypervigilance and an exaggerated startle response. These PTSD and SAD symptoms are reactions to the same social threat, and involve the same fundamental fear, with a conceptually linked set of responses, such as avoidance in many forms. We cannot be certain about causality, but a plausible hypothesis is that the experience of severe social trauma makes it more likely for an individual to develop both PTSD and SAD, as one integrated problem rather than two distinct disorders. Treatment for this condition will likely require addressing the maintaining processes of how individuals react to this experience, which has resulted in a sense of continued and constant social threat.

4.3. Study limitations and strengths

There are several limitations to the current study. We used the most recent diagnostic interview validated in Icelandic, which was based on DSM-IV. The sample size in the clinical control group was small, thereby affecting statistical power. It is important to replicate this study with a larger clinical sample, other clinical control groups and with a diagnostic interview based on DSM-5. Furthermore, future studies should systematically compare threat to life to social threat and their associations with PTSD and SAD and whether there is a shared vulnerability for both disorders (Collimore et al., 2010). Also, the validity of assessing events that happened in the (sometimes distant) past can be affected by several well-known biases in memory (see e.g. Hardt & Rutter, 2004). Longitudinal studies are needed to evaluate the effects of different types of threat on future development of PTSD, SAD and other disorders. The strengths of the study include the use of clinical interviews instead of relying solely on self-report questionnaires and the careful training and supervision of the assessment team.

4.4. Conclusion

The current study is to our knowledge the first to assess, describe and evaluate the impact of social trauma. These early findings suggest that this new construct is viable and that it may add to our understanding of how PTSD, SAD, and possibly other disorders, develop and are maintained. Our results suggest that one third of individuals with SAD may suffer from PTSD in response to social trauma and moreover, that this group reports greater anxiety and depressive symptoms. This group may be best understood as not having two distinct disorders, but rather one integrated condition which consists of a reaction to the social trauma which leads to a sense of constant and serious social threat involving recurring intrusive memories of the experience, vigilance and avoidance of social situations. These findings are compelling and raise the question of whether this PTSD group should be accounted for in future editions of nosological systems such as DSM and the ICD, and in current theoretical models of both PTSD and SAD. It is, furthermore, clear that the idea of different types of threat (threat to life, social threat and potentially more) may have to potential to bridge the gap between different literatures such as the trauma literature, bullying and peer victimization and adverse childhood experiences. There may be therapeutic implications as well. There are already fascinating developments in treating intrusive images, that are, in many cases, based on social trauma, with imagery rescripting (Norton & Abbott, 2016; Romano, Mosvocitch, Huppert, Reimer, & Mosvocitch, 2020; Wild & Clark, 2011). It would be interesting to explore if other empirically validated interventions from the treatment of PTSD may be effective for individuals that suffer from PTSD in response to social trauma.

Declaration of Competing Interest

None.

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Review Paper

SOCIAL TRAUMA AND EMOTIONAL ATTACHMENT

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Abstract. *Trauma can be described as an injury that leaves permanent consequences, latent traces that can be activated in periods of crisis (Krstić, 2009). In the second part of the 20th century, the term trauma started being used ever more outside the medical and psychiatric context and entering the domain of social sciences (Sztompka, 2009). In the scope of this, one way the concept of trauma is used is in confronting negative and dysfunctional consequences that social change can leave in its wake. Various authors have studied social and psychological consequences of social changes on individuals and society. In this way, they opened the road to recognizing a new meaning of trauma, which they titled cultural or social trauma. It is known that the theory of emotional attachment states that in crisis or traumatic situations, members of a family group feel insecure, that risks in the environment can lead to lowered responsiveness of the parents, but it is less widely known if unresolved traumatic experiences of parents can be transferred to children and their later emotional attachment patterns. There is particularly little knowledge on whether significant social changes leave consequences on emotional lives of individuals and the emotional lives of their children. In this paper, we try to make a brief review of the literature on the topic, and summarize the theoretical and partly empirical knowledge in the area that exists so far.*

Key words: Social trauma, psychological trauma, attachment.

INTRODUCTION

Trauma can be described as an injury that leaves permanent consequences, latent traces, that can be activated in periods of crisis (Krstić, 2009). In the second part of the 20th century, the term trauma started being used ever more outside the medical and psychiatric context and entering the domain of social sciences (Sztompka, 2009). In this area the concept of psychological trauma gained widespread use in the last decades.

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Psychological trauma can be defines as a set of responses to extraordinary, emotionally overwhelming and personally uncontrollable life events (e.g. Goodman, Saxe, and Harvey 1991). Similar to this, a traumatic event would be an event that triggered the set of responses representing psychological trauma.

1. SOCIAL TRAUMA

According to the dialectical approach, the personality of an individual is defined by an interaction of its biological, hereditary factors and factors of the environment (Wang 2014). A pronounced position in this second group of factors has the influence of social, political, institutional and cultural reality on the behavior of an individual and his personal experience (de Tubert 2006). Some social changes can represent a trauma for an individual (Sztompka 2000). Such social changes are those that have the following properties: they are sudden and fast, deep, essential, radical and all-encompassing, they are externally enforced, meaning that they come from some other party and are not caused by the individual, or were not caused intentionally by the individual, and are perceived as unexpected, unpredictable and repulsive. Such changes include, among other things, forced migrations, ethnic cleansing, genocide, mass murders, a lost war (Volkan 2009, 2001). These events may produce trauma, but need not.

Taking a constructivist perspective, Alexander (Alexander et al. 2004) writes about cultural trauma, as an experience of the members of a community that they have been subjected to a horrible event that left indellible marks on their group consciousness, making their feeling permanent, and essentially and irreversibly changing their identity. Certain events gain the meaning of trauma based on the way they are represented by social entities (e.g. mass media, bureaucracy, science and law) and on the selection of this information by entities with power in the society. Information that leads to trauma contains information about desecration of important values, about a destructive social process or processes, about infliction of injuries upon the community and about demands for emotional, institutional and symbolical reparation and reconstruction (Alexander et al. 2004).

Alexander (Alexander et al. 2004) states that events considered to be causes of trauma need not be traumatic in themselves. According to this author, trauma is attributed to "real or imagined phenomena, not because of their real harmfulness and suddenness, but because they are believed to have harmful influence on the collective identity" (Alexander et al. 2004). An event can be perceived as traumatic while it is happening; before it happens; after it happens, through reconstruction in memory; but trauma perception can also be a consequence of an imagined event, an event that never happened.

Unlike psychological or physical trauma, which necessarily include an injury and experience of great emotional pain suffered by the individual, cultural trauma refers to a dramatic loss of identity and social structure, and influences a group of people that have achieved a certain level of cohesion (Eyerman 2001). Due to this, this type of trauma need not be directly experienced by the individual or all of the members of a community. Although an event that would be a significant cause is necessary, it is important that traumatic meaning is established and accepted, and this is a process that requires time. According to Neil, a trauma like this can have permanent consequences, that cannot easily be dismissed, and events connected to it will replay again and again in individual consciousness thus becoming rooted in "collective memory" (Eyerman 2001).

This collective memory is defined as memories from the collective past, which are retained with members of the groups and are propagated forward in two possible ways. It can be in a continual process that could be called "public commemoration", in which rituals are used to establish a collective past or through discourses specific for a certain group or collective (Eyerman 2001). This socially constructed and historically rooted collective memory has a function of creating social solidarity in the present.

In the discourse on cultural trauma, it is understood as a dynamic process, a process that develops over time, hence authors in the area propose the existence of traumatic sequences or phases through which social trauma and its consequences develop (Sztompka 2000). According to Sztompka, trauma includes six phases (Sztompka 2000). The first phase includes the existence of structural and cultural bases for the appearance of trauma. Conditions favorable for the development of trauma are those that lead to destabilization of basic values, beliefs and norms. Various factors can lead to these conditions: conflicts and separations within a previously singular culture; a conflict between the traditional and novel cultural norms, as in migrant communities for example; constant confrontations of cultures in multicultural communities; technological, economic, political or any other changes that, among other things, require a change of traditional behavior patterns and a reevaluation of beliefs. For cultural trauma to appear, the emergent lack of adaptation must be perceived as a problem, as something that is painful, and so requires an intervention. This intervention then happens in subsequent phases.

The second phase is the existence of a potentially traumatic event. Cultural destabilization makes people anxious and sensitive to the influence of aversive events (unemployment, inflation, crime rate rise, etc.), in this way making them vulnerable to the development of trauma symptoms. The third phase refers to a certain interpretation of the event, which also depends on the narrative created in the culture of the community or that stems from the cultural heritage. This cultural relativization is so powerful that these interpretations can not only make some real events traumatic, but can also make objectively nonexistent events be felt as traumatic. It can also make real events with real, adverse consequences be perceived as nontraumatic. The fourth phase consists of trauma symptoms, and the fifth consists of post-traumatic adaptation. How will a person respond to trauma depends on many factors like education, social support, attitudes, etc. Together with the increase in the education level, sensitivity to cultural trauma also rises, as does the range of functional strategies for coping with that trauma. Available social support and attitudes that imply tolerance rather than ethnocentrism and dogmatism also have a positive effect on post-traumatic adaptation. The last phase is the overcoming of trauma, which, in the case when strategies used to overcome trauma are not constructive, can also lead to a new cycle of traumatic sequences (Sztompka 2000).

2. Psychoanalytical Understanding of Social Trauma

Perceiving a social system as an object, psychoanalysts consider this relationship between an individual and its social system to be similar to the relationship between a child and a mother (de Tubert 2006). This similarity manifests itself in the function of containing, about which Bion writes (de Tubert 2006). As a mother is a container for physiological and emotional needs of a child, so should society be sensitive to the needs and sufferings of an individual and group, ready to recognize their existence and solve

them through taking appropriate actions. If the social system does not perform this function, trauma appears as the result and it can be equally important as the one experienced by a child in a relationship with an unresponsive mother.

Hernandez de Tubert (de Tubert 2006) lists three types of this failure:

1. When the social system fails to contain, protect, provide aid and compassion to victims of poverty, disease, natural catastrophes, social upheavals, economic crises or wars;
2. When the social system fails to protect individuals in case of an undisputed attack on a certain subpopulation (on those in power, on the privileged or on minority groups) or on the majority of the population, like in cases of social repression, wars, racism, genocide or purges;
3. When the social system publicly supports, and clandestinely brakes current social values and laws, as in cases of corruption, fraud, lying.

If the social system negates the suffering of a victim, be it an individual or a group, and if it also, unjustly, considers the victim responsible for the suffering and events leading to it, trauma becomes even more complex (de Tubert 2006). Even if the social system is unable to provide aid, it is important that it recognizes the existence of the crime and the suffering of the victim. If justice is satisfied quickly enough, the victims will regain their hope in the survival of the community and in humanity. On the other hand, if an individual recognizes that it has been cheated by the social system, it will lose trust in it. The perception that a government does not perform its function, that it disrespects the law, or works against the community or a part of the community, produces suffering that is extremely intensive and can even lead to individuals negating that traumatic events have taken place at all. According to the psychoanalytic standpoint, intense anxiety and perception, as part of a traumatic event, are not a consequence of the event itself, but of its repression (Alexander et al. 2004). When deception becomes completely obvious, its victims can become depressive, apathic, desperate, unless they find a way to express their dissatisfaction immediately (de Tubert 2006). As individuals in power are rarely ready to recognize and accept their own errors, social trauma becomes even more complex.

Eyerman (Eyerman 2001) points out that, according to the psychoanalytic theory of trauma, it is not the traumatic event itself that produces the psychological consequences of trauma, but memories of that event. According to this explanation, after a traumatic experience comes a period of latency between the event itself and the experience of trauma, that is characteristic of forgetting. However, trauma, as a reflexive process, connects the past through representations and through imagination (Eyerman 2001). This can lead to disturbances in the formation of identity, where the person attributes a disproportionate importance to certain participants in the traumatic events, either victims or perpetrators. This further leads to the person becoming preoccupied with them and causes them to compulsively repeat that picture. Resolution of trauma can thus be achieved through reconstructing memories of the event. Psychoanalytically oriented authors (Aarelaid-Tart 2006) are of the opinion that social trauma exists as an unconscious emotional fear, negating the existence of collective effort to attribute responsibility to the traumatic social event that once happened. According to them, trauma will be resolved when memory about the traumatic events is “repaired” and when things “return to their rightful places” in our collective consciousness. Eyerman (Eyerman 2001) states that with social trauma, having in mind the importance of imagination and mediation, one should not consider the traumatic event itself, but the traumatic influence. Cultural trauma is also a consequence of an event

or series of events, but these need not be personally experienced. These experiences are mainly transferred through the media, and this includes a spatial and temporal distance between the traumatic event and experience. Conveyance through the media always includes selective presentation and construction of information, and the decision of someone else on the nature of the presented content. Due to this, the mentioned author states that social trauma mainly includes the meaning of struggle, suffering, events connected to the source of pain, sacrifice and a sense of responsibility.

3. Consequences of Social Trauma

Social and cultural traumas, like the ones caused by subjugation of indigenous peoples, are common when nations fight for sovereignty, when the population strives for equality or when a civilization strives for power (Famula 2007). Leaders of the society promise that similar traumas will never happen again and emphasize the need for traumas like this and events that caused them to be forgiven and forgotten as unhappy parts of history. In doing this, they do not understand or ignore the consequences of social trauma, but, as is the case with individual victims of trauma, symptoms remain with certain social groups as negative consequences of the so-called "neglected trauma" (Famula 2007). Societies influenced by a collective traumatic event develop a similar worldview, collective consciousness, that determines the way they will try to heal themselves from these traumas, but also the way in which they will face future conflicts. According to this author, many psychologists believe that traumatic events often generate future traumatic events. This happens because collective consciousness of the traumatized population transforms itself so that it accepts trauma as natural behavior. The author states that similarly to the way traumatized individuals, who were abused in childhood, are more prone to be violent in adulthood because they were unable to heal themselves from trauma, so will populations that were hurt by trauma connected to violence also react violently. Unresolved social traumas leave only negative consequences not only on the society, but also on individuals and their physical, cognitive, behavioral and emotional aspects. Regardless of whether individuals develop less pronounced or more pronounced trauma related disorders, a traumatic event in itself leaves deeply rooted, harmful results if these are not worked on (Famula 2007).

According to Volkan (Volkan 2009) the specificity of trauma resulting from war or states similar to war or from an existing destructive political system is that the enemy is recognizable and that he inflicts pain and suffering on his victims on purpose. Such trauma influences a member of a society differently than the trauma caused by natural catastrophes and accidents, in which causes are seen in destiny or "god's will"; or traumas like the loss of a leader in which the members of society blame individuals or the government for negligence. After states of war, when a society becomes a "purposeful goal of an aggression" victims must confront five different psychological phenomena that are related between themselves:

1. Joint feelings of shame, humiliation, dehumanization and guilt.
2. Joint lack of the ability to be assertive.
3. Joint identification with tyrants (if the influence of usurpers, who restrain activities and freedom of victims lasts long enough, it becomes internalized as a joint "external superego").
4. Joint mourning of loses.
5. Transgenerational transfer of trauma.

These phenomena permeate the lives of members of the endangered society and influence the appearance of problems such as poverty, lack of experience of a democratic way of life, corruption in the new political system, international manipulations (Volkan 2009).

4. Affective Attachment

According to the attachment theory, interpersonal experiences with one's significant other, one that emerged as the dominant figure of affective attachment in the early years of one's life, are important for social and emotional development of personality i.e. the development of capacities for establishing behavioral and affective regulation (Stefanović-Stanojević 2010). These emotional experiences lead to the formation of certain beliefs about oneself and significant others, of internal working models and corresponding styles of affective attachment: secure, avoidant, preoccupied or disorganized.

Internal working models are acquired in early childhood and potentially influence future behavior, expectations and feelings (Stefanović-Stanojević 2005). A working model of the self represents a collection of expectations and beliefs of a child about itself, which it acquires based on the quality of its parents' relationship towards it. The basic property of this working model is the extent to which he or she is acceptable or unacceptable to figures of attachment. The model of others is a collection of beliefs and expectations in relation to others, based on the perceived behavior of parents. The main property of this model is the expectation about who the figures the person attaches to are, where they can be found, and how they are expected to respond.

Properties of the four affective attachment styles are the following (Bartholomew and Horowitz 1991):

- The secure attachment style includes low anxiety and low avoidance. Persons with this style of attachment enter relationships with others with trust and openness. Children with this style grow up to be self-confident and autonomous persons, and their capacities to deal with difficulties of life are great and unburdened with traces of childhood. A good picture of oneself and others gives a chance to persons of this type to build authentic and open partner relationships.
- The avoidant attachment style includes low anxiety and high avoidance. These persons avoid closeness because they have negative expectations of others, but manage to maintain their feeling of self-worth through defensive negation of value of close relationships and attachment. Children with this style of affective attachment grow up into rigid, defensively focused personalities. View of others is colored by distrust. They enter partner relationships rarely and without expectations, hence their partner relations are frequent, shallow and short.
- The preoccupied attachment style involves high anxiety and low avoidance. Children with this attachment style grow up into persons that are blocked by anger, unresolved conflicts, prone to exaggerated involvement in affective relationships. Contaminated by their own expectations and disappointments they have no energy to adequately assess reality. When establishing relationships, these persons start from a position of lower value and attempt to secure unconditional acceptance from others. They are prone to symbiotic relationships and dramatization.

- The disorganized affective attachment style includes high anxiety and high avoidance. Persons having this style of attachment are dependent on the acceptance of others and have negative expectations of others. This leads to the avoidance of intimacy, in order to avoid the pain of loss or rejection. Children like these grow up into people prone to excessive control of others, who attempt to secure themselves from irrational fears. Their relationships are rare and chaotic.

5. Social Trauma, Parent-Child Relationship, Later Relationships with Others

Internal working models may remain stable, reflecting precisely secure and insecure relationships, but an affective change in the working models is also possible (Stefanović-Stanojević 2005). Parents who used to be adequate may change for numerous reasons (disease, loss of job, war, etc.), may start behaving aggressively, may threaten to commit suicide. In every case, a child's previous trust in them will be shaken and will lead to the reconstruction of the model of a parent.

Liotti (Liotti 2004) points to a significant relation between unresolved traumatic memories of the parents and the disorganized attachment of children, which can be primarily explained by inherited nature of interpersonal affective relations. According to this author, the theory of affective attachment states that people, like other mammals, are born with an evolutionary tendency to seek protection from members of their social group whenever there is danger and when they suffer from physical and emotional stress. This system of seeking protection i.e. attachment remains operational through person's entire life and is activated strongly after experiencing fear or physical or psychological pain. On the other hand, an inborn tendency to provide protection to one's closest persons enables this connection of seeking and providing to function smoothly. However, in parents that have experienced some sort of trauma, unresolved traumatic memories may "emerge to the surface", leading to psychological pain associated with these traumatic memories, that influences their affective system and their protection providing system. Activation of systems of affective attachment in parents and the lack of a soothing response from their significant others can lead to emotions of rage and fear in the parent. This disturbs their responses to the attachment demands of their children. The combination of rage and fear that comes into existence in this way leads to fear in children and initiates their defensive escape reaction. After this, the increased distance from the parents additionally activates their system of affective attachment that is independent of parental behavior. This makes the parent figure, one that leads to the disorganized behavior, be seen as both a source of fear and a solution (Liotti 2004). Liotti states that there is no unified and coherent way of behavior in a child's experience that is able to overcome these contradictions. Mihić cites Belski (Mihić, Zotović, and Petrović 2007) who states that stressful experiences in a developmental environment lower capacities for the sensitivity and responsivness of caregivers, thus increasing the risk of depression and other problems that reflect on the fulfillment of the role of the caregiver and the quality of the relationship with the child. Due to lowered sensitivity of caregivers, a child has higher chances of developing some insecure attachment styles.

In her study Wiese (Batista-Pinto Wiese 2010) used the example of migration to study the influence of social trauma on the psychological states of individuals. Migrations have a deep influence on family history and comprise both the culturological frame of the

family and the internal psychological frame of the individual. In other words, this social change influences both the psychological and cultural identity of the parents, who convey this to their children (Batista-Pinto Wiese 2010). The parent exposed to a new culture, in the process of acculturation, can lose trust in the outside, social and cultural world. They may come to feel that the outside world is no longer safe, because they left the safety of their home. Out of this, a state of confusion about the surrounding world can also develop. Parents can transfer such a perception to their children, thus creating feelings of uncertainty and insecurity in them. Traumatized parents violate their affective basis with the child, are not able to recognize its needs, act anxiously and fearfully, thus leaving consequences for the affective development of the child. The mentioned author concludes that social changes can represent a great vulnerability factor for the parent-child relationship and emotional development of children, one that can, unfortunately, have consequences on the child's later life and its social relations.

While studying the influence of social trauma on the lives of new generations of indigenous peoples in America, Kathleen Brown-Rice (Brown-Rice 2013) uses the concept of historical trauma, that she defines as the heritage of chronic trauma and unresolved pain among generations. New generations of these populations suffer from physical, emotional and social consequences of past traumas. This author emphasizes that this does not enable overall generalizations, but can explain some discrepancies in disease rates, abuse and neglect, poverty, family disorders in new generations of indigenous peoples of America. The reasons for these sufferings are multifold. Repeated thoughts about suffered historical losses lead to stress with which individuals have to cope, and perceptions of the new generations that they are discriminated can even lead to serious health problems.

Historical trauma of the parents is transferred to new generations over the identification of children with the suffering of their parents, where children, by indirect learning, acquire symptoms of historical loses. Another method of transfer is over the communication style with the parents, through stories about traumatic experience, descriptions of parent's traumas, and generally over parenting style and affective relations with the children. (Brown-Rice 2013). This last method of trauma transfer is explained by the fact that problems with trust and intimacy appear in the parents, as a consequence of their experience with being victims of a traumatic event. This influences the development of their affective attachment to the child. Some people who were subjected to violence, enter "the circle of violence" with their children (Brown-Rice 2013). This compromises family stability, and develops a risk that unhealthy parenting styles and patterns of social relations will appear in subsequent generations.

Haskell and Randall (Haskell and Randall 2009) write about social, historical trauma as a historical injury, which they define as "collective complex trauma inflicted on a group of people who share ethnic, national or religious denomination. It represents the heritage of numerous traumatic events which the community experiences through generations and encompasses psychological and social responses to such events" (Haskell and Randall 2009). It can also be characterized as a collective emotional injury that appears during one's lifetime and through generations (Haskell and Randall 2009). Studying the influence of trauma on the lives of the Aboriginal Peoples of Canada, these two authors point to the conclusion that due to a feeling of lowered security and freedom, feeling of guilt, shame and inadequacy, caused by this trauma, an altered relationship toward oneself and others may appear, and these changes can be interpreted in the frames of theory of affective attachment. Parental responses to big traumatic events, including reactions to traumas of

their personal histories can play a significant role in the mental health of their children. Children whose parents are traumatized, depressive or suffering from chronic stress may often be neglected. Traumatized parents are not capable of reliably comforting and soothing their children, due to their impoverished or unrecognized emotional states. Feelings of desperation and fear also appear, leading to a reduced ability to give an appropriate emotional response. What might be the most important, according to the mentioned authors, is that children, who were unable to establish a secure style of attachment due to these reasons, may, later in life, be less capable to utilize relations with close persons as sources of security and comfort. This also refers to compromised intimate relationships with partners, their own children and other family members.

Haskell and Randall, using the example of the Aboriginal Peoples of Canada, state that stress in children is caused not only by traumatized parents, but also by nonaccepting outside environment, teachers and peers, who play an important role in the lives of the children. More specifically, in this population, a correlation was found between the rate of child abuse and "intergenerational trauma", that represents the result of the parents' and grandparents' attempts to confront the outside world, isolation, poverty, school and other institutions (Haskell and Randall 2009).

When talking about the territory of the former Yugoslavia, although there are numerous studies dealing with the individual mental health of people personally victimized by war (e.g. refugees) (Porter and Haslam 2005; Fazel et al. 2012; Saadi, Bond, and Percac-Lima 2015; Steel et al. 2011), there are relatively few studies treating the issue from the social trauma perspective. It can be stated that social changes brought by the Yugoslav wars of the 1990s had great traumatic potential. In the situation of war and dissolution of the country, in which the population of the Socialist Federal Republic of Yugoslavia found itself, emotional suffering was very intensive. Feeling that the government, that was trusted, could not find a solution and avoid war, led to the increase of anxiety of the population, and the experience of a sudden change and injury of the collective identity created a cultural trauma that manifested itself as a state of shock and intense fear. In the countries of the former Yugoslavia, moral lessons of this cultural trauma have been objectified through various monuments, museums, holy places and customs, that enable the new national identity, resulting from the experienced trauma to remain deeply rooted in the community (Alexander et al. 2004). The capability of the social system to contain the emotional needs of war victims was brought into question. Also, it is questionable how much could persons in a state of extreme anxiety be a source of security for their children. A question arises of which style of affective attachment could be characteristic for these children and would it manifest itself in their partner relationships? A study conducted by Tatjana Stefanović-Stanojević (Stefanović-Stanojević 2007) in Niš (Serbia), pointed to the increase in the disorganized style of affective attachment, a style that is characteristic for children who perceive their parents as frightened or are frightened of their parents themselves. On a sample of students of service profession in Slovenia, Croatia, Serbia, Macedonia and the two entities of Bosnia and Hercegovina, Hedrih, Pedović and Pejičić (Hedrih, Pedović, & Pejičić, in press) report participants from Slovenia having the lowest average scores on Avoidance and the highest average scores on Anxiety. They also report that their samples differ in Anxiety, where, on the one hand we have Slovenia and Croatia with relatively higher levels of Anxiety compared to the samples from other countries included in the study. These differences were interestingly less related to the exposure of the country to war (according to indicators used in the study) and more to the differences in religion and economy.

CONCLUSION

Social trauma is a relatively new concept of psychological trauma in literature, although its consequences have been present for long time and are deeply rooted in many societies and cultures. Through an overview of the available literature it can be concluded that social trauma can have consequences both on society as a whole and on individuals and their cognitive, emotional, behavioral and interpersonal life. Serbian literature currently has very few references on social trauma and its consequences although the history of our country shows a very strong need for this. It is clear that social changes brought by the Yugoslav wars of the 1990s left consequences for both the society and individual personalities that were caused by intense emotional sufferings. In spite of this, there are a few research studies done on the topic of social trauma, be they theoretical or empirical. Is it because time is needed to accept the new concept or were these events forgotten? Or is the reason the fact that consequences of this trauma are deep and permanent, so the concept of avoiding the "touching of old wounds" has been transferred to the new generation? If this is the case, that is yet another indicator of the importance of studying social trauma.

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SOCIJALNA TRAUMA I AFEKTIVNA VEZANOST

Trauma se može okarakteristati kao povreda koja ostavlja trajne posledice, latentne tragove, koji u kriznim periodima ličnosti mogu biti aktivirani (Krstić, 2009). U drugoj polovini 20. veka izraz trauma počeo je sve više da se koristi i van medicinckog i psihijatrijskog konteksta, i da zalazi u domen socijalnih nauka (Sztompka, 2009). U okviru toga, jedan vid upotrebe koncepta traume je i suočavanje sa negativnim i disfunkcionalnim posledicama koje društvene promene mogu ostaviti za sobom. Različiti autori su proučavali socijalne i psihološke posledice društvenih promena na pojedince i društvo. Time je otvoren put ka sagledavanju novog značenja traume, koja je nazvana kulturna ili socijalna trauma. Poznato je da teorija afektivne vezanosti ukazuje na to da se u kriznim ili traumatskim situacijama članovi porodice osećaju nesigurno, da rizici u okruženju mogu uticati na smanjenu responzivnost roditelja, ali je manje poznato da li se nerazrešena traumatska iskustva roditelja prenose na decu i njihove kasnije afektivne obrasce. Naročito je malo saznanja o tome da li značajne socijalne promene, ostavljaju posledice po pojedince, njihov, i emocionalni život njihove dece. U ovom radu pokušali smo da napravimo kratak pregled postojeće literature na ovu temu i sumiramo postojeća teorijska i delom empirijska znanja koja za sada postoje na ovu temu.

Ključne reči: *socijalna trauma, psihološka trauma, afektivno vezivanje*.

Frequent loss of heterozygosity in CRISPR-Cas9–edited early human embryos

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CRISPR-Cas9 genome editing is a promising technique for clinical applications, such as the correction of disease-associated alleles in somatic cells. The use of this approach has also been discussed in the context of heritable editing of the human germ line. However, studies assessing gene correction in early human embryos report low efficiency of mutation repair, high rates of mosaicism, and the possibility of unintended editing outcomes that may have pathologic consequences. We developed computational pipelines to assess single-cell genomics and transcriptomics datasets from OCT4 (*POU5F1*) CRISPR-Cas9–targeted and control human preimplantation embryos. This allowed us to evaluate on-target mutations that would be missed by more conventional genotyping techniques. We observed loss of heterozygosity in edited cells that spanned regions beyond the *POU5F1* on-target locus, as well as segmental loss and gain of chromosome 6, on which the *POU5F1* gene is located. Unintended genome editing outcomes were present in ∼16% of the human embryo cells analyzed and spanned 4–20 kb. Our observations are consistent with recent findings indicating complexity at on-target sites following CRISPR-Cas9 genome editing. Our work underscores the importance of further basic research to assess the safety of genome editing techniques in human embryos, which will inform debates about the potential clinical use of this technology.

genome editing | CRISPR-Cas9 | human embryo | segmental aneuploidy | loss of heterozygosity

Clustered regularly interspaced short palindromic repeat (CRISPR)-CRISPR associated 9 (Cas9) genome editing is not only an indispensable molecular biology technique (1) but also has enormous therapeutic potential as a tool to correct disease-causing mutations (2). Genome editing of human embryos or germ cells to produce heritable changes has the potential to reduce the burden of genetic disease, and its use in this context is currently a topic of international discussions centered around ethics, safety, and efficiency (3, 4).

Several groups have conducted studies to assess the feasibility of gene correction in early human embryos (5–7), and they all encountered low efficiency of gene repair and high levels of mosaicism (i.e., embryos with corrected as well as mutant uncorrected blastomeres or blastomeres with unintended insertion/deletion mutations), which are unacceptable outcomes for clinical applications. In 2017, Ma et al. set out to correct a 4-bp pathogenic heterozygous deletion in the *MYBPC3* gene using the CRISPR-Cas9 system (8). The experimental strategy involved coinjection of Cas9 protein, a single guide RNA (sgRNA) that specifically targeted the *MYBPC3* mutation and a repair template into either fertilized eggs (zygotes) or oocytes, coincident with intracytoplasmic sperm injection. Analysis of the resulting embryos revealed a higher than expected incidence, with respect to controls, of samples where only WT copies of the gene were detectable (8). Intriguingly, the excess of apparently uniformly homozygous WT embryos in both cases was not associated with use of the provided repair template for gene correction. Instead, the authors suggest that in edited embryos the WT maternal allele served as a template for the high-fidelity homology directed repair (HDR) pathway to repair the double-strand lesion caused by the Cas9 protein in the paternal allele (8).

Ma and coworkers' interpretation of gene editing by interhomolog homologous recombination (IH-HR) in the early human embryo has been met with skepticism because alternative explanations can account for the observed results (9–11). One of these is that the CRISPR-Cas9 system can induce large deletions and complex genomic rearrangements with pathogenic potential at the on-target site (9, 10, 12–14). These events can be overlooked because genotyping of the targeted genomic locus often involves the amplification of a small PCR fragment centered around the on-target cut site. CRISPR-Cas9–induced deletions larger than these fragments in either direction would eliminate one or both PCR primer annealing sites. This, in turn, can lead to amplification of only one allele, giving the false impression that targeting was unsuccessful or that there is a single homozygous event at the on-target site (9, 10, 15). Loss of heterozygosity (LOH) can also be the result of more complex genomic rearrangements like inversions, large insertions, translocations, chromosome loss, and even IH-HR with crossover, whereby a large piece of one parental allele is integrated by the other parental chromosome at the on-target cut site (15).

The reported frequencies of unintended CRISPR-Cas9 on-target damage are not negligible. Adikusama et al. targeted six genes in a total of 127 early mouse embryos and detected large deletions (between 100 bp and 2.3 kb) in 45% of their samples using long-range PCR (10). Of note, large deletions were generally more prevalent when they targeted intronic regions (>70%) than

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when they targeted exons (20%). Consistent with this, Kosicki et al. observed large deletions (up to 6 kb) and other complex genomic lesions at frequencies of 5–20% of their clones after targeting the *PigA* and *Cd9* loci in two mouse embryonic stem cell (mESC) lines and primary mouse cells from the bone marrow, as well as the *PIGA* gene in immortalized human female retinal pigment epithelial cells (12). Moreover, Owens et al. used CRISPR-Cas9 with two sgRNAs to delete 100–150 bp in the *Runx1* locus of mESCs and found that 23% of their clones had large deletions (up to 2 kb) that escaped genotyping by short-range PCR (giving the impression that they were homozygous WT clones), with these complex on-target events becoming evident using long-range PCR (14). Similar damage and frequencies were also observed with the $Cas9^{D10A}$ nickase (14). More dramatic events were identified by Cullot et al., who CRISPR-targeted the *UROS* locus in HEK293T and K562 cells for HDR correction with a repair template (13). Their experiments suggest that CRISPR-Cas9 can induce megabase scale chromosomal truncations (~10% increase compared to controls). However, these cells have abnormal karyotypes and are p53 deficient, which may impact on their DNA damage repair machinery. In fact, they did not see the same effect in human foreskin fibroblasts but knocking out of *TP53* in these primary cells increased the large deletion events by 10-fold (13). More recently, Przewrocka et al. observed a 6% incidence of chromosome arm truncations when targeting *ZNF516* in p53-competent HCT116 cancer cell lines with CRISPR-Cas9, suggesting that TP53 expression alone may not predict predisposition of cells to large on-target mutations (16).

Our laboratory used CRISPR-Cas9 genome editing to investigate the function of the pluripotency factor OCT4 (encoded by the *POU5F1* gene on the p-arm of chromosome 6) during human preimplantation development (17). We generated a number of single-cell amplified genomic DNA (gDNA) samples for genotyping and confirmed on-target genome editing in all microinjected embryos and a stereotypic insertion/deletion (indel) pattern of mutations with the majority of samples exhibiting a 2-bp deletion (17). However, we noted that in five of the samples analyzed, the genotype could not be determined because of failures to PCR amplify the on-target genomic fragment. This finding suggested complexity at the on-target region that may have abolished one or both PCR primer binding sites. Moreover, we identified that 57 of the 137 successfully genotyped samples (42%) exhibited a homozygous WT genotype based on PCR amplification of a short genomic fragment (17). We originally interpreted these cases as unsuccessful targeting events, however, given the frequencies of the on-target complexities noted above, we speculated that our previous methods may have missed more complex on-target events.

Here, we have developed computational pipelines to analyze single-cell low-pass whole genome sequencing (WGS), transcriptome, and deep-amplicon sequencing data to assess the prevalence of LOH events in the context of CRISPR-Cas9–edited early human embryos. Our results indicate that LOH events on chromosome 6, including chromosomal and segmental copy number abnormalities, are more prevalent in OCT4-edited embryos compared to both Cas9-injected and Cas9-uninjected controls, adding to the growing body of literature reporting that CRISPR-Cas9 genome editing can cause unintended on-target damage. Altogether, this underscores the importance of evaluating genome-edited samples for a diversity of mutations, including large-scale deletions, complex rearrangements, and cytogenetic abnormalities, undetectable with methods that have routinely been used to interrogate targeted sites in previous studies. Our results sound a note of caution for the potential use of the CRISPR-Cas9 genome editing technology described here for reproductive purposes.

Results

Segmental Losses and Gains at a CRISPR-Cas9 On-Target Site Identified by Cytogenetics Analysis. In our previous study (17), in vitro fertilized zygotes donated as surplus to infertility treatment were microinjected with either an sgRNA-Cas9 ribonucleoprotein complex to target *POU5F1* or Cas9 protein alone as a control and cultured for up to 6 d (targeted and control samples, respectively). We collected a single cell or a cluster of 2–5 cells from these embryos for cytogenetic, genotyping, or transcriptomic analysis (*SI Appendix*, Fig. S1).

To determine whether CRISPR-Cas9 genome editing leads to complex on-target DNA damage that would have been missed by our previous targeted amplicon sequencing, we reanalyzed low-pass WGS data following whole-genome amplification (WGA) from 23 OCT4-targeted and 8 Cas9 control samples (*SI Appendix*, Table S1). Given the small sample size, we microinjected additional human embryos with a ribonucleoprotein complex to target *POU5F1*, or the Cas9 enzyme as a control, followed by single-cell WGA and low-pass WGS, as before (17). Here and below, the prefix that distinguishes the processing steps is followed by an embryo number and a cell number. The samples used for low-pass WGS were identified with prefix L_ (*SI Appendix*, Fig. S1). The letter C precedes the embryo number to distinguish CRISPR-Cas9 targeted from control samples (*SI Appendix*, Fig. S1). Low-pass WGS data were used to generate copy number profiles for each sample to investigate the presence of abnormalities with a focus on chromosome 6 (Fig. 1*A*). As an additional comparison, we performed single-cell WGA and low-pass WGS of uninjected control embryos and distinguish these samples with a letter U preceding the embryo number (*SI Appendix*, Fig. S1)

After preprocessing and quality control, we examined the profiles of 65 samples (25 CRISPR-Cas9 targeted, 16 Cas9 controls, and 24 uninjected controls; *SI Appendix*, Fig. S2 *A* and *B*). Fifty-six samples exhibited two copies of chromosome 6 with no obvious cytogenetic abnormalities (Fig. 1 *C* and *D* and *SI Appendix*, Figs. S3–S5). Seventeen of the CRISPR-Cas9–targeted samples, or 68%, had no evidence of abnormalities on chromosome 6. By contrast, we observed that 8 of the 25 targeted samples had evidence of abnormalities on chromosome 6. Four targeted samples presented a segmental loss or gain that was directly adjacent to or within the *POU5F1* locus on the p-arm of chromosome 6 (Fig. 1 *B* and *D* and *SI Appendix*, Fig. S5). Interestingly, this included two cells from the same embryo where one exhibited a segmental gain and the other a reciprocal loss extending from 6p21.3 to the end of 6p (Fig. 1*B*). Altogether, segmental abnormalities were detected in 16% of the total number of CRISPR-Cas9–targeted samples that were evaluated. We also observed that four targeted samples had evidence of a whole gain of chromosome 6 (Fig. 1 *B* and *D* and *SI Appendix*, Fig. S5), which also represents 16% of the targeted samples examined. Conversely, a single Cas9 control sample (6.25%) had evidence of a segmental gain on the q-arm of chromosome 6, which was at a site distinct from the *POU5F1* locus (*SI Appendix*, Fig. S4). The uninjected controls did not display any chromosomal abnormalities (Fig. 1*D* and *SI Appendix*, Fig. S3).

The number of segmental and whole-chromosome abnormalities observed in the CRISPR-Cas9–targeted human cells was significantly different from that in the Cas9 ($P = 0.0144$, two-tailed Fisher's test) and uninjected control ($P = 0.0040$, two-tailed Fisher's test) samples (Fig. 1*D*). Moreover, this significant difference can be attributed to the observed segmental abnormalities on 6p, because excluding them from the comparison results in a negligible difference in whole-chromosome abnormalities between targeted and Cas9 control samples ($P = 0.1429$, two-tailed Fisher's test). This conclusion is further supported by the fact that none of the targeted samples show segmental losses or gains on the p-arm of chromosomes 5 and 7, the closest in

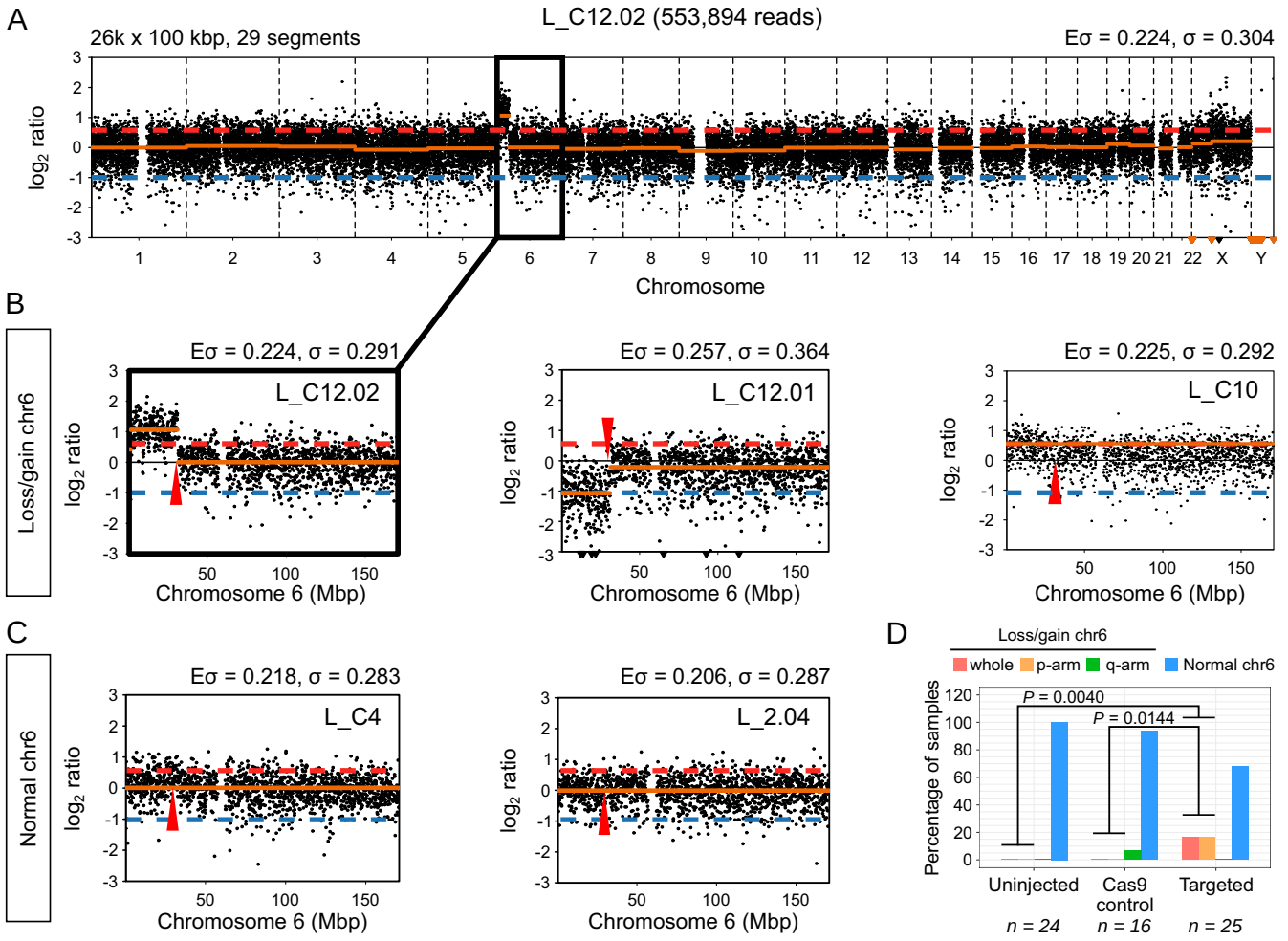

Fig. 1. Segmental losses/gains of chromosome 6 are prevalent in OCT4-targeted embryo samples. (*A*) Copy number profile of sample L_C12.02. The segmental gain of chromosome 6 is highlighted. The profile was constructed with 26,000 bins of size 100 kbp, which produced 29 segments. The expected (Eσ) and measured (σ) SD of the profile are reported. (*B*) Zoomed-in view of the copy number profile for samples with segmental losses or gains of chromosome 6. (*C*) Zoomed-in view of the copy number profile for samples with normal chromosome 6. The Eσ and σ reported in *B* and *C* correspond to the chromosome only. The approximate position of the *POU5F1* gene is indicated by a red arrowhead. The red dashed line indicates a copy ratio of 3:2, while the blue dashed lines corresponds to a copy ratio of 1:2. (*D*) The percentage of control and targeted samples with whole or segmental losses/gains of chromosome 6 according to their copy number profiles. *P* values are the result of two-tailed Fisher's tests.

overall size to chromosome 6, but the frequency of whole chromosome abnormalities is similar to that observed for chromosome 6, suggesting that genome editing does not exacerbate the rates of whole chromosome errors (*SI Appendix*, Fig. S2*C*). The comparison we performed between Cas9 control and CRISPR-Cas9 genome edited samples includes a combination of both cleavage and blastocyst stage samples (*SI Appendix*, Table S1). Because rates of aneuploidy are known to be significantly higher at the cleavage stage compared to the blastocyst (18), we wondered whether excluding the samples at the earlier cleavage stage would alter the conclusions drawn about the rates of aneuploidy in CRISPR-Cas9–targeted cells. Here, we found that in comparison to uninjected controls there remained a significantly higher proportion of chromosome 6 aneuploidies in OCT4-targeted cells collected at the blastocyst stage (*SI Appendix*, Fig. S2*D*). Altogether, low-pass WGS analysis suggests that a significant proportion of unexpected on-target events leads to segmental abnormalities following CRISPR-Cas9 genome editing in human preimplantation embryos.

LOH Identified by Targeted Deep Sequencing. The copy-number profiles described above with low-pass WGS data can only provide a coarse-grained karyotype analysis. To independently investigate the prevalence of LOH events at finer resolution and increased sequencing depth, we designed PCR primer pairs to amplify 15 fragments spanning a ∼20-kb region containing the *POU5F1* locus. We also included a control PCR amplification in the *ARGFX* locus located on chromosome 3 (*SI Appendix*, Table S4). The PCR amplicons were used to perform deep sequencing by Illumina MiSeq using the gDNA isolated and amplified from 137 single cells or a cluster of 2–5 microdissected cells (111 CRISPR-Cas9 targeted and 26 Cas9 controls) (*SI Appendix*, Fig. S1 and Table S2). The prefix W_ distinguished samples whose gDNA was isolated solely for WGA and the prefix G_ was used to demarcate samples that underwent WGA via the genome and transcriptome-sequencing (G&T-seq) protocol (19). All of these samples were different from the samples used for the cytogenetic analyses above.

We then took advantage of the high coverage obtained at each of the sequenced fragments to call single-nucleotide polymorphisms (SNPs), which allowed us to identify samples with putative LOH events: Cases in which heterozygous variants, indicative of contribution from both parental alleles, cannot be confidently called in the amplicons flanking the CRISPR-Cas9 on-target site directly. Since we do not have the parental genotype from any of

the samples that we analyzed, we cannot exclude the possibility that they inherited a homozygous genotype. Therefore, we required the presence of heterozygous SNPs in at least one additional cell from the same embryo to call putative LOH events.

The variant-calling pipeline that we implemented was specifically adjusted for MiSeq data from single cell amplified DNA and includes stringent preprocessing and filtering of the MiSeq reads (*Methods*). To have sufficient depth of coverage and to construct reliable SNP profiles, we only considered samples with ≥5× coverage in at least two-thirds of the amplicons across the *POU5F1* locus (*Methods* and *SI Appendix*, Fig. S6*A*). This threshold allowed us to retain as many samples as possible and still be confident in SNP calling (20). In addition, we implemented a step in our SNP calling pipeline to control for allele overamplification bias, which is a common issue with single cell-amplified DNA (21). This step changes homozygous calls to heterozygous if the fraction of reads supporting the reference allele is above the median value across samples (*SI Appendix*, Fig. S6 *B* and *C* and *Methods*). Thus, we proceeded with 42 CRISPR-Cas9–targeted and 10 Cas9 control samples with reliable SNP profiles for subsequent analysis. These data led to the identification of four different patterns: samples without clear evidence of LOH, samples with LOH at the on-target site, bookended, and open-ended LOH events (Fig. 2*A* and *SI Appendix*, Figs. S7–S12).

In samples without LOH (20% of control and 11.9% of targeted samples), we were able to call heterozygous SNPs in multiple amplified fragments (G_8.04, G_C16.05, and W_C16.05, Fig. 2*A*). Cases with putative LOH at the locus have heterozygous SNPs in

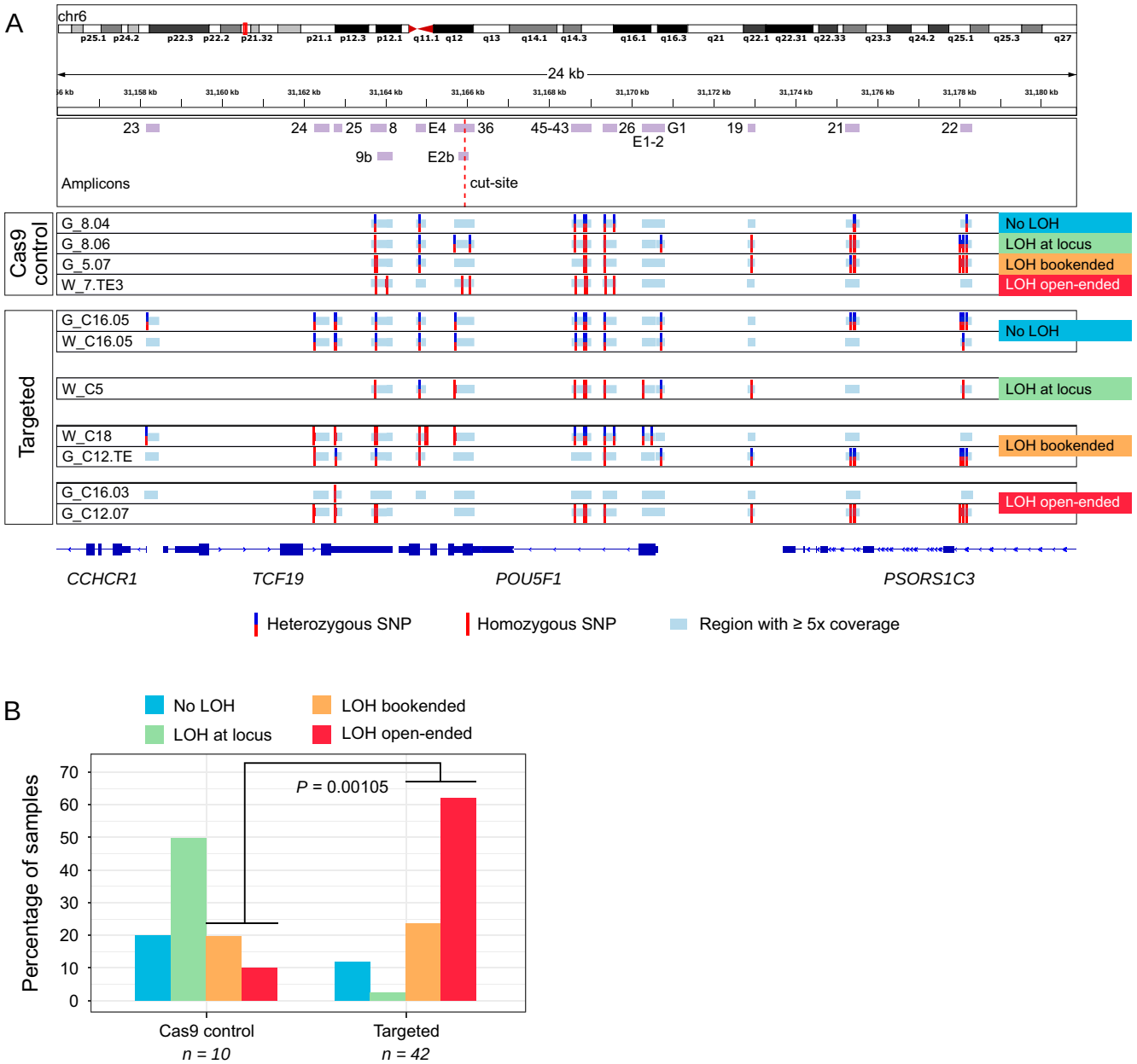

Fig. 2. LOH in the *POU5F1* locus is prevalent among OCT4-targeted embryo samples. (*A*) SNP profiles constructed from deep sequencing of the depicted amplicons. The four types of LOH events observed are exemplified. Note that there are amplicons with ≥5x coverage in which SNPs were not called because all reads agree with the reference genome. (*B*) The frequency of each type of LOH event in control and targeted samples. *P* value is the result of a two-tailed Fisher's test.

the amplicons covering exons 1 and 5 of the *POU5F1* gene (fragments E1-2, G1, and E4 in Fig. 2*A*) and homozygous SNPs in between (50% of control and 2.4% of targeted samples). These putative LOH samples would have had to have a cell isolated from the same embryo that had a detectable SNP(s) anywhere in between these flanking exons (e.g., see samples G_8.03 versus G_8.04 in *SI Appendix*, Fig. S7). Interestingly, this was the most prevalent pattern in Cas9 control samples (Fig. 2*B* and *SI Appendix*, Fig. S7), which may indicate the possibility of technical issues due to sequencing or overamplification of one parental allele (see below). Bookended samples have two heterozygous SNPs flanking the cut site but in fragments outside the *POU5F1* locus (20% of control and 23.8% of targeted samples). These LOH events could represent deletions of lengths between ∼7 kb (G_C12.03, *SI Appendix*, Fig. S10) and ∼12 kb (W_C11.04, *SI Appendix*, Fig. S9). Finally, in open-ended samples (10% of control and 61.9% of targeted samples), it was not possible to find heterozygous SNPs in any of the amplified fragments (G_C12.07, Fig. 2*A*) or there was one or a few heterozygous SNPs on only one side of the region of interest (G_C16.02, *SI Appendix*, Fig. S12). This was the most common pattern in targeted samples (Fig. 2*B* and *SI Appendix*, Figs. S8–S12) and could represent large deletions of ∼20 kb in length (the size of the region explored) or larger.

As mentioned above, the MiSeq data must be interpreted with caution given the presence of LOH in Cas9 controls. The gDNA employed in these experiments was extracted and amplified with a kit based on multiple displacement amplification (MDA, *Methods*), which is common in single-cell applications but is known to have high allelic dropout and preferential amplification rates (22). Although, as mentioned above, we implemented a step to control for these biases, this estimate likely undercalls samples with heterozygosity. For example, some homozygous SNPs had 5% of reads mapping to the reference allele but remained homozygous because they fall below the threshold that we used. Considering that we lack the parental genotypes as a reference to choose a more informed cutoff, our method to calculate one from the data represents an unbiased means to correct the presumed allele overamplification in the samples. Moreover, we cannot exclude the possibility that the analyzed single cells inherited a homozygous genotype in the explored region. Nevertheless, the fact that there is a significant number of CRISPR-Cas9–targeted samples with the largest LOH patterns is notable (Fig. 2*B*).

Unexpected CRISPR-Cas9–Induced On-Target Events Do Not Lead to Preferential Misexpression of Genes Telomeric to *POU5F1*. Our low-pass WGS and SNP analysis above indicate mutations at the *POU5F1* locus that are larger than discrete indels. We therefore wondered if this on-target complexity may encompass the mutations of genes adjacent or telomeric to *POU5F1* that could complicate the use of CRISPR-Cas9 to understand gene function in human development or other contexts where the analysis of primary cells is required. To address this, we reanalyzed the single-cell RNA sequencing (scRNA-seq) transcriptome datasets (*SI Appendix*, Table S6) we generated previously (17) and focused on the chromosome location of transcripts (Fig. 3 *A*–*C*). This analysis indicated that differentially expressed genes are not biased to a specific chromosome (Fig. 3*A*). Moreover, differentially expressed genes are not enriched to either chromosome 6 or the region telomeric to the CRISPR-Cas9 on-target site (Fig. 3*D*). These results suggest that the transcriptional differences observed as a consequence of *POU5F1* targeting are not confounded by mutations of genes adjacent, or telomeric, to the on-target locus. This could be due to a number of reasons. For example, given that the proportion of samples that exhibit unintended CRISPR-Cas9–induced mutations (e.g., segmental aneuploidies or LOH events) is low, the sample size used is sufficiently high to mask any transcriptional differences in genes adjacent to the cut site in samples with segmental loss of the p-arm of chromosome 6. It is also possible that the extent of the on-target complexity is exaggerated using the gDNA-based pipelines we developed. Notably, because we use single-cell samples, as mentioned above, these are prone to allele overamplification and this can confound the interpretation of on-target mutation complexity.

No Evidence of On-Target Complexity Using Digital Karyotype and LOH Analysis of the Single-Cell Transcriptome Data. The use of RNA-sequencing (RNA-seq) data to detect chromosomal abnormalities (23) has great potential to complement the informative low-pass WGS or array CGH methods currently used for embryo screening in the context of assisted reproductive technologies (24, 25). In addition to karyotype analysis, transcriptome data may also provide information about embryo competence at the molecular level. Groff et al. have demonstrated that aneuploidy can be estimated based on significant variations in gene expression in the affected chromosome(s) compared to reference control samples (24). In addition, Weissbein et al. developed a pipeline, called eSNP-Karyotyping, for the detection of LOH in chromosome arms (26). eSNP-Karyotyping is based on measuring the ratio of expressed heterozygous to homozygous SNPs. We applied these two approaches, hereinafter referred to as z-score– and eSNP-Karyotyping, to the scRNA-seq samples (distinguished with the prefix T_) obtained using the G&T-seq protocol (14) (*SI Appendix*, Table S3). This allowed us to investigate whether transcriptome data could be used to determine the frequency of LOH events in CRISPR-Cas9–targeted embryos.

Since eSNP-Karyotyping relies on SNP calls from gene expression data, it is very sensitive to depth and breadth of sequencing (26). Therefore, we used results from this method as a reference to select high quality samples for our transcriptome-based analyses (*SI Appendix*, Fig. S13 *A*–*C*). After these filtering steps, we retained 38 samples (22 CRISPR-Cas9 targeted and 16 Cas9 controls) to analyze further.

In general, we found good agreement between the chromosomal losses detected by z-score–karyotyping and the LOH events identified by eSNP-Karyotyping (*SI Appendix*, Fig. S14 *A* and *B*). For example, the digital karyotype of *SI Appendix*, Fig. S14*A* shows the loss of chromosome 4, the p-arm of chromosome 7, and the q-arm of chromosome 14 in sample T_7.01, as well as the loss of chromosome 3 and the p-arm of chromosome 16 in sample T_C16.06. These abnormalities are identified as LOH events in the eSNP-Karyotyping profiles of the same samples (*SI Appendix*, Fig. S14*B*). Moreover, the copy number profiles built from low-pass WGS data for different cells from the same embryos also corroborates these chromosomal abnormalities (*SI Appendix*, Fig. S13 *D* and *E*). In terms of events that could be associated with CRISPR-Cas9 on-target damage, z-score–karyotyping identified the loss of chromosome 6 in sample T_C12.07 (Fig. 4*A*), which is consistent with the open-ended LOH pattern observed in the gDNA extracted from the same cell G_C12.07 (*SI Appendix*, Fig. S10) and the segmental loss detected in sample L_C12.01 from the same embryo (Fig. 1*B*). Also, the gain of the p-arm of chromosome 6 was detected in sample T_C12.15 (Fig. 4*A*), which is consistent with the segmental gain observed in sample L_C12.02 from the same embryo (Fig. 1*B*). The gains and losses of chromosome 6 in samples T_2.02, T_2.03, T_2.14, T_7.02, and T_C16.06 (Fig. 4*A*) are difficult to interpret due to the low quality of their MiSeq data or the lack of amplicon information for the q-arm (*SI Appendix*, Figs. S7 and S12). Interestingly, eSNP-Karyotyping did not detect any LOH events in chromosome 6 (*SI Appendix*, Fig. S15), suggesting that this approach is not sensitive enough to detect segmental abnormalities in single-cell samples. Overall, the transcriptome-based karyotypes did not confirm the trends observed in the gDNA-derived data (Fig. 4*B*).

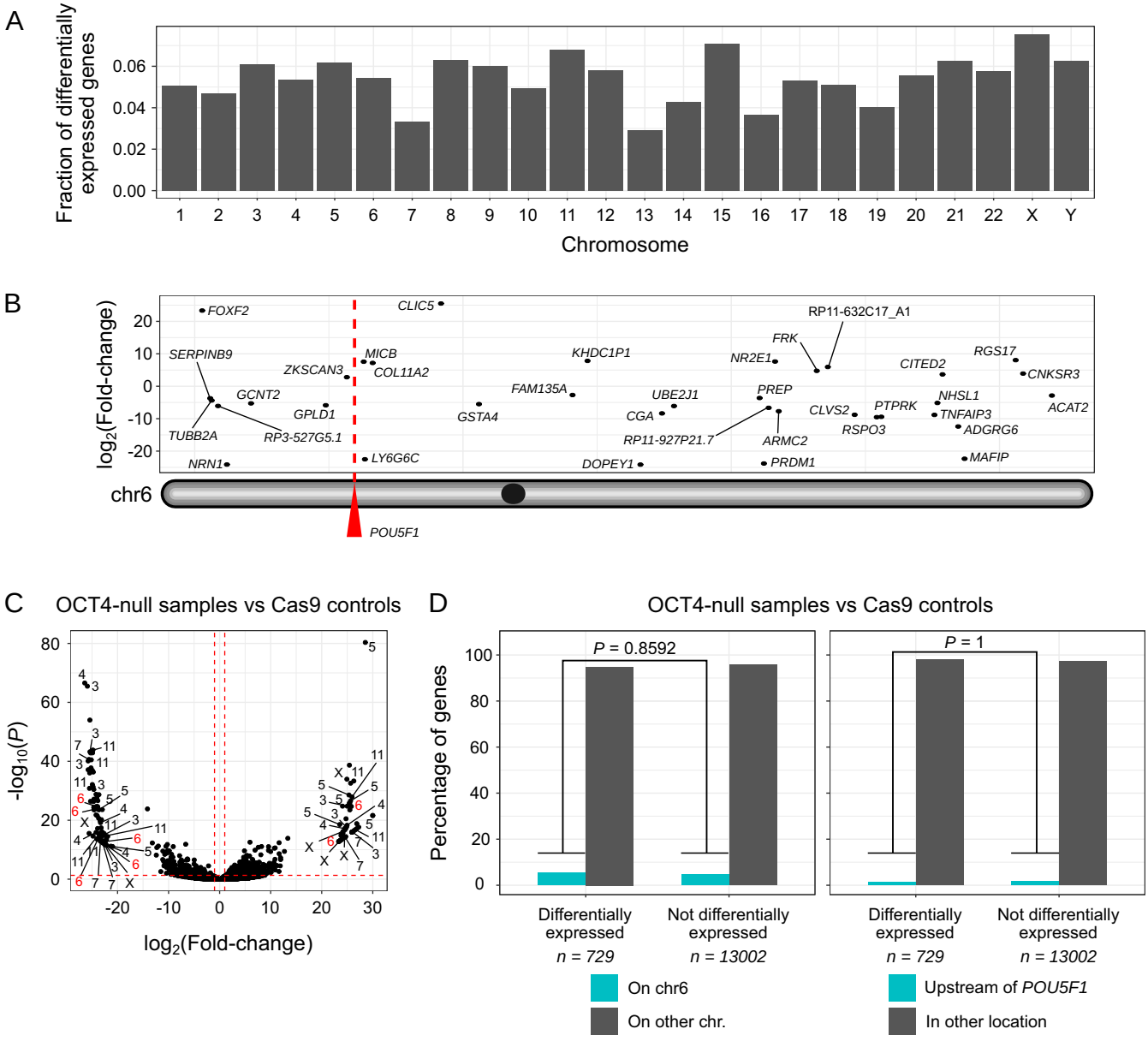

Fig. 3. LOH in OCT4-targeted samples does not lead to preferential misexpression of genes located on chromosome 6. (*A*) The fraction of differentially expressed genes per chromosome from the comparison between OCT4-null samples and Cas9 controls. (*B*) Location of differentially expressed genes along chromosome 6. (*C*) Volcano plot summarizing the comparison between OCT4-null samples and Cas9 controls with differential gene expression analysis. The chromosome location of some of the most dysregulated genes is shown (absolute $\log_2$ fold change > 20 and Benjamini–Hochberg adjusted $P < 0.05$). The red dashed lines correspond to absolute $\log_2$ fold changes > 1 and Benjamini–Hochberg adjusted $P < 0.05$. (*D*) Genes located on chromosome 6 are not over-represented in the list of loci whose expression is disturbed upon OCT4 knock out. The same applies for genes directly upstream to the *POU5F1* gene. *P* values are the result of two-tailed Fisher's tests.

Discussion

In all, we reveal unexpected on-target complexity following CRISPR-Cas9 genome editing of human embryos. Our data suggest ~16% of samples exhibit segmental losses/gains adjacent to the *POU5F1* locus and LOH events that span 4 kb to at least 20 kb. Chromosome instability, including whole or segmental chromosome gain or loss, is common in human preimplantation embryos (27, 28). However, in contrast to Cas9 control embryos, we noted a significantly higher frequency of CRISPR-Cas9–targeted embryos with a segmental gain or loss that was directly adjacent to the *POU5F1* on-target site. The segmental errors were observed in embryos from distinct genetic backgrounds and donors. Therefore, together with their on-target location, this suggests that the errors may have been an unintended consequence of CRISPR-Cas9 genome editing. This is supported by the higher frequency of larger LOH events that we observed in CRISPR-Cas9–targeted embryos compared to Cas9 controls using an independent targeted deep-sequencing approach. However, due to the nature of our datasets (shallow sequencing, MDA-amplified gDNA, lack of parental genotypes), we may be overestimating LOH events. This may explain some of the on-target complexity observed in Cas9 control samples but does not account for the significantly higher proportion of LOH in the CRISPR-Cas9–targeted samples. It is important to note that 68% of CRISPR-Cas9–targeted cells did not exhibit any obvious segmental or whole chromosome 6 abnormalities, indicating that their genotype and phenotype, with

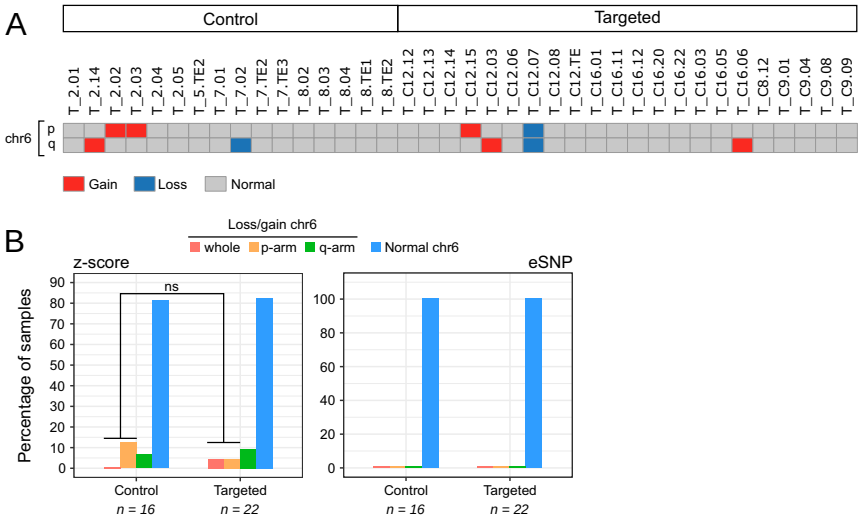

Fig. 4. Transcriptome-based karyotypes do not capture segmental losses/gains of chromosome 6 in OCT4-targeted embryo samples. (*A*) Digital karyotype based on the total gene expression deviation from the average of each chromosome arm (z-score-karyotyping). Only chromosome 6 is shown (see *SI Appendix*, Fig. S14*A* for the rest of the chromosomes). (*B*) The percentage of control and targeted samples with segmental losses/gains of chromosome 6 according to their transcriptome-based karyotype (*SI Appendix*, Figs. S14*A* and S15). *P* value is the result of a two-tailed Fisher's test.

respect to OCT4 function, are interpretable. Moreover, our transcriptome-based digital karyotypes and differential gene expression analysis indicate biallelic transcripts and gene expression upstream and downstream of the *POU5F1* locus in so far as is resolvable from scRNA-seq data, suggesting that in these samples the LOH does not lead to the misexpression of other genes adjacent to the *POU5F1* locus. Also, our work and previous accounts of unexpected CRISPR-Cas9–editing outcomes (9, 10, 12–14, 16) indicate that the frequency of discrete on-target events predominates, which should increase the confidence of the interpretation of functional studies in human embryos. Given the likelihood of mosaicism, it is unclear whether the segmental abnormalities we observed in any one cell analyzed from each embryo are representative of the entire CRISPR-Cas9–targeted embryo or a subset of cells within the embryo. Altogether, this points to the need to use robust techniques to distinguish cells affected by on-target complexity and large deletions following CRISPR-Cas9–mediated genome editing from cells with less complex mutations and our computational pipelines and multiomics analyses are approaches that may be used in the future.

By contrast, we did not observe significantly more abnormalities on chromosome 6 using methods to determine LOH or karyotype from scRNA-seq datasets. There are several factors that could account for the discrepancy between these datasets. First, we do not have the transcriptome from the same samples that showed gains and losses of chromosome 6 in the cytogenetics analysis. A follow-up study in which both transcriptomics and cytogenetics data are extracted from the same sample would be very informative and could be performed by modifying the G&T-seq protocol (19) to incorporate a multiple annealing and looping-based amplification cycles (MALBAC) method for WGA (29) in place of MDA, which was used here due to the proofreading activity of the phi29 MDA polymerase at the expense of high preferential amplification rates (22). Second, mosaicism is common in human preimplantation embryos (30), and this could explain why the digital karyotypes based on gene expression did not detect abnormalities at the same rate as the copy number profiles. Another possibility is that the LOH events are not sufficiently large to impact total gene expression of chromosome 6, which is what z-score– and eSNP-Karyotyping rely on. This could also account for the cytogenetics results, as LOH up to a few megabases in size could cause mapping issues due to the very low coverage of shallow sequencing that are reflected as gains and losses of whole chromosome segments. Finally, the LOH events detected by gDNA-derived data may only affect genes that are not expressed in the embryo context or whose expression is so low that it cannot be accurately measured by scRNA-seq. So, when z-score– and eSNP-Karyotyping compare gene or SNP expression of targeted versus control samples, no significant differences are identified.

The segmental aneuploidies identified by cytogenetics analysis (Fig. 1*B* and *SI Appendix*, Figs. S3–S5) most probably point to the occurrence of complex genomic rearrangements in OCT4-targeted samples, such as chromosomal translocations or end-to-end fusions, as it seems unlikely that the rest of the chromosome would continue to be retained without a telomere (31–33). It is likely that human embryos tolerate aneuploidy up to embryo genome activation, given that even embryos with observed multipolar spindles continue to develop during early cleavage divisions (34). Following this, chromosomal anomalies are likely to become increasingly detrimental to cellular viability, although a degree of tolerance may persist in trophectoderm cells (28). Why early embryos fail to arrest despite chaotic chromosomal errors such as multipolar spindle formation or presumptive unresolved double-strand breaks following CRISPR-Cas9 genome editing is unclear and crucial to understand. An important next step to gain insights into the extent of the damage would be to use alternative methods. One possibility to understand the complexity would be to perform cytogenetic analysis using fluorescence in situ hybridization (FISH) (35) to probe for segments of chromosome 6. Another option is a chromosome walk-along approach to amplify genomic fragments even further away from the 20-kb genomic region that we evaluated, in order to bookend heterozygous SNPs on either side of the *POU5F1* on-target site. This may be kilobases or megabases away from the on-target site based on previous publications in the mouse or human cell lines (9, 10, 12–14).

Based on our data, the possibility of gene editing via IH-HR cannot be definitely excluded. A preprint by Liang et al. (36) suggests that IH-HR could be one of the major DNA double-strand break repair pathways in human embryos. Following a similar approach to their previous study (8), the authors used CRISPR-Cas9–mediated genome editing to target a paternal mutation and were able to amplify an ∼8-kb genomic DNA fragment which, together with G-banding and FISH of ESCs

derived from targeted embryos, suggests that repair from the maternal chromosome by IH-HR results in a stretch of LOH. Of note, due to the selection bias that occurs during ESC derivation and the mosaicism observed following genome editing, it is not possible to draw definitive conclusions about the extent of LOH or its cause in an embryo context, whereby cells with complex mutations may be preferentially excluded from ESC derivation. By contrast, another study by Zuccaro et al., using the same microinjection method, suggests that the LOH observed following CRISPR-Cas9–mediated genome editing is a consequence of whole chromosome or segmental loss adjacent to the on-target site and that microhomology-mediated end-joining (MMEJ) is the dominant repair pathway in this context (37). This corroborates our previous findings in human embryos targeted postfertilization, where we noted a stereotypic pattern to the type of indel mutations and speculated that this was likely due MMEJ (17). Although microhomologies can promote gene conversion by, for example, interchromosomal template switching in a RAD51-dependent manner (38), based on our previous transcriptome analysis, we found that components of the MMEJ pathway (i.e., *POLQ*) are transcribed in early human embryos, while factors essential for HDR (i.e., *RAD51*) are not appreciably expressed. This suggests that MMEJ-derived large deletions (14, 37) are more likely than microhomology-mediated gene conversion in this context, although protein expression has yet to be fully characterized. Consistent with this, a significant fraction of somatic structural variants arises from MMEJ in human cancer (39). Moreover, microhomology-mediated break-induced replication underlies copy number variation in mammalian cells (40) and microhomology/microsatellite-induced replication leads to segmental anomalies in budding yeast (41). The discrepancy between the Liang et al. and Zuccaro et al. studies could be due to locus-dependent differences of CRISPR-Cas9 genome editing fidelity. For example, Przewrocka et al. demonstrate that the proximity of the CRISPR-Cas9–targeted locus to the telomere significantly increases the possibility of inadvertent chromosome arm truncation (16). To fully elucidate the LOH that has occurred at the on-target site in our study, and to resolve the controversy over the IH-HR reported by others (8, 9, 36, 37), will require the development of a pipeline to enrich for the region of interest and then perform deep (long-read) sequencing to evaluate the presence and extent of on-target damage. By bookending SNPs on either side of an LOH event, primers could be designed to incorporate the SNPs and ensure that both parental alleles are amplified. However, this is difficult to perform, and alternative methods include using CRISPR gRNAs to cut just outside of the LOH region followed by long-read sequencing (42).

It would also be of interest to evaluate whether other genome editing strategies, such as prime and base editing, nickases, or improvements in the efficiency of integrating a repair template, may reduce the on-target complexities observed by us and others using spCas9. However, nonnegligible frequencies of editing-associated large deletions have been reported after the use of the $Cas9^{D10A}$ nickase in mESCs (14) and prime editing in early mouse embryos (43). By contrast, while proof-of-principle studies suggest that base editors could be used to repair disease-associated mutations in human embryos, further refinements to reduce the likelihood of unexpected conversion patterns and high rates of off-target edits would be of benefit (2). There are too few studies to date using repair templates. Of the studies that have been conducted, the reported efficiencies of repair with templates in human embryos are very low (5, 7, 8). Modulation of DNA damage repair factors or tethering Cas9 enzymes with a repair template may yield improvements that could allow for the control of editing outcomes.

Our reevaluation of on-target mutations, together with previous accounts of unexpected CRISPR-Cas9 on-target damage (9, 10, 12–14), strongly underscores the importance of further basic research in a number of cellular contexts to resolve the damage that occurs following genome editing. Moreover, this stresses the significance of ensuring whether one or both parental chromosome copies are represented when determining the genotype of any sample to understand the complexity of on-target CRISPR mutations, especially in human primary cells.

Methods

Ethics Statement. We reprocessed the DNA and reanalyzed the data generated in our previous study (17). This corresponds to 168 samples (134 OCT4-targeted and 34 Cas9 controls) across 32 early human embryos (24 OCT4-targeted and 8 Cas9 controls). For the present work, we used 56 additional single-cell samples (19 OCT4-targeted, 12 Cas9 controls, and 25 uninjected controls) across 22 early human embryos (1 OCT4-targeted, 1 Cas9 control, and 20 uninjected controls). This study was approved by the UK Human Fertilization and Embryology Authority (HFEA) (research license no. R0162) and the Health Research Authority's Research Ethics Committee (Cambridge Central reference no. 19/EE/0297). Our research is compliant with the HFEA code of practice and has undergone inspections by the HFEA since the license was granted. Before giving consent, donors were provided with all of the necessary information about the research project, an opportunity to receive counseling, and the conditions that apply within the license and the HFEA Code of Practice. Specifically, patients signed a consent form authorizing the use of their embryos for research including genetic tests and for the results of these studies to be published in scientific journals. No financial inducements were offered for donation. Patient information sheets and the consent documents provided to patients are publicly available (https://www.crick.ac.uk/research/labs/kathy-niakan/human-embryo-genome-editing-licence). Embryos surplus to the in vitro fertilization treatment of the patient were donated, cryopreserved, and transferred to the Francis Crick Institute, where they were thawed and used in the research project.

CRISPR-Cas9 Targeting of *POU5F1*. We analyzed single cells or trophectoderm biopsies from human preimplantation embryos that were CRISPR-Cas9 edited in our previous study (17) plus an additional 56 samples used in the present work. In vitro fertilized zygotes donated as surplus to infertility treatment were microinjected with either a sgRNA–Cas9 ribonucleoprotein complex or with Cas9 protein alone and cultured for 5–6 d (targeted and control samples, respectively). The sgRNA was designed to target exon 2 of the *POU5F1* gene, and experiments were performed as previously described (17). Genomic DNA from Cas9 control and OCT4-targeted samples was isolated using the REPLI-g Single Cell Kit (QIAGEN, 150343). DNA samples isolated for cytogenetic analysis were amplified with the SurePlex Kit (Rubicon Genomics). See *SI Appendix* for more details.

Cytogenetic Analysis. Low-pass whole genome sequencing (depth of sequencing <0.1×) libraries were prepared using the VeriSeq PGS Kit (Illumina) or the NEB Ultra II FS Kit and sequenced with the MiSeq platform as previously described (17) or with Illumina HiSeq 4000, respectively. Reads were aligned to the human genome hg19 using BWA v0.7.17 (44) and the copy number profiles generated with QDNaseq v1.24.0 (45). See *SI Appendix* for more details.

PCR Primer Design and Testing. PCR primer pairs were designed with the Primer3 webtool (https://bioinfo.ut.ee/primer3/, *SI Appendix*, Table S4). We restricted the product size to 150–500 bp and used the following primer temperature settings: Min = 56, Opt = 58, Max = 60. We tested all primers using 1 μL of genomic DNA from H9 human ES cells in a PCR containing 12.5 μL of Phusion High Fidelity PCR Master Mix (NEB, M0531L), 1.25 μL of 5 μM forward primer, 1.25 μL of 5 μM reverse primer, and 9 μL of nuclease-free water. Thermocycling settings were: 95 °C at 5 min, 35 cycles of 95 °C at 30 s, 58 °C at 30 s, 72 °C at 1 min, and a final extension of 72 °C at 5 min. We confirmed the size of the PCR products by gel electrophoresis. See *SI Appendix* for more details.

PCR Amplification and Targeted Deep Sequencing. Isolated DNA was diluted 1:100 in nuclease-free water. We used the QIAgility robot (QIAGEN, 9001531) for master mix preparation (see above) and distribution to 96-well plates (*SI Appendix*, Table S5). Then, the Biomek FX liquid handling robot (Beckman Coulter, 717013) was used to transfer 1 μL of DNA to the master mix plates and to mix the reagents. The PCR was run with the settings described above. PCR products were cleaned with the Biomek FX robot using the chemagic SEQ Pure20 Kit (PerkinElmer, CMG-458). Clean PCR amplicons

from the same DNA sample were pooled to generate 137 libraries that were sequenced by Illumina MiSeq v3. See *SI Appendix* for more details.

SNP Typing. We trimmed the MiSeq paired-end reads with DADA2 (46), corrected substitution errors in the trimmed reads with RACER (47), and mapped the corrected reads to the human genome hg38 with BWA v0.7.17 (44). Subsequently, SAM files were converted to the BAM format and postprocessed using Samtools v1.3.1 (48). SNP calling was performed with BCFtools v1.8 (49) using mpileup and call. SNPs supported by less than 10 reads and with mapping quality below 50 were filtered out. To control for allele overamplification, homozygous SNPs were changed to heterozygous if the fraction of reads supporting the reference allele was at least 6% of the total (21). This threshold corresponds to the median of the distribution of the fraction of reads supporting the reference allele across samples. See *SI Appendix* for more details.

scRNA-Seq Data Analysis. scRNA-seq reads from G&T-seq samples were processed as previously described (17). Samples with a breadth of sequencing below 0.05 were not considered for any downstream analysis (*SI Appendix*, Fig. S13 *A*–*C*). Differential gene expression analysis was carried out with DESeq2 v1.10.1 (50). For digital karyotyping based on gene expression, we adapted the method described in ref. 24 to identify gains or losses of chromosomal arms (z-score-karyotyping). For digital karyotyping based on SNP expression, we applied the eSNP-Karyotyping pipeline with default parameters (26). See *SI Appendix* for more details.

Data and Software Availability All data supporting the findings of this study are available within the article and its *SI Appendix*. MiSeq and low-pass WGS data have been deposited to the Sequence Read Archive under accession no. PRJNA637030 (51). scRNA-seq data were extracted from the Gene Expression Omnibus using accession no. GSE100118 (52). A detailed analysis pipeline is available at the following site: https://github.com/galanisl/loh_scripts (53).

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Molecular Therapy
Review

CRISPR-Cas9: A Preclinical and Clinical Perspective for the Treatment of Human Diseases

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At present, the idea of genome modification has revolutionized the modern therapeutic research era. Genome modification studies have traveled a long way from gene modifications in primary cells to genetic modifications in animals. The targeted genetic modification may result in the modulation (i.e., either upregulation or downregulation) of the predefined gene expression. Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated nuclease 9 (Cas9) is a promising genome-editing tool that has therapeutic potential against incurable genetic disorders by modifying their DNA sequences. In comparison with other genome-editing techniques, CRISPR-Cas9 is simple, efficient, and very specific. This enabled CRISPR-Cas9 genome-editing technology to enter into clinical trials against cancer. Besides therapeutic potential, the CRISPR-Cas9 tool can also be applied to generate genetically inhibited animal models for drug discovery and development. This comprehensive review paper discusses the origin of CRISPR-Cas9 systems and their therapeutic potential against various genetic disorders, including cancer, allergy, immunological disorders, Duchenne muscular dystrophy, cardiovascular disorders, neurological disorders, liver-related disorders, cystic fibrosis, blood-related disorders, eye-related disorders, and viral infection. Finally, we discuss the different challenges, safety concerns, and strategies that can be applied to overcome the obstacles during CRISPR-Cas9-mediated therapeutic approaches.

Clustered regulatory interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein 9 (Cas9) is a novel and competent RNA-guided endonuclease-based genome-editing technique[1] that is adapted from the naturally occurring bacterial immune system. The CRISPR-Cas9 technique is easily scalable and very cost-effective, and thus it can be applied for a wide range of directed genome editing.[2–4] After the first report of CRISPR in 1987, the technology has evolved step by step (Figure 1). At the present time, CRISPR-Cas9 technology-mediated genetic experiments can be performed on a wide range of models such as plants, yeast, *Caenorhabditis elegans*, *Drosophila*, zebrafish, mice, and humans.[5–11] More than 2,000 publications on CRISPR-Cas9 technology have been recorded in PubMed during the last 2 years. This increasing research trend has been portrayed as the "CRISPR craze."[12]

CRISPR-Cas9 technology utilizes a single guide RNA (sgRNA) sequence and Cas9 endonuclease. sgRNA is a combination of CRISPR RNA (crRNA) and *trans*-activating crRNA (tracrRNA), which identify and attach the sgRNA/Cas9 ribonucleoprotein complex to the target DNA.[13] After DNA targeting, Cas9 generates double-stranded breaks (DSBs) at the site of target DNA.[14] These DSBs are further repaired by insertions, deletions, additions, or inversions. The DNA repair mechanism can be performed by either the host's natural repair machinery or by using customized DNA sequences.[15]

The highlights of CRISPR-Cas9 technology involve its ability to treat various human diseases via genome editing (Figure 2).[15] Accumulating evidence suggests successful genome editing in mammalian cells via CRISPR-Cas9 technology.[16,17] CRISPR-Cas9 technology has now entered clinical trials in the United States through the National Institutes of Health (NIH) Recombinant DNA Advisory Committee, which has permitted CRISPR technology to assist cancer therapies, relying on the enlistment of a patient's T cells at the NIH.[18] In addition, an analogous type of gene therapy clinical trials received ethical approval in China.[19] These clinical trials might establish an efficient therapeutic genome-editing system against hereditary or non-hereditary genetic disorders in humans.

Although the CRISPR-Cas9 tool has therapeutic potential, unexpected outcomes have challenged the development of more simple and specific gene-editing methodologies.[20] In this review, we discuss the preclinical studies on the mechanism of action of CRISPR-Cas9 systems against various diseases, such as cancer, allergies, and immunological disorders. We also discuss the clinical advances, challenges, safety concerns, and strategies to develop efficient CRISPR-Cas9-based gene-editing technology.

Advantages of CRISPR-Cas9 and Other Genome-Editing Tools

Genome-editing technology has gained attention as a therapy against human diseases. However, its success has been previously challenged

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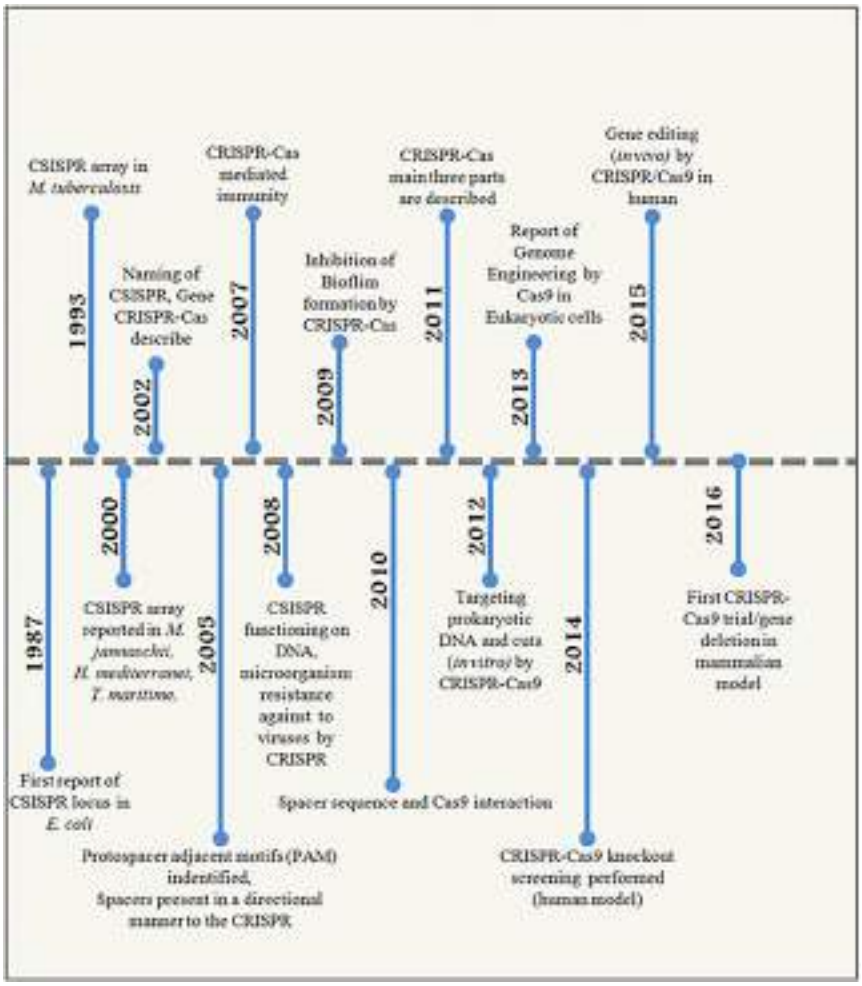

Figure 1. Timeline of the Breakthrough and Progression of CRISPR-Cas9 Systems

by unpredictable outcomes. In early gene therapy trials, 5 children, out of 20 participants from different studies, suffering from the severe combined immunodeficiency (SCID) X-1 condition developed T cell leukemia due to non-specific insertion of a correcting gene near to tumor-promoting genes, which resulted in transcriptional activation.[21–25] In another trial, an 18-year-old male with ornithine transcarbamylase (OTC) deficiency developed a lethal immune response induced by viral vector.[26] Both of these misfortunes were associated with poor or uncontrolled therapeutic delivery methods.[23]

Lately, more advanced gene therapy technologies, such as zinc finger nucleases (ZFNs),[27] transcription activator-like effector nucleases (TALENs),[28] and CRISPR-Cas9,[29] were developed, which were capable of site-specific gene editing. ZFNs are a combination of a non-specific FokI cleavage domain and zinc finger proteins (ZFPs). In eukaryotes, ZFPs are associated with protein-protein interaction and regulation of DNA transcription.[30] For gene editing, paired ZFNs, one downstream and one upstream of the target site, are used to generate DSBs.[31] ZFNs, however, can only recognize nucleotide triplets in the DNA, thus restricting the number of site selections due to limited binding sites for ZFPs.[32] Various interventional clinical trials based on ZFN-mediated gene editing are ongoing, e.g., for the treatment of Hunter's syndrome,[33] to cure human immunodeficiency virus (HIV) infection,[34] and others. Similar to ZFNs, TALENs include a complex of transcription activator-like effectors (TALEs) and FokI endocuclease.[28] TALEs are the amino acid sequences that flank a DNA binding site. TALENs have a benefit over ZFNs, as they can recognize a single nucleotide and are more specific than ZFNs.[35] Still, packaging and delivery of TALENs might be a challenge because they have a large size than ZFNs.[23]

CRISPR-Cas9 is latest gene-editing technique with various advantages over ZFNs and TALENs. First, CRISPR-Cas9 is more cost-effective than other gene-editing techniques.[36] Second, the target specificity of CRISPR-Cas9 depends on the ribonucleotide complex, which is probably more specific to protein-based DNA bindings in ZFNs and TALENs. Moreover, it is easy to design sgRNA for a wide range of target DNAs. In addition, various modifications can be performed in the CRISPR-Cas9 cargo system, i.e., plasmid DNA encoding sgRNA and Cas9, the combination of sgRNA and Cas9 mRNA, and the combination of sgRNA and Cas9 protein. Other advantages of CRISPR-Cas9 include the possibility of direct genome modification in the embryo and introduction of more than one mutation at the same time.[37] In addition, base edition (i.e., the conversion of cytidine to uracil [C→T] or guanine to adenine [G→A]) that is mediated by the binding of CRISPR-Cas9 with cytidine deaminase is also possible.[38] These advancements indicate the possibility of safe and successful clinical application of CRISPR-Cas9 technology in the future.

Preclinical Studies of CRISPR-Cas9

CRISPR-Cas9 research has been applied for the treatment of different human diseases (Table1), which are discussed below.

Cancer

Cancer is among the most prevalent lethal diseases that can be illustrated by the accumulation of epigenetic modifications in the genome.[64,65] The drawback of conventional chemotherapy is the lack of specific targeting and resistance to chemotherapeutic drugs.[66] Therefore, there is a need to identify novel molecular targets that may facilitate cancer treatment. It has been proposed that the mutated oncogenes and tumor suppressor genes in cancer cells might function as

smart therapeutic targets, suggesting that the modulation of tumor suppressor genes can induce apoptosis in tumor cells.[67,68] Liu et al.[69] observed the effective inhibition of bladder cancer cell proliferation, reduced cell motility, and induction of apoptosis via CRISPR-Cas9-mediated regulation of tumor suppressor genes, i.e., hBax, E-cadherin, and p21.

It has been reported that epigenetic regulators are often mutated in myeloid malignancies.[70] CRISPR-Cas9 technology corrected the additional sex combs-like 1 (ASXL1) gene and re-established ASXL1 protein expression that significantly decreased leukemia cell growth in mouse xenografts.[39] The CRISPR-Cas9 system was also used to delete the myeloid cell leukemia-1 (MCL-1) gene, a member of the emerging B cell lymphoma 2 (BCL2) gene family, in human Burkitt lymphoma (BL) cells for the induction of apoptosis in the BL cells,[40] suggesting that the MCL-1 gene can be a novel target for cancer treatment, as it plays a role in cell differentiation, proliferation, and tumorigenesis.[71]

Cyclin-dependent kinases (CDKs) are critical regulators of the cell cycle. Therefore, dysregulated activation of CDKs may lead to tumorigenesis.[72,73] CRISPR-Cas9 technology can silence the CDK11 gene for the treatment of osteosarcoma[41] and the CDK7 gene for the treatment of triple-negative breast cancer cells.[74] This indicates that CDKs can be novel targets for cancer treatment.

Resistance to chemotherapeutic drugs is a common disadvantage of chemotherapy. The multidrug resistance-1 (MDR1) gene encodes for membrane efflux pump P-glycoprotein. The overexpression of MDR1 facilitates the efflux of anti-cancer drugs from the cells, which results in chemotherapeutic drug resistance. CRISPR-Cas9-mediated knockdown of MDR1 in osteosarcoma cell lines restored the sensitivity toward chemotherapeutic drugs.[75] Likewise, the possible management of drug resistance acquired by the secondary mutation in exon 20 at position 790 (T790M) in epidermal growth factor receptor (EGFR) can also be an effective strategy to cure lung cancer.[44]

SHC SH2-domain binding protein 1 (SHCBP1) is a member of the collagen homolog family that is critical for the regulation of cell proliferation. As overexpression of the SHCBP1 gene is reported in several diseases, especially cancer, it may be a potential therapeutic target as well as a suitable diagnostic biomarker for cancer.[42] It has been demonstrated that the CRISPR-Cas9-mediated knockout of the SHCBP1 gene might inhibit cancer cell proliferation and induce apoptosis in breast cancer cells.[42]

The Kelch-like (KLHL) gene family encodes a group of proteins that are related to several human diseases, along with cancer.[76] It was observed that CRISPR-Cas9-mediated knockout of the Kelch domain containing 4 (KLHDC4) gene in a nasopharyngeal carcinoma cell line considerably inhibited cancer cell migration and growth, and it induced apoptosis in both *in vitro* and *in vivo* models.[43]

In addition to the therapeutic domain, CRISPR-Cas9-mediated modification of genes can also be used to develop a mutant cancer model in mice, opening new opportunities to generate mutants in various species and in almost any genetic background to accelerate *in vivo* studies.[77,78] Platt et al.[10] developed lung adenocarcinoma mice by knockout of three significant genes (i.e., tumor protein [p53], serine/threonine kinase 11 [STK11] or Lkb1, and Kirsten rat sarcoma 2 viral oncogene homolog [KrasG12D]). In 2015, Chen et al.[79] developed *in vivo* loss-of-function Cas9 screening (genome-wide CRISPR screen) for a tumor metastasis and growth study. CRISPR-Cas9 technology was also used to initiate multiple gene mutations to develop human colonic epithelium in the colorectal cancer model.[80] CRISPR-Cas9-mediated knockout of single gene, i.e., patched 1 (Ptch1), or multiple genes, i.e., transformation-related protein 53 (TRP53), neurofibromin 1 (Nf1), and phosphatase and tensin homolog (PTEN), in the brain resulted in the progression of glioblastoma and medulloblastoma in mice.[81] CRISPR-Cas9 technology was also used to generate an acute myeloid leukemia (AML) mouse model with a combinatorial genetic lesions system by inducing multiple mutations in the genes of epigenetic modifiers, as well as cytokine signaling and transcription factors in the hematopoietic stem cells of mice.[82]

Cancer immunotherapy is among the four major line of treatments along with surgery, chemotherapy, and radiotherapy. Clinical trials on gene editing-based immunotherapies have been focusing on chimeric antigen receptor (CAR) T cell therapy[83–85] and genetically modified T cell receptor (TCR) therapy. In recent years, Kymriah from Novartis and Yescarta of KITE Pharma received US Food and Drug Administration (FDA) approval of their CAR T cell therapy products.[86,87] CAR, a synthetic receptor, acts as a gene insert that contains a transmembrane domain, a hinge segment, an antibody-derived extracellular-specific target protein binding domain, and a T cell-activating intracellular signaling unit.[88] CARs are inserted into the autologous T cells that are collected from the patients, resulting in the expression of CARs on the surface of T cells. When these T cell constructs are introduced again into the patient, they multiply and bind to the target protein and eliminate tumor cells. CAR T cell therapy showed 80%–100% remission in patients with relapsed or refractory B cell acute lymphocytic leukemia (ALL).[83,89] However, cytokine release during the therapy may result in various manageable side effects. While CARs recognize surface antigens, TCRs recognize intracellular proteins presented on major histocompatibility complex I (MHC class I). Moreover, TCR therapy is preferred over CAR T cell therapy due to low incidence of cytokine release syndrome.[90] The most recent clinical trials are working on CRISPR-Cas9-based immunotherapy against various types of cancer, which are detailed later in this review.

Allergy and Immunological Disorders

The therapeutic role of CRISPR-Cas9 genome editing for allergic and immunological conditions has also been reported.[91] It was observed that expression of cell surface glycoprotein MUC18 or CD146 is increased in the alveolar macrophages of bacterial- or viral infection-mediated chronic obstructive pulmonary disease (COPD) or asthma.[92] Knockout of the MUC18 gene reduced the level of interleukin (IL-8), a pro-inflammatory chemokine, in human primary

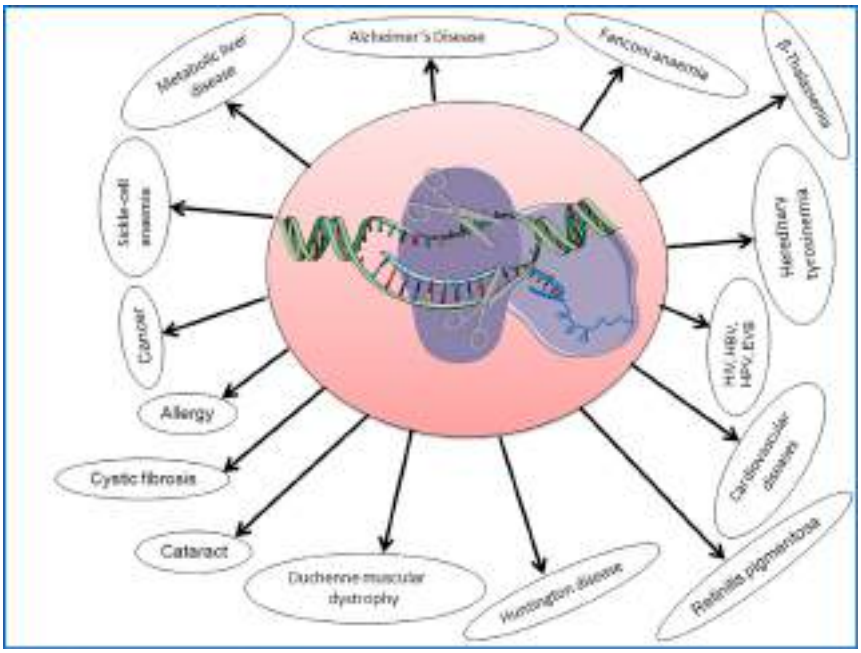

Figure 2. CRISPR-Cas9 System Dealing for Treatment of Multiple Human Diseases

nasal airway epithelial cells (AECs) that were stimulated by microbial infection, mimicking Toll-like receptor (TLR) agonists (i.e, TLR2, TLR3, and TLR4).[45]

It was noted that targeting receptors genes, such as programmed death-1 (PD-1), can stimulate immune responses. PD-1 is a T cell surface protein that is associated with T cell activation. CRISPR-Cas9-mediated disruption of the PD-1 receptor gene in human primary T cells isolated from cancer patients resulted in upregulated interferon (IFN)-γ production and enhanced cytotoxicity,[93] suggesting checkpoint inhibitors as novel targets for cancer treatment.

X-linked hyper immunoglobulin M (IgM) syndrome is an immune deficiency disorder identified by defective CD40/CD40L signaling via dysregulated class-switch recombination and somatic hypermutation in B cells.[94] It has been observed that the CRISPR-Cas9 gene-editing technique can correct mutations in the CD40 ligand.[95] Cheong et al.[96] edited the mouse and human Ig genes to obtain class switching of IgH, which might assist in the study of B cell (both normal and lymphoma) biology.

JAK3 (Janus kinase 3) is a protein tyrosine kinase that regulates various pathogenic processes in allergic asthma.[46] The deficiency in JAK3 is related to the reduced number of circulating natural killer (NK) cells and T cells, and with normal numbers of inadequately functioning B cells.[97] It has been noted that the mutations in the JAK3 gene can cause SCID. CRISPR-Cas9-mediated correction in the human JAK3 gene restored the differentiation potential of T cell progenitors, which are capable of producing T cells/NK cells.[97] This suggests that the CRISPR-Cas9 technique can reprogram cells for the prevention of various allergic conditions.

Duchenne Muscular Dystrophy (DMD)

DMD is an X-linked disorder and is characterized by proximal muscle weakness caused by small mutations in the DMD gene that lead to the absence of dystrophin protein. A number of knockout mouse models were produced to imitate the human DMD phenotype by genetic inhibition of dystrophin and/or utrophin/$\alpha_7\beta_1$-integrin genes.[98–100] It was demonstrated that genome editing can be used to restore the DMD gene mutation and correct the DMD disorder.[47,101–103] CRISPR-Cas9 technology has provided a platform for the treatment of DMD.[1,104] The CRISPR-Cas9-mediated gene-editing method was used to correct the DNA of an entire region containing CTG/CAG repeats, suggesting a new therapeutic opportunity against DMD.[105] Moreover, gold nanoparticles (NPs) were also used as a delivery vehicle for Cas9 ribonucleoprotein and donor DNA to correct the DMD gene in mice with minimal off-target DNA damage.[106] Recently, Zhang et al.[107] suggested that the self-complementary adeno-associated virus (ScAAV) delivery system can substantially improve the efficiency of CRISPR-Cas9-mediated DMD gene correction.

Cardiovascular Disorders (CVDs)

The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene has an important role in the regulation of cholesterol homeostasis.[108] The gain-of-function mutation of the PCSK9 gene can result in hypercholesterolemia and associated artherosclerosis.[48] Jiang et al.[109] reported CRISPR-Cas9-mediated therapeutic targeting of the PCSK9 gene in mice. In addition, the CRISPR-Cas9 genome-editing tool was also reported to disrupt the low-density lipoprotein receptor (Ldlr) gene and overexpress the PCSK9 gene in adult mice in atherosclerosis research.[110] Tessadori et al.[111] applied a CRISPR-Cas9-based genome-editing tool in a zebrafish model to correct human genetic cardiovascular disorders. These studies suggest the use of CRISPR-Cas9 as a potential genome-editing tool against cardiovascular disorders, especially conditions associated with hereditary lipid disorders.

Neurological Disorders

Huntington's disease (HD) is an autosomal inherited neurological disorder that is caused by the extension of CAG repeats in exon 1 of the huntingtin (HTT) gene.[112] A CRISPR-Cas9 nucleotide-editing tool was effectively applied to selectively suppress the HTT gene in a mouse model.[49] Other studies also supported the use of the CRISPR-Cas9 genome-editing system against HD conditions.[113,114]

Alzheimer's disease (AD), a neurodegenerative condition, leads to progressive memory loss. Mutations in the presenilin 1 (PSEN1)

Table 1. CRISPR-Cas9 Research and Its Application for the Treatment of Different Human Diseases

Disease Type	Disease-Related Gene/ Protein	Remarks	References
Cancer	additional sex combs like 1 (ASXL1)	CRISPR-Cas9 was used to decrease leukemia cell growth in mouse xenografts	39
	myeloid cell leukemia 1 (MCL-1)	CRISPR-Cas9 was used to delete MCL-1 in human BL cells and induce apoptosis in the BL cells	40
	cyclin-dependent kinase 11 (CDK11)	CRISPR-Cas9 was used to silence CDK11 in osteosarcoma	41
	SHC SH2-binding protein 1 (SHCBP1)	SHCBP1 inhibits the proliferation of breast cancer through CRISPR-Cas9	42
	Kelch domain containing 4 (KLHDC4)	CRISPR-Cas9 was used to knock out the KLHDC4 gene in a nasopharyngeal carcinoma cell line	43
	epidermal growth factor receptor (EGFR)	CRISPR-Cas9 was used for possible correction of acquired drug-resistant mutations in EGFR	44
Allergy	melanoma cell adhesion molecule (MCAM/MUC18)	CRISPR-Cas9 technology was used to knock out cell surface glycoprotein MUC18 in human primary nasal airway epithelial cells	45
	Janus kinase 3 (JAK3)	CRISPR-Cas9 was used to re-establish the development of normal T cells in JAK3-deficient cells	46
Duchenne muscular dystrophy	dystrophin	CRISPR-Cas9 was used to fix DMD gene mutation for the DMD disorder	47
Cardiovascular diseases	proprotein convertase subtilisin/kexin type 9 (PCSK9)	CRISPR-Cas9 was used to correct the PCSK9 gene in an atherosclerosis mouse model	48
Huntington disease	huntingtin (HTT) gene	CRISPR-Cas9 was used to suppress the mHTT gene selectively in a mouse model	49
Alzheimer's disease	presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes	CRISPR-Cas9 was used to correct ancestral mutations in AD related to the PSEN gene	50,51
Metabolic liver disease	*Pah*^{enu2}	CRISPR-Cas9 was used to correct the Pah^{enu2} gene in metabolic liver disease	52
Fanconi anemia	17 Fanconi anemia (FA)	CRISPR-Cas9 was used to correct Fanconi anemia	53
Hereditary tyrosinemia	fumarylacetoacetase (Fah)	CRISPR-Cas9 was used to correct the Fah mutation in mouse models	54
Sickle cell anemia	β-globin gene	CRISPR-Cas9 was used to treat sickle cell disease patient blood	55
β-Thalassemia	hemoglobin subunit beta (HBB) gene	CRISPR-Cas9 was used to corrected the HBB gene mutation in human iPSCs from β-thalassemia patients	56
Cystic fibrosis	cystic fibrosis transmembrane conductance regulator (CFTR) gene	CRISPR-Cas9 was used to correct the CFTR gene in cultured stem cells of cystic fibrosis patients	57
Retinitis pigmentosa	RP1, RHO, and RPGR genes	CRISPR-Cas9 was used to interrupt the Rho (S334) mutation	58
Cataract	αA-crystallin gene	CRISPR-Cas9 was used to study the relationship of αA-crystallin mutations and human congenital cataracts	59
Human immunodeficiency virus (HIV)	long terminal repeats (LTRs) in HIV	CRISPR-Cas9 was used as a tool to mutate LTRs of HIV-1 DNA	60
Hepatitis B virus (HBV)	covalently closed circular DNAs (cccDNAs) in HBV	CRISPR-Cas9 was used to target cccDNAs of HBV	61
Human papilloma virus (HPV)	HPVE6 gene	CRISPR-Cas9 was used to target HPVE6 for cancer treatment	62
Epstein-Barr virus (EBV)	ephrin receptor tyrosine kinase A2 (EphA2)	using the EphA2 extracellular domain, a therapeutic strategy was developed	63

and PSEN2 genes are reported in the familial AD condition.[115] PSEN1 is a catalytic subunit of γ-secretase, a protease enzyme that cleaves amyloid precursor protein (APP), generating amyloid-β (Aβ). The A79V mutation in the PSEN1 gene increases the Aβ42/Aβ40 ratio by decreasing Aβ40. Studies have reported the correction of A79V and L150P mutations in PSEN1 in an induced pluripotent stem cell (iPSC) line derived from AD patients.[50,116] The CRISPR-Cas9 nucleotide-editing system was used to edit the point mutation "T" with wild-type "C" nucleotide in the A79V-hiPSC line. Moreover,

mutation in the APP gene increases β-secretase cleavage of APP, resulting in abnormally high Aβ levels in the brain. CRISPR-Cas9 was also used to correct the APP allele, thereby decreasing Aβ pathogenesis.[117] CRISPR-Cas9-based genome editing against AD has been reviewed in detail by Rohn et al.[51] In summary, CRISPR-Cas9 gene-editing technology can be used as an efficient strategy against genetically-induced neurological disorders.[104]

Metabolic Disorders

Metabolic liver disease (MLD) is caused by the defect of a transporter protein that results in abnormal metabolism of carbohydrates, protein, and fat. Recently, Villiger et al.[52] corrected mutations in the phenylalanine hydroxylase (Pah)^{enu2} gene to treat phenylketonuria (PKU), an autosomal recessive liver disease, using CRISPR-Cas9 editor systems in mice. In another study, computationally designed hepatocyte-specific CRISPR-Cas9 was used to target the murine factor IX (F9) gene against an MLD-related condition.[118] Yang et al.[119] worked on CRISPR-Cas9-mediated gene editing-based correction of X-linked deficiency in OTC to treat urea cycle disorder in an infant mice model.

Hereditary tyrosinemia (HT) is an autosomal recessive inherited disease that is associated with a deficiency of the enzyme fumarylacetoacetate hydrolase due to mutations in the Fah gene.[120,121] HT type I (HTI) causes severe hepatic disorders, such as cirrhosis, liver failure, and hepatic cancer, due to toxin accumulation. The CRISPR technology-based therapeutic strategy to correct HT was one of the first known studies in mice demonstrating delivery of CRISPR-Cas9 system components to adult mammalian organs.[122] In this study, reconstitution of a disease-causing mutation in the Fah gene was done via hydrodynamic injection of Cas9 nuclease, a sgRNA, and a donor oligonucleotide that led to a significant step toward gene therapy.[122] VanLith et al.[123] also showed hepatocyte-directed Fah gene repair in an HTI mice model using CRISPR-Cas9 against metabolic liver diseases. CRISPR-Cas9-based correction of the Fah gene in the HTI mice model showed weight stability prevention of liver cirrhosis in mice.[54]

Hunter syndrome, a metabolic disorder, is caused by the mutational dysfunction of an enzyme called iduronate-2-sulfatase (IDS) that leads to damage in lungs, heart, and brain. At the end of 2017, *in vivo* genetic editing for the treatment of Hunter syndrome via ZFNs was reported.[124] This is the first trial reporting the possibility of *in vivo* gene editing-mediated treatment of genetic diseases. At the end of 2018, Sangamo Therapeutics (Richmond, CA, USA) reported ZFN-based in-body gene editing in people with Hunter syndrome. Although they obtained mixed results, no adverse side effects were observed with this therapy.[125,126] This initiative in gene editing-based therapy suggests the possible use of CRISPR-Cas9 for the treatment of metabolic disorders. Nevertheless, CRISPR-Cas9 technology against metabolic disorders needs efforts to enter into clinical trials.

Cystic Fibrosis

Cystic fibrosis (CF), an autosomal recessive monogenic condition, is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene,[127] causing damage to the lungs and digestive system. It has been noted that the CRISPR-Cas9 approach may be a suitable method to correct mutations in the CFTR gene.[128] Crane et al.[129] corrected the mutation of CFTR in iPSCs via the CRISPR-Cas9 approach. In another study, sheep models ($CFTR^{-/-}$ and $CFTR^{+/-}$) were developed by CRISPR-Cas9-mediated CFTR gene disruption to understand CF pathogenesis.[130] The mutated CFTR sheep model is supposed to be a useful resource for the advanced development of new CF therapeutics. In another study, the CRISPR-Cas9 approach was used in the cultured stem cells of CF patients to correct the CFTR gene.[57] In primary adult stem cells, CFTR gene alteration was done through homologous recombination.[57] Therefore, CRISPR technology might be a potential approach for the treatment of CF in future.

Blood-Related Disorders

Fanconi anemia (FA), an autosomal recessive disorder, is caused by mutations in genes that are responsible for replication-dependent excision of interstrand DNA crosslink.[131] CRISPR-Cas9-mediated homology-directed recombination (HDR) in the FA gene implicate the application of genome editing for correcting the defects in the DNA repair pathway.[53] CRISPR-Cas9-mediated corrections of disruptive mutation in the FA complementation group F (Fancf) gene[132] and correction of the Fanconi anemia I (FANCI) gene[133] were reported in iPSCs from primary fibroblasts. The correction of FA mutations is implicated with the therapeutic approach of CRISPR-Cas9 against bone marrow failure.[132] Richardson et al.[134] found that human Cas9-induced single-strand template repair (SSTR) requires the FA pathway for DNA interstrand crosslink repair in cells.

Sickle cell (SC) anemia, a blood-related disorder, is caused by a mutation in the β-globin gene that results in the formation of abnormal hemoglobin S (HbS) protein.[135] As evidenced, CRISPR-Cas9 is a safe and promising gene therapy approach for SC anemia.[136–138] CRISPR-Cas9-based correction of the Hbs gene in hematopoietic stem and progenitor cells (HSPCs) from SC disease patient blood confirmed normal functional reinstitution of hemoglobin.[55] In an *in vitro* study, CRISPR-Cas9 components showed more than 18% gene modifications in $CD34^+$ cells.[139] They also reported correction of $CD34^+$ HSPCs derived from the bone marrow of SC anemia patients via CRISPR-Cas9 technology.[139] Ye et al.[140] created a hereditary persistence of fetal hemoglobin (HPFH) genotype in normal HSPCs using CRISPR-Cas9 and indicated safe autologous transplantation for patients with SC disease and β-thalassemia.

β-Thalassemia, another widespread genetic blood-related disease, is caused by the decreased synthesis of the β-globin chains of the hemoglobin tetramer, which reduces the production of hemoglobin.[56,141] Correction of the β-thalassemia splice mutation (IVSII-1G>A) in iPSCs using Cas9 along with the piggyBac transposon-modified donor vector strategy showed repair of the mutated gene with enhanced specificity and accuracy.[142] This might be a critical therapeutic approach toward the stem cell-based gene therapy against monogenic disorders in future clinics.

Eye-Related Disorders

Retinitis pigmentosa (RP), an inherited pigmentary retinal dystrophy, may cause loss of vision.[143,144] There are several mutations associated with this disease, such as mutations in RP1, rhodopsin (RHO), and RP GTPase regulator (RPGR) genes.[145] The CRISPR-Cas9 gene-editing technique can correct the Rho (S334) gene by subretinal injection of guide RNA (gRNA)-Cas9 plasmid, causing improvement of visual function through the discontinuation of retinal degeneration in rats.[58] Suzuki et al.[146,147] applied CRISPR-Cas9 using homology-independent targeted insertion (HITI), a method that allows the targeted insertion of a gene in non-dividing cells to improve the visual condition in rats. This suggests the possibility of *in vivo* gene correction using CRISPR-Cas9 technology.

Several mutations at different genetic loci are reported in the cataract condition, i.e., cloudiness of the crystalline lens.[148] It has been noted that αA-crystallin gene mutations are associated with an autosomal recessive cataract.[149] To understand the role of the αA-crystallin gene in congenital cataracts, Yuan et al.[59] used CRISPR-Cas9 to develop mutations in the αA-crystallin gene in an animal model. Recently, it has been noted that missense mutation of GJA8 is also associated with congenital cataracts.[150] Yuan et al.[151] have developed a GJA8 knockout rabbit model using the CRISPR-Cas9 system to study congenital cataracts in human. Currently, CRISPR-Cas9-mediated *in vivo* correction of a blindness condition is in a clinical trial that is discussed later in this review.

Viral Infection

HIV. HIV is a pathogen that attacks the human immune system and causes acquired immunodeficiency syndrome (AIDS). Although AIDS is now manageable due to highly active antiretroviral therapy (HAART), the life-long treatment of AIDS is of a great concern. It has been noted that expression of the HIV-1 gene is induced by long terminal repeats (LTRs), which are repeated identical sequences of DNA and assist in the insertion of retroviral DNA into the host chromosome. The genetic variation in the binding sites of LTRs may alter LTR-driven viral transcription.[152] It was observed that CRISPR-Cas9 can mutate LTRs in the DNA of HIV-1 provirus, leading to the breakdown of latent HIV-1 provirus.[60] In a negative feedback regulation of HIV-1, the Cas9 gene was placed under the control of a minimal HIV-1 promoter to express Cas9 in HIV-1 contagious cells. This might also reduce the complications attributed to the unusual high expression of Cas9 in the cells.[153] It has been reported that CRISPR-Cas9-mediated gene editing can inhibit multiple steps of HIV-1 infection.[154]

Hultquist et al.[155] used CRISPR-Cas9 technology for mechanistic examination of HIV host factors in $CD4^+$ T cells. Hartweger et al.[156] edited B cells using CRISPR-Cas9 in wild-type mice to reduce the effect of HIV-1 infection. Some factors, such as an apolipoprotein B mRNA-editing enzyme (APOBEC3G) and TRIM5α gene expression, can cause host restriction against HIV infection. CRISPR-Cas9 technology enhanced the expression of these host restriction factors against HIV infection,[157,158] suggesting the importance of CRISPR-Cas9 strategies as anti-HIV therapies. However, no curative therapy has been approved at this time.

Hepatitis B Virus (HBV). HBV causes chronic hepatitis, which is a frequent infectious disease worldwide. It has been observed that covalently closed circular DNAs (cccDNAs) of HBV reside in the contaminated cells, suggesting cccDNA as a potential therapeutic target to treat HBV infection.[159–161] It was found that CRISPR-Cas9 nuclease can mediate interference of episomal cccDNA in reporter cell lines, causing disruption in chromosomally integrated HBV sequences.[162] Dong et al.[61] demonstrated that CRISPR-Cas9 can reduce HBV cccDNA by inhibiting viral replication. Ramanan et al.[163] also showed that CRISPR-Cas9 cleaves viral DNA and suppresses HBV. Wang et al.[164] used an RNA interference (RNAi) technique with a sgRNA-microRNA (miRNA)-gRNA cassette along with Cas9 to inhibit the replication of HBV. Thus, it can be suggested that the disruption of the HBV genome through CRISPR-Cas9 technology might be a promising approach as an anti HBV therapy.

Hepatitis C Virus (HCV). HCV, a single-stranded RNA (ssRNA) virus, is the causative agent of hepatitis C, an inflammatory condition of the liver.[165] It has been found that the Cas9 endonuclease enzyme from the Gram-negative bacterium *Francisella novicida*, known as FnCas9, can target endogenous RNA.[166] The CRISPR-FnCas9 system has been used to inhibit HCV within eukaryotic cells.[167]

Human Papillomavirus (HPV). HPV, a double-stranded DNA (dsDNA) virus, infects mucosal cells or skin. It causes sexually transmitted disease and accounts for an estimated 11% of the global cancer incidence in women.[168,169] The RNA-guided endonuclease offers a therapeutic approach against HPV.[170] It was reported that the CRISPR-Cas9-mediated cervical cancer treatment can be done by targeting HPVE6.[62] CRISPR-Cas9 technology can also target the conserved regions of HPV6/11 E7 genes, indicating the therapeutic potential of gene editing against genital warts.[171]

Epstein-Barr Virus (EBV). EBV, a dsDNA virus, spreads primarily through saliva and causes mononucleosis.[172] CRISPR-Cas9 technology has been used for genome editing of EBV in human cells by modifying the BART promoter gene encoding viral miRNAs.[173] Ma et al.[174] showed that 87 lymphoblastoid cell line (LCL) and 57 BL genes are significant for the survival and growth in LCL and BL cells. Ephrin receptor tyrosine kinase A2 (EphA2) facilitates the entry of EBV in human cells. CRISPR-Cas9-mediated knockout experiments demonstrated that the EphA2 extracellular domain can bind with the EBV- glycoprotein gHgL and provide entry to the cell.[63] Thus, EphA2 might be a new potential target for therapeutic development.

Translation of Preclinical Studies into Clinical Use

Although preclinical studies on rodent models show evident efficiency of CRISPR-Cas9-mediated genome editing, variable results may be obtained during clinical translation of preclinical studies due to various reasons.[175] Inadequate analysis of the preclinical experimental data is one of the major reasons for variable results.[176]

In addition, the presence of various backgrounds of the most extensively used C57BL/6 and 129 strains of rodent models might result in improper data analysis.[177] Moreover, inbred mice cannot mimic the diversity of humans.[178] Another limitation of CRISPR-Cas9-mediated genome editing in rodents is the precise knowledge of the reproductive cycle of rodents, e.g., time of fertilization and time to recover the fertilized eggs. Therefore, it is important to consider these limitations and obtain in-depth knowledge of the animal model used in preclinical studies before entering into clinical use.

Clinical Trials

China performed the first *ex vivo* clinical trial (ClinicalTrials.gov: NCT02793856) using gene editing with the CRISPR-Cas9 technique in patients with metastatic non-small-cell lung cancer.[179] They targeted the PD-1 gene in T cells from peripheral blood of patients using electroporation of sgRNA and Cas9 plasmid, and infused them back into the patients. Very recently, they reported the presence of edited T cells in the peripheral blood of all patients who received infusions.[180] They concluded that although this method is feasible and safe, more advanced gene-editing technology is required to enhance the therapeutic efficacy.

Recently, Stadtmauer et al.[181] reported the results of a phase 1 in-human CRISPR-Cas9 technology-based clinical trial (ClinicalTrials.gov: NCT03399448), performed in three patients with refractory cancer in advanced stages. They removed TRAC and TRBC genes that encode the chains of endogenous TCR and PDCD1 (encoding PD-1 loci) from the T lymphocytes retrieved from the patients to increase the anti-tumor immunity. They further introduced a transgene (NY-ESO-1) that can recognize tumors. These engineered T lymphocytes were well tolerated by the patients up to 9 months after reintroduction into the patients.[181] However, chromosomal translocation was observed, which was reduced after some time.

Another clinical trial (Clincialtrials.gov: NCT03398967) proposed CAR T cell therapy for relapsed or refractory hematological malignancies due to $CD19^{-}$ tumor cells. They performed integration of two CARs (i.e., CD19 and CD20 or CD22) into the TRAC locus of T cells, which were able to recognize $CD19^{-}$ cells.[182] In addition, the use of gene-disrupted allogeneic universal CD19-specific CAR T cells (UCART019) using lentivirus (LV) delivery of CARs in patients with relapsed or refractory $CD19^{+}$ leukemia and lymphoma is also in a clinical trial (ClinicalTrials.gov: NCT03166878). In this study electroporation of CRISPR RNA was used to disrupt endogenous TCR and B2M genes. This system could minimize immunogenicity by avoiding graft-versus-host disease (GVHD). However, the results are still not published. Most recently, the FDA approved a clinical trial (ClinicalTrials.gov: NCT04438083) of CTX130, an allogeneic CRISPR-Cas9-modified T cell line, targeting CD70 against hematologic malignancies and renal cell carcinoma.

In 2019, successful treatment of SC disease and β-thalassemia was reported by Sangamo (ClinicalTrials.gov: NCT03432364) via CRISPR-Cas9-mediated disruption of the BCL11A gene in stem cells that were isolated from the peripheral blood of patients with hemoglobinopathies.[183] BCL11A is a transcription regulator that suppress the expression of the β-globin gene. In another partially successful trial (ClinicalTrials.gov: NCT03164135), *CCR5*-deleted hematopoietic stem cells were transplanted into patients with HIV-1 and acute lymphoblastic leukemia. Although the desired objective was not achieved, no major side effects were observed.[184] The study suggested the need for increasing the efficiency of CCR5 disruption in lymphocytes.[184]

In an *in vivo* clinical trial (ClinicalTrials.gov: NCT03872479) registered in 2019, the CRISPR-Cas9 gene therapy-based drug AGN-151587 was given directly into the eye, via subretinal injection, to cure a rare blindness condition called Leber's congenital amaurosis 10 (LCA10) that is caused by mutations in the gene CEP290.[185] This trial is the first approach that deploys CRISPR-Cas9 gene-editing therapy directly into the human body. At present, there are approximately 19 registered interventional clinical trials on CRISPR-Cas9-mediated gene-editing technology (Table 2).

Challenges and Future Directions

Although both preclinical work and clinical trials focusing on curative therapies are proceeding globally, the clinical translation of CRISPR-Cas9-mediated gene correction is associated with unpredictable outcomes.[186] Factors affecting the success rate of CRISPR-Cas9-mediated gene editing in humans includes off-target effects and cargo delivery methods. It has been observed that off-target effects are principally guided by sgRNAs, and thus rational designs of sgRNAs are necessary to ensure the efficiency of CRISPR-Cas9 gene-editing technology. It was observed that off-target effects were common in human cell culture with persistent Cas9 expression.[187,188] while these effects were less common in *in vivo* models.[189] It might be plausible that the occurrence of off-target effects in cell cultures are due to the influence of various factors, such as cell type, expression level, transfection method, cell culture maintenance, consecutive nuclease expression, guide sequence, and repair events.[186]

Earlier, cuts at off-target sites that generate single-stranded breaks (SSBs) in DNA were considered as a major obstacle and raised concerns about the specificity of CRISPR-Cas9 technology.[190] To reduce the possibility of SSBs, paired CRISPR-Cas9 nickase that binds to each forward and reverse DNA sequence on the flanking sides of target DNA was used to generate DSB formation.[191,192] Another approach suggested the use of inactive fusion protein consisting of Cas9 and FokI endonuclease enzyme, which becomes functional only after precise binding of sgRNA to both forward and reverse DNA sequences.[193] Although these approaches might reduce off-target cutting, there are certain limitations concerning restrictions in the location of protospacer-adjacent motifs (PAMs) near target DNA and designing sgRNAs for PAM alternatives.[194] In addition, these approaches might also increase the size of cargo that may generate constraint in the delivery system.

More importantly, repair events or a genomic rearrangement after sgRNA-induced DSBs is also a safety concern in CRISPR-Cas9-based

Table 2. Currently Registered Interventional Clinical Trials with CRISPR-Cas9-Based Gene Editing

Serial No.	NCT No.: ClinicalTrials.gov	Target Gene and Effect	Disease	Intervention	Phase	Study Start Date	Country
1	NCT04426669	cytokine-induced SH2 (CISH) protein inhibition	gastrointestinal (GI) cancer	tumor-infiltrating lymphocytes (TILs) inhibited immune checkpoint CISH	I/II	May 15, 2020	US
2	NCT04178382	target adjustment of antibiotics	severe sepsis	detection of alveolar lavage fluid changes the choice of early antibiotics in patients with pneumonia	–	August 1, 2019	China
3	NCT04037566	disruption of HPK1	refractory B cell malignancies	CD19-CAR-modified T cells with CAR delivered by lentivirus and Cas9 knockout of HPK1	I	August 2019	China
4	NCT03164135	CCR5 knockout	HIV	modified $CD34^+$ hematopoietic stem cells	–	May 30, 2017	China
5	NCT03545815	programmed cell death protein 1 (PD-1) and TCR knockout	mesothelin-positive solid tumors	CAR T cells to mesothelin with added PD-1 and TCR knockout	I	June 1, 2018	China
6	NCT03057912	E6 and E7 oncogenes of HPV16 and HPV18 deletion	HPV-related malignancy	plasmid in a gel containing a polymer to facilitate delivery	I	January 15, 2018	China
7	NCT03342547	stem cell-derived human intestinal enteroids	gastrointestinal infection	duodenal biopsies, followed by differentiation into mini-guts	–	April 18, 2018	China
8	NCT03655678	disruption of the erythroid enhancer to the BCL11A gene	β-thalassemia	*ex vivo*-modified hematopoietic stem cells	I/II	September 14, 2018	UK, Germany, Canada, Italy
9	NCT03728322	Correction of the hemoglobin subunit β-globulin gene	β-thalassemia	*ex vivo*-modified hematopoietic stem cells	I	January 2019	not specified
10.	NCT04244656	CTX120 B cell maturation antigen (BCMA)-directed T cell immunotherapy	multiple myeloma	biological safety and efficacy of CTX120 in multiple myeloma	I	January 22, 2020	US, Spain, Australia
11.	NCT04438083	CTX130 CD70-directed T cell immunotherapy comprised of allogeneic T cells	renal cell carcinoma	safety and efficacy of CTX130 in relapsed or refractory renal cell carcinoma	I	June 16, 2020	Australia
12.	NCT03747965	PD-1 knockout	mesothelin-positive solid tumors	CAR T cells to mesothelin with PD-1 knockout	I	November 2018	China
13.	NCT03398967	Cas9-mediated creation of CD19 and CD20 or CD19 and CD22 CAR T cells	B cell leukemia	CAR T cells to CD19 and CD20 or CD19 and CD22	I/II	January 2, 2018	China
14.	NCT04035434	creation of a CD19-directed T cell	refractory B cell malignancies	CD19-directed T cell immunotherapy	I/II	July 22, 2019	U.S.A., Australia
15.	NCT03745287	disruption of the erythroid enhancer to the BCL11A gene	sickle cell anemia	*ex vivo*-modified hematopoietic stem cells	I/II	November 27, 2018	US
16.	NCT03166878	βTCRα, TCRβ, β_2-microglobulin (B2M) knockout	B cell leukemia	CD19-CAR-modified T cells with CAR delivered by lentivirus and Cas9 knockout B2M and TCR to create universal T cells	I/II	June 2017	China
17.	NCT03044743	PD-1 knockout	EBV-positive, advanced stage malignancies	modified T cells selected for those targeting EBV-positive cells	I/II	April 7, 2017	China
18.	NCT04417764	PD-1 knockout engineered T cells	hepatocellular carcinoma	TACE combined treatment to block the blood supply of the tumor	I	June 20, 2019	China
19.	NCT03872479	removal of alternative splice site in CEP290	Leber congenital amaurosis 10	ZFN-mediated removal of intronic alternative splice site in retinal cells	I	September 26, 2019	U.S.A.

Search date: July 5, 2020.

therapeutic interventions. Although CRISPR-Cas9 technology can induce desired changes in the genomic sequences, the poorly understood and less controlled DNA repair mechanism is associated with the undesirable risk of biological dysfunctions. Deletion of a few kilobases in the neighboring CRISPR-Cas9 nickase activity, unexpected insertion (incorrect or partial) of donor DNA sequence to the site

of integration, and inversion are also unpredictable consequences of DNA repair mechanisms,[195] which might result in unexpected mutations.[196] The DSBs are repaired via non-homologous end joining (NHEJ) or HDR. NHEJ is a natural process to join spontaneous breaks in DNA and does not require any DNA template. However, HDR requires either a donor DNA template or DNA that is synthesized by the host's molecular recombination machinery. NHEJ is an error-prone mechanism that possibly leads to mutations. On the contrary, although HDR repairs DSBs more precisely, the incidence of HDR is very low when compared to NHEJ.[197] Various methods are suggested to suppress NHEJ, i.e., chemical suppression of NHEJ,[198] cell cycle synchronization,[199] silencing of genes,[200] and NHEJ-deficient cell lines.[201] Therefore, enhancing the efficiency of HDR and decreasing NHEJ is a critical challenge that needs to be fully explored before entering into therapeutic regimes to ensure the desired result of CRISPR-Cas-mediated gene editing.

As the treatment of human diseases needs to be tissue-specific, it is essential to efficiently deliver the CRISPR-Cas9 cargo into target tissue. Therefore, additional consideration should be given to the suitable delivery system that is based on the charge, size, and content of the CRISPR-Cas9 cargo. CRISPR-Cas9 cargo may be of three types, i.e., plasmid DNA encoding sgRNA and Cas9, a combination of sgRNA and Cas9 mRNA, and a combination of sgRNA and Cas9 protein. Various physical, viral, and non-viral systems have been used as vectors for the delivery of CRISPR-Cas9.

AAVs and LVs are the most commonly used viral vectors for gene editing.[202] The advantages of AAVs includes a less immunogenic property, serotype specificity, a good safety profile, and the ability to transduce both dividing and non-dividing cells.[203] However, mild toxicity is reported at high doses in animal models.[204] In addition, LVs also have the advantage of high transducing efficiency and non-immunogenicity. Moreover, LVs have the ability to be pseudotyped, allowing alterations in their cellular tropism. Another important aspect to consider while using viral delivery vectors is their packing limitation. However, it has been observed that the carrying capacity of AAVs can be extended up to 35 kb after modifications. It may be possible that the CRISPR-Cas9 gene-editing complex can activate the host immune response system,[205] indicating the need for modifications that can help to avoid an immune response in the host.

In addition to viral delivery systems, the use of non-viral systems or NPs for the delivery of CRISPR-Cas9 is also suggested.[205] Lipofectamine is a commercially available source of lipid NPs for sgRNA and Cas9 delivery in various systems.[206,207] The cationic property of lipid NPs might allow better packaging of the anionic Cas9/sgRNA complex in NPs. As observed, lipid NPs have low delivery efficiency due to their reduced uptake by cells, low translocation in the nucleus, and the possible entrapment of NPs in the endosomes. However, the use of optimal lipids for the synthesis of lipid NPs, surface modification by a cell targeting agent, avoidance of the immune system, and addition of an endosomal escape system can enhance the delivery efficiency of liposomes.[208]

Various other non-liposomal delivering techniques are also suggested for the delivery of Cas9 and sgRNA, i.e., FuGENE-6 reagent based on electrostatic interactions,[170] calcium phosphate transfection,[209], cell-penetrating peptides,[210] DNA nanoclew,[211], inorganic NPs,[212] and polyethylenimine and poly-L-lysine (PLL) polymers. PLL was used to develop a therapeutic delivery system, called multifunctional envelope-type nano devices MENDs, consisting of plasmid DNA and a lipid shell.[213] Further modifications in MENDs might allow the targeting of delivery cargo to mitochondria and the nucleus of cells.[214] Although MENDs showed a high transfection rate, *in vivo* validation of this delivery system is still required. Therefore, most of the delivery methods for the CRISPR-Cas9 system have both advantages and disadvantages. This generates a need for extensive work on the development of a suitable delivery system with high specificity, high transfection rate, high capacity, and low immunogenicity. Moreover, long-term safety and low toxicity associated with any delivery system also need consideration before developing CRISPR-Cas9-based gene-editing therapy against human diseases.[23]

Conclusions

The forthcoming applications of CRISPR-Cas9 are promising for the clinical world. With the progression of genome-editing techniques, the genome-editing research related to therapy for human diseases using CRISPR-Cas9 is developing quickly. Just a few years before, this technology was started, and presently a large number of scientists are working on this technology. Among them, most of the researches are using this genome-editing technology for therapy for human diseases.

However, CRISPR-Cas9 is still a budding technology that is applied to patients with severe conditions at a life-threating stage. Most of the clinical trials are currently in phase I/II. Until now, the clinical trials have been focused on the safety and efficacy of genome editing in humans, to improve molecular processes involved in genome editing. Therapeutic gene-editing technology is now expanding to ethically controversial alteration in the genome of human early-stage embryos to provide protection from HIV infection.[215] Such attempts can also suggest that the scientific community establish regulations on gene editing. However, the journey of CRISPR-Cas9 is highly interesting, and it offers a significant hope to researchers for the treatment of human deadly diseases.

AUTHOR CONTRIBUTIONS

Conceptualization, C.C. and S.-S.L.; Writing – Original Draft, C.C., G.S., and A.R.S; Writing – Review & Editing, A.R.S. and M.B.; Supervision and Funding, S.-S.L. and A.R.S.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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CHILDREN WHO HAVE EXPERIENCED TRAUMA: AN EXAMINATION OF THE ROLE OF RACE, ETHNICITY, AND CULTURAL FACTORS IN PRESENTING SYMPTOMS AND AT THREE MONTH (OR FIRST RECORDED) FOLLOW UP

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Abstract

CHILDREN WHO HAVE EXPERIENCED TRAUMA: AN EXAMINATION OF THE ROLE OF RACE, ETHNICITY, AND CULTURAL FACTORS IN PRESENTING SYMPTOMS AND AT THREE MONTH (OR FIRST RECORDED) FOLLOW UP

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Child traumatic stress is a pervasive problem that affects the well-being and healthy development of children from all races, ethnicities, and cultures. Major factors known to affect trauma symptoms include type of trauma, level or severity of trauma exposure, and age and gender of children. Utilizing Bronfenbrenner's ecological model, this study measured the additional influence of children's race, ethnicity, and cultural factors on symptoms after trauma. A dataset of children in treatment after experiencing trauma (0-21 years, N = 10,115) from The National Child Traumatic Stress Network (NCTSN), a federally funded initiative that collected longitudinal data across 56 research and treatment centers in the US, was examined, looking at clinical symptoms at baseline and at three month (or first recorded) follow-up. Predictors for symptoms included number of trauma types, age, gender, race, ethnicity (Latino/non-Latino), and three cultural markers, born outside the United States, English as the primary language not spoken at home, and refugee/immigrant status. Results (hierarchical regressions, logistic regressions) confirmed that age, gender, and number of trauma types predict the scores and clinical level of eight validated outcomes (e.g., CBCL externalizing, internalizing; PTSD measures) as well as the total numbers of functional

problems and clinical problems. Results also demonstrated that race, ethnicity, and culture affect symptoms but to a very small extent (i.e., these accounted for little variance) and in varying directions. For example, Black/African American children had lower internalizing scores compared to White/Caucasian children, while being Latino was associated with lower externalizing and higher internalizing scores than non-Latinos. Children with differing cultures sometimes scored better, sometimes worse, than their counterparts. For example, children who spoke English at home and were born in the United States had more functional problems, though fewer clinical problems. At three month (or first recorded) follow up, results demonstrated all children's scores improving. No differences at three month (or first recorded follow up) were found between our predictors in clinical rates except for children with more types of trauma who continued to show a greater likelihood of falling into the clinical range for externalizing and internalizing. Discussion focuses on the possible protective effects of cultural factors and the importance of an ecological model in understanding trauma symptoms in diverse populations.

Children Who Have Experienced Trauma: An Examination of the Role of Race, Ethnicity, and Cultural Factors in Presenting Symptoms and At Three Month (Or First Recorded) Follow Up

Child traumatic stress is a pervasive problem that affects the well-being and healthy development of children from all races, ethnicities, and cultures. Post-trauma symptoms experienced by child sufferers stem from a variety of occurrences, including illness (Catherall, 2004), family violence (Grych, Jouriles, Swank, McDonald, & Norwood, 2000), community violence (Cook-Cottone, 2004), natural disasters (Lieberman & Van Horn, 2004), and war (Balaban, 2009). While the majority of children are resilient and will not suffer long-term consequences, nor necessarily need treatment, many others–both with and without pre-trauma vulnerability–will suffer short-term and long-term effects of trauma exposure (Vijayakumar, Kannan, & Kumar, 2006). Whether a child is exposed to one specific type of traumatic event, or to a series of traumatic occurrences, a variety of physiological, developmental, and psychological consequences may result (Catherall, 2004). Such effects can range from mild anxiety symptoms to diagnosed Posttraumatic Stress Disorder (PTSD) and beyond (Cook-Cottone, 2004). It is critical to more fully understand post-traumatic effects in children, as poor developmental outcomes have been found for those children whose symptoms are not identified and treated (Grych et al., 2000). Despite this importance, the literature is in the early stages of understanding child response to trauma (Balaban, 2009), particularly regarding whether children of differing races, ethnicities, and cultures have different responses to trauma and its treatments (Himle, Baser, Taylor, Campbell, & Jackson, 2009).

To examine these factors, we must clearly define them before we are able to explore any effects. *Race* refers to phenotype, specifically physical differences that have a biological route that can be observed by physical appearance (Bradby, 2012). *Ethnicity* refers to membership in a group that has a specific heritage and shares core values, beliefs, and customs (Phinney, 1996; Schwartz, Unger, Zamboanga, & Szapocznik, 2010). In contrast, *culture* refers to shared meanings and understandings that are held by a group of people (Schwartz et al., 2010; Shore, 2002). Included in the definition of culture can be national affiliation and norms (Schwartz et al., 2010). Cultural factors include a broad array of descriptors such as acculturation, country of birth, and language choice. They also may include experiences that create shared meanings, understandings, and norms, such as being a refugee/immigrant.

Some literature suggests that trauma exposure, experience, and coping mechanisms may differ across races, ethnicities, and cultural factors (Chipman, Palmieri, & Hobfoll, 2011; Himle, Baser, Taylor, Campbell, & Jackson, 2009; Roberts, Gilman, Breslau, Bresalau, & Koenen, 2011), but few studies exist that specifically explore the possible roles that race, ethnicity, and cultural factors may have on trauma (Balsam, Lehavot, Beadnall, & Circo, 2010; Harrington, Crowther, & Shipherd, 2010; Lester, Artz, Resick, Young-Xu, 2010; Marshall, Schell, & Miles, 2009; Triffleman & Pole, 2010). Race, ethnicity, and cultural factors may contribute to the range of responses children have to trauma, from serving protective functions to leaving the children with more vulnerability (Wilson & Tang, 2009). Race, ethnicity, and cultural factors may also have unique roles in the way trauma is defined and understood (Aptekar & Stocklin, 1997; Wilson & Tang, 2009). The present study aimed to further expand our understanding of this topic in order to better diagnose and treat children from all backgrounds.

In the following literature review, child trauma and the possible influences of race, ethnicity, and cultural factors will be explored. The specific cultural factors of whether the child was or was not born in the United States, primary language spoken at home, and Refugee/Immigrant status will be focused upon.

First, an ecological framework will be introduced in order to provide a roadmap of how the individual, and his or her race, ethnicity, and cultural factors, can overlap with other environmental and self-factors to contribute to a child's response to trauma. Then, an overview of child trauma and its effects will be presented. Next, the review will discuss factors that have been identified to impact trauma effects, including the type and severity of trauma exposure, and the age and gender of the child. Finally, the review will explore the topics of race, ethnicity, and the cultural factors of country of birth, language spoken at home, and refugee/immigrant status and how they may impact the effects of trauma.

Review of Literature

Ecological Framework Applied To Trauma

Ecological frameworks within psychology have been put forth since the 1960s, and have developed from their initial use to later include Bronfenbrenner's ecological classification system (1979, 1986) and Moos' socio-ecological model of human adaptation (2002). Bronfenbrenner's classification system suggests that development occurs among multiple levels of interaction between the individual and his or her environment. These interactions are bidirectional, occurring both by the individual affecting the environment and by the environment affecting the individual. The levels include the *ontogenic* (individual factors), the *microsystem* (relationships/interactions the child has directly with surroundings including family, school, neighborhood), the *mesosystem* (interactions among the child's microsystems such as the child's parents' interactions with the child's teachers), the

exosystem (larger social system in which child may not be directly involved, such as community resources available and parental work hours) and the *macrosystem* (society and cultural beliefs) (Bronfenbrenner, 1979). Bronfenbrenner identifies the proximal processes as being the most influential in development, especially at the microsystem level, but affirms that outer levels can also have strong influences on inner structures (Berk, 2006).

An ecological framework as applied to trauma can be defined as taking into account Bronfenbrenner's classifications and examining the interactions among the person, event, and environment that led to the individual's posttraumatic response and resilience. Such a model informs treatment by aiming to achieve the best "ecological fit" for the person through the incorporation of the following: a person's unique constellation of experiences/characteristics; the specific factors of the event or events that can be classified as traumatic; and the social, cultural, and political context within which the person and the event has been framed. This model allows for capitalization of resilient factors and community support, without assuming that all victims of trauma need formalized treatment programs (Harvey, 2007). The model further defines "resilience" as multidimensional rather than binary, something that a person either has or does not have. Resilience is seen as transactional, shaped by the interactions among biological traits, social interactions, and other environmental factors which allow for the individual's active participation in shaping–and being shaped–into a resilient being (Rigger, 2001). Because resilience is not all-or-nothing, it becomes possible for a person to suffer and to tap into resilient resources simultaneously (Harvey, 2007).

Current work in the trauma field has begun to yield results regarding identification of some of the areas that should fit within the overall ecological framework, including cultural demands, cultural resources (Hobfoll et al., 2002) and the generational transmission of trauma (Prelow, Danoff-Burg, Swenson, & Pulgiano, 2004). Despite this progress, many

more cultural factors have yet to be identified and explored in the effort to fully understand how trauma is experienced and can be overcome.

The ecological model defines recovery from trauma through examining functioning in eight domains (Harvey, 1996). A person may be impaired in certain domains but express resilience in others. The model, while encouraging and including individual-focused treatment, recognizes that many survivors will not seek or be comfortable with specialized care. For this reason the model looks also towards environmental and community resources that can support recovery. Additionally, its assessment process is robust, and includes not just an evaluation of distress and functioning- but also inquiry into attitudes and values of the society surrounding the person (and relevant family and friends, service providers, community leaders, etc.), as well as any other factors that may impact the ecological map of the person's life. This dynamic set of influences work together in an individual's response and recovery (Harvey, 2007).

Currently, the majority of research involving children and trauma focuses more on individual risk factors and associated psychopathology, and far less on resiliency or group factors in general (Betancourt & Khan, 2008; Fergus & Zimmerman, 2005). By applying an ecological model, resilience and group factors can be better focused upon and explored.

There is a dearth of research that tests and explores the ecological model for trauma, and even less research concerning children. However, a few findings do exist. In two studies involving child soldiers of Sierra Leone, an ecological framework was applied. One study, using a sample of 260 children ages 10-17, involved an understanding of internalizing, externalizing, risk, and protective factors in mental health outcomes. The study identified community acceptance as being associated with decreases in externalizing and internalizing problems of Sierra Leone child soldiers (Betancourt, Brennan, Rubin-Smith, Fitzmaurice, &

Gilman, 2010). In a second study with this population, the focus was on stigma and psychosocial adjustment. Researchers found that the higher the discrimination experienced by the child soldier, the less family/community acceptance that occurred. Additionally, the higher familial acceptance experienced, the less hostility expressed by the child soldiers (Betancourt, Agnew-Blais, Gilman, Williams, & Ellis, 2010). Both of these studies were able to identify factors unique to the Sierra Leone population concerning the effect of trauma that would not have been uncovered had domains beyond the individual not been explored.

Other research conducted using an ecological framework includes studies utilizing the framework for understanding parenting in the face of domestic violence (Levendosky & Graham-Berman, 2000). One study, based on a sample of 69 outpatients of 5-12 years old, tested an ecological suicide risk model across six domains: family support, family stressors, child risk factors, child protective factors, child traumas, and social supports. The child's ethnicity was embedded as a component within the child protective factors, though no mention of cultural values was included (Jackson & Nuttall, 2001). In another study, a cross-sectional community sample involving 654 Australian maltreated children tested outcomes of a therapeutic intervention based on the ecological framework, which allowed the authors to identify and explore variables–including culture–as both a potential risk factor (intergenerational trauma, being part of the non-dominant culture, lack of belonging) and a potential resilience source (Jackson, Frederico, Tanti, & Black, 2009). In a third study, which tested a grief and trauma group model among Hurricane Katrina child survivors, an ecological perspective was utilized to create and test the treatment (Salloum et al., 2009).

Though the literature that utilizes an ecological framework for trauma is sparse, the ability of such an approach to discern more layers beyond the individual–including culture–is profound and suggests a need for further consideration. The study reported here attempts to

begin filling in these gaps by exploring ways in which race, ethnicity, and the cultural factors of country of birth, primary language spoken at home, and refugee/immigrant status may be contributing factors in a child's response to trauma.

Child Trauma Response

Childhood trauma can impact personality, cognitive performance, self-esteem, impulse control, and outlook concerning the future (Pynoos & Nader, 1993). In the immediate aftermath of a traumatic event, children will often cry, be extremely frightened, and exhibit high levels of distress (Cohen et al., 2009). From the time of trauma, most children begin to have repetitive and intrusive thoughts about the event. Intrusive thoughts will often occur during times of relaxation, or when attempting to sleep. Such thoughts may happen in response to environmental triggers that remind them of the traumatic event or elements of the experience. While intrusive thoughts appear common, it is far more unusual for a child to experience dissociative flashbacks, in which the event is re-experienced in vivid detail. Instead, children will often have sleep disturbances in the immediate weeks after the event, including fears of the dark, nightmares, and an inability to remain asleep for extended periods of time (Eth, 2001).

Separation anxiety is another common effect of trauma on children. This may take the form of the child not wanting the caregiver to leave his or her side and may also entail a return to co-sleeping, even for adolescents (Stien & Kendall, 2004).

Child trauma survivors are often pressured by those around them to talk about their experiences, but may feel reluctant or unable to share the full extent of their suffering. Their reluctance may be due to developmental limitations or a fear of upsetting their caregivers. Peers will often hesitate to ask children about the trauma, to avoid further upsetting them and

as a result of being unsure how to broach the topic. Sometimes this may lead to children feeling alienated, different from others, or that others do not care (Smith et al., 1999).

Cognitive changes experienced by traumatized children can be profound. These changes can include concentration problems, which lead to difficulty in recalling past learned skills and in progressing successfully in their education (Stien & Kendall, 2004). Studies have found that traumatized children experience difficulty with memory (Dalgleish et al., 2005; Moradi, Neshat Doost, Taghavi, Yule, & Dalgleish, 1999), with attention (Meesters, Merckelbach, Muris, & Wessel, 2000), and with abstract reasoning (Beers & De Bellis, 2002).

Neurophysiological and biological changes have also have been found to occur within traumatized children (Perry, Pollard, Blakley, Baker, & Vigilante, 1995). The fight-or-flight mechanism is less fully formed in children, and thus traumatized children will often experience hyper-arousal. If not calmed via parental intervention or subsiding of the threat, hyper-arousal can lead to immobilization and then to dissociation as a mechanism of coping. Once dissociation occurs, the child is then able to normalize his or her heart rate and feel calm; however, the dissociation may have other more profound long-term effects (Putnam, Hornstein, & Peterson, 1996;Van der Kolk, 2007). Some traumatized children lose control of the startle response (Ornitz & Pynoos, 1989) or experience changes in their circadian rhythm (Glod & Teicher, 1996). Traumatized children may also be adversely affected by sustained increases of neurotransmitter activity, which can lead to inhibited development of the brain and potential developmental disorders (Pfefferbaum, 1997; Perry, 1994).

Another impact of trauma on children is that trauma survivors will often become mature beyond their years, developing an understanding of their own mortality. This results

in a loss of innocence and can lead to further estrangement from peers and to overall feelings of pessimism about the world and their future (Eth, 2001).

Further, children often develop fears related to the trauma they encountered. These fears can lead to avoidance of many situations and can interfere with daily functioning (Cohen et al., 2009). Child survivors also have been identified as sometimes having survivor guilt, leading to feeling badly that they survived and others did not, or even feelings of self-blame for what happened to them (Tobin & Friedman, 1984).

While all children may become depressed and suffer from high levels of anxiety and even panic attacks as a result of the trauma, adolescents tend to have higher incidences of depression and suicidal ideation (Eth, 2001).

The amount and severity of symptoms experienced often is directly related to the level of exposure to the trauma, with higher levels of exposure leading to more intense symptoms. This effect has been found with different ethnicities and cultures around the world – including Nicaragua (Goenijian et al., 2001), South Korea (Lee et al., 2004), Australia (McDermott et al., 2005), Armenia (Pynoos et al., 1993), and other countries.

In summary, trauma in children can lead to depression, anxiety, and a variety of other internalizing and externalizing symptoms. Trauma can also cause neuropsychological symptoms and physiological changes within the brain (Cohen et al., 2009). The higher the level of exposure to the trauma, the more likely the effects will be profound (Pynoos et al., 1993).

Post traumatic stress disorder (PTSD). PTSD can be defined as an anxiety disorder which occurs in response to a traumatic stressor. PTSD is differentiated according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) by (1) persistent re-experiencing of thoughts or dreams about the event, (2) avoidance of cues associated with the

trauma or emotional numbing, and (3) persistent physiological hyperactivity or arousal. These symptoms must be present for more than one month following the traumatic event and cause clinically significant disturbance in functioning. PTSD is classified as acute when present for less than three months, chronic when present for more than three months, or delayed onset when symptoms initially develop six months or more after the trauma (American Psychiatric Association, 1994, DSM IV). In the immediate aftermath of a trauma, some children may experience Acute Stress Disorder (ASD) while some may develop PTSD after a period of time has passed. For diagnosis, ASD and PTSD both require re-experiencing, avoidance, and arousal symptoms for diagnosis. However, in addition to these core symptoms, ASD also requires evidence of dissociative symptoms, such as feeling disconnected to surroundings and difficulty in recalling important parts of the trauma. ASD can only be diagnosed between two days and four weeks after the traumatic event, unlike PTSD, which can only be diagnosed after four weeks (DSM-IV TR; Harvey & Bryant, 1999). It is estimated that one-third of those diagnosed with ASD will develop PTSD (Harvey & Bryant, 1999).

Prevalence rates of PTSD. Estimates of PTSD prevalence are for the most part conducted after different types of disasters. The rates reported differ dramatically as a result of several dissimilar aspects of applied methodologies, including different measures being used, different sample sizes, different time periods between the traumatic incident and the survey, and many others. However, where standard methodologies have been used, incidence is often between 30-60% of survivors (Yule, 2001).

PTSD prevalence rates also differ based on the type of trauma encountered, with intentional traumas (such as sexual abuse) and personal exposure to war being more traumatic overall than natural disasters (Peltonen & Punamaki, 2010). PTSD prevalence rates

further differ based on the severity of the traumatic event, how close the child was to the trauma, and the time elapsed since the trauma occurred (McCart, Sawyer, & Smith, 2008). Other variables that may increase risk of PTSD include being injured from the trauma, perceiving a threat to one's life during the trauma, a family history of psychopathology, and lower levels of perceived social support (McCart et al., 2008). Finally, prevalence rate differences can be found throughout the literature as a function of whether full diagnosis of PTSD is being reported versus merely reporting of PTSD symptoms (Dyregrov & Yule, 2006).

Flaws of applying PTSD classification to children. The diagnosis of PTSD has many flaws when being applied to children. Its primary flaw is that the diagnostic criteria were developed specifically for adults, based on research on adults, without special consideration for application to children (Putnam, 1997, Van Der Kolk, 2007). As such, some children who suffer from PTSD may not fit the criteria, while other children who fit the criteria may actually have another disorder (Stien & Kendall, 2004, Van Der Kolk, 2007).

Assessing whether the PTSD criteria have been met in children may be difficult to impossible, for a variety of reasons. First, many children have limited verbal skills and developmentally different ways of reacting to stressors. Such differences can include an inability to verbalize symptoms or to demonstrate numbing and withdrawal. The re-experiencing of symptoms may also be manifested differently than adults–such as through dreams and reenacted play–versus the flashbacks or intrusive thoughts that are common in adults with PTSD (Balaban, 2009; Eth & Pynoos, 1985; Scheeringa, Zeannah, Drell, & Larrieu, 1995). Children who have suffered trauma will often have vivid dreams, in which they re-live the event or events with all the feelings experienced at that time. Traumatized children may end up being killed in their dreams; they often will repeat the same dream every

night (Terr, 1991). With regards to play, post-trauma children may engage in two-dimensional monotonous play, in which the same themes surrounding the trauma are carried out. This type of play differs from normal three-dimensional play in which children use play as a tool to expand their mind and explore their environment, and in which the themes change as the children develop (Terr, 1991).

There are other symptom manifestations of trauma that exist only in children, or have a higher rate of occurrence in children, and are not fully accounted for by the current DSM IV diagnosis (Putnam, 1997; van der Kolk, 2007). Such symptoms include somatization, a heightened level of normal fears, impaired concentration, hyperactivity, increased aggression and tantrums, irritability, a heightened startle response, pessimism, and magical thinking (Stien & Kendall, 2004). It is for this reason that the current study chose to look at a full array of potential symptoms from trauma–beyond just PTSD–to include internalizing/externalizing symptoms and behavioral indicators.

Factors That May Impact Trauma Effects

Some of the major factors that have been identified to impact the effects of trauma on children include the type and level of exposure to trauma, children's age, and children's gender. Children can be exposed to a variety of traumatic events occurring in the different ecological layers of their lives, including the ontogenic level, microsystem, exosystem, and macrosystems in which they function. Depending on the trauma, various symptoms may be more or less present (Karr, 2009).

Ontogenic. Within the ontogenic level, children can experience a medical trauma or traumatic loss and grief. A medical trauma can include injury, illness, medical procedures, and treatments. Common symptoms include anxiety and irritability, intrusive thoughts about the illness or medical issue, and avoidance of going to the doctor or the hospital (Brown,

Pearlman, & Goodman, 2004; The National Child Traumatic Stress Network, n.d.). Thoughts and feelings surrounding the medical issues can differ between children and their family members, sometimes adding to the stress burden. The symptoms can also have a spillover effect interfering with the children's functioning at home, with peers, and in school (Brown et al., 2004).

Traumatic loss and grief occurs when children experience the death of a loved one, leading to traumatic symptoms that interfere with their ability to process the loss in a developmentally appropriate manner (Brown et al., 2004). The death may be caused by traumatic means—such as violence or a large-scale disaster—but it may also be from natural causes. The essential characteristic of traumatic grief is the child's own interpretation of the experience as traumatic, beyond what is typically expected surrounding such a loss (Friedman & Keane, 2007). One common symptom specific to traumatic grief is children re-experiencing the loss through images of death; the child may have intrusive thoughts about the person who has died. Children may also engage in avoidance of reminders of both the actual death and the persons they have lost. Such avoidance can include avoiding specific places or activities that used to be enjoyed with the person. Additional traumatic grief symptoms common in all trauma types include irritability, sleep interference, concentration, and hyper-arousal (Pearlman, Schwalbe, & Cloitre, 2010).

Microsystem. Within the microsystem children can experience maltreatment, domestic violence, and resulting complex trauma. Child maltreatment includes physical abuse, sexual abuse, emotional abuse, and neglect (Wolf & Nayak, 2003). Unique trauma-specific symptoms often seen are feelings of powerlessness, stigmatization surrounding the events, and feelings of betrayal leading to difficulties in interpersonal relationships (Finkelhor & Browne, 1985). Particular to children who have been physically abused, they

will often exhibit higher levels of aggression, delinquency, and risk-taking behaviors (Margolin & Gordis, 2000). Children who have been sexually abused, by contrast, will often suffer from sexual development problems as well as gender identity and sexual orientation concerns (Tharinger, 1990).

Domestic violence includes physical, sexual, or emotional abuse occurring between adults within children's homes. This abuse can be actual or threatened and can encompass the children witnessing such an occurrence and/or mere exposure to its presence (Moroz, 2005). Common symptoms arising from such trauma include parentification of the children, aggression, violent outbursts, isolation, and psychosomatic problems (Fantuzzo & Mohr, 1999).

Intra-family trauma tends to lead to the greatest severity in symptoms. This may be partially due to survivors' tendency to internalize fault. With increased self-blame often comes an increase of symptoms (Chaffin, Wherry, & Dykman, 1997; Ford, Stockton, Kaltman, & Green, 2006). Child maltreatment and domestic violence often co-occur and cause children exposure to multiple traumatic events. When such events occur for a prolonged period of time or in extensive amounts, they are often classified under the umbrella term, complex trauma. Complex trauma can have a profound impact on children's development in all domains. Complex trauma typically occurs beginning in early childhood, within the primary caregiving system, and is chronic in nature (The National Child Traumatic Stress Network, n.d.). As a result, children may develop severe emotional dysregulation that can have a cascade effect, causing them to become more vulnerable to experiencing subsequent traumas throughout childhood and beyond (The National Child Traumatic Stress Network, n.d.).

Exosystem. Within a child's exosystem, children can experience community or school violence that can have a profound impact on development. Community violence is violence between persons who are not related. Such violence can include but is not limited to shootings, physical assaults, and rapes. Children may experience community violence in a variety of roles, including as victims, witnesses, or perpetrators (The National Child Traumatic Stress Network, n. d.). School violence also transpires between non-relatives and tends to encompass a broad range of occurrences to both students and teachers, including but not limited to violence, threats, victimization, bullying, and overall disruption of a positive educational climate (The National Child Traumatic Stress Network, n.d.). School violence can result in children becoming hyper-vigilant at school (in order to avoid becoming a victim), wary of their peers, and less able to learn, thereby inhibiting academic success (Flannery, Wester, & Singer, 2004). Children may also feel powerless, become angry, exhibit increased aggression, and have an increased likelihood for engaging in self-harm (Flannery et al., 2004).

Macrosystem. Within the macrosystem in which the children functions, children may experience a natural disaster, refugee/immigrant or war zone trauma, or acts of terrorism. A natural disaster is defined as any natural catastrophe such as hurricanes, earthquakes, and fires that cause widespread damage. Such destruction must be so extensive as to require government and other relief organizations to help with the aftermath (The National Child Traumatic Stress Network, n.d.). Factors unique to natural disaster trauma often include specific threats to children's lives or near death experiences, the loss of loved ones, and/or the loss of children's homes and possessions. Children will often experience extreme feelings of helplessness, personal responsibility for not mitigating the harm, and potential dislocation from family and home (Carswell & Carswell, 2008; Baker & Shalhoub-Kevorkian, 2008).

War zone trauma includes war related exposures, political violence, Refugee/Immigrant experiences, and forced servitude as soldiers. The trauma symptoms from such exposure tend to resemble those seen in veterans of combat (The National Child Traumatic Stress Network, n.d.). Exposure leads to high levels of PTSD, depression, and other psychiatric disorders (Masinda & Muhesi, 2004). The most common effects of war trauma exposure across cultures are PTSD and anxiety disorders, followed by aggression and depression (Baker & Shalhoub-Kenorkian, 1999). Such effects have been seen in children from a variety of cultures including Lebanon (Macksoud et al, 1996), Mozambique (Boothby, 2006), and Cambodia (Sack, Seeley, & Clarke, 1997).

Additionally, terrorism often occurs in relation to war zone trauma. Terrorism is defined as the use of violence in order to coerce governments or populations to follow certain political or religious paths. Such acts can occur as large-scale events that affect masses of persons, or as individual occurrences such as a sniper attack (The National Child Traumatic Stress Network, n.d.). Symptoms most commonly seen in relation to terrorism acts include intrusive memory of the event, heightened startle reactions, and insomnia (Shaw, 2002; Stuber et al., 2002). Additionally, parental anxiety and extensive news coverage have been demonstrated to increase children's symptoms of distress (Shaw, 2002).

Age. Children's age has also been demonstrated to be a factor in the severity of reaction to trauma (Green et al., 1991). In Western cultures, pre-school age children demonstrated less psychological distress after disasters than older children with the same exposure (Scheeringa, Zeanah, Myers, & Putnam, 2003), including less emotional numbing and avoidance (Dyregrov & Yule, 2006). However, pre-school children exhibited higher occurrences of fears, regression in toileting, aggressive actions (Green et al., 1991), repetitive play, and re-enacting the event (Dyregrov & Yule, 2006). In this age group, parental reaction

has been demonstrated to have the strongest effect on the children's adjustment. If the parents react calmly, they serve to model how to adapt to the circumstance for the children (Handford et al., 1986; Scheeringa et al., 2003). For children over the age of ten, their reactions come closer to adult responses to trauma (Dyregrov & Yule, 2006). Such children are more able to cognitively understand the event, reflect upon their experience, and grasp consequences of the trauma (Dyregrov & Yule, 2006). For these reasons, older children have been found to have a greater overall incidence of emotional distress than their younger counterparts (Yule, Perrin, & Smith, 1999).

The influence of children's age on the severity of their reaction to trauma has also been found across cultures. In different cultures there is some evidence that age is associated with more severe PTSD symptoms. For example, younger age was associated with PTSD symptoms in children who experienced an earthquake in Japan (Endo, Shioiri, & Someya, 2009) and in Polish children after a flood (Bokszczanin, 2007). However, in China, older children who experienced an earthquake were found more at risk for depression and PTSD than other age groups (Fan et al., 2010). By contrast, other studies have found little age difference in PTSD rates; for example, a meta-analysis examined 34 samples of 2,697 children and found no notable differences based on children's ages (Fletcher, 1996). No differences were also found in a study of Turkish children (ages 8-15) following an earthquake (Bal, 2008).

Gender. Children's gender plays an influence in the incidence and level of PTSD experienced, with the majority of the literature finding that girls have higher rates and more severe levels of PTSD (Green et al., 1991). Some estimate that girls have up to five times a greater likelihood of developing PTSD, and that girls are also more likely to report symptoms they are experiencing (Breslau, Davis, Andreski, Peterson, & Schultz, 1997). Such findings

are consistent with other research demonstrating girls' tendency to internalize distress more in the form of anxiety and depression, whereas boys tend to externalize problems in their outward behavior, leading to aggression (Ostrov & Keating, 2004).

Gender differences in PTSD symptoms have been found across cultures. Girls were found to have higher rates of PTSD in several studies, including a study of children displaced after the war in Croatia (Durakovic-Belko, Kulenovic, & Dapic, 2003), a study of Turkish children after an earthquake (Bokszczanin, 2007), and a literature review examining mental health issues of unaccompanied Refugee/Immigrant minors (Huemer et al., 2009).

Some studies, however, contradict gender differences in PTSD symptoms. A group of studies suggest that sex differences do not exist for pre-school age children (Burke et al., 1982; Green et al., 1991), but instead begin to appear for school age children (Gleser et al., 1981) and continue to be found for adolescents (Milgram et al., 1988). In another study, involving children living in Kabul, girls were found to have a lower prevalence of PTSD (14%) than boys (26%). The study examined a school sample of children and their cumulative experiences. Its prevalence rates may be different because the PTSD was not associated with a specific common experience such as a natural disaster or war (Catani et al., 2009).

Race and ethnicity. The race and ethnicity of children may change their risk of experiencing certain types of trauma (Roberts et al., 2011). Race and ethnicity may also change the likelihood of experiencing PTSD (Adams, Boscarino, & Galea, 2006; Kulka et al., 1990) or of experiencing certain symptoms from trauma (Choi & Park, 2006). Additionally, race and ethnicity may play a role in treatment seeking and response to treatment (Anderson & Mayes, 2010).

There is some evidence that trauma exposure has been found to differ by racial and ethnic minority status, but few studies pertain specifically to children. These few studies have examined sexual abuse prevalence rates and suggest higher rates for Latino female adolescents as compared to other ethnic minority groups (Newcomb, Munoz, & Carmona, 2009) and lower rates among Asian women (Russell, 1986). According to one study, African Americans and Latinos in the U.S. had a higher risk of child maltreatment than European Americans and other ethnic minorities. Furthermore, Asians, African American males and Latino females had a higher risk of exposure to war related trauma (Roberts et al., 2011). Notably, these findings were in a retrospective study of 34,653 adult respondents and not with a child sample (Roberts et al., 2011).

Some studies suggest that there is an increased risk for PTSD in racial and ethnic minority persons (Norris & Alegria, 2005; Pole, Gone, & Kulkarni, 2008). Reasons that have been suggested include cumulative burden of previous trauma, the severity of the trauma, psychiatric comorbidity, and lack of access or utilization of mental health treatment (Brewin, Andrews, & Valentine, 2000). In one study conducted in the U.S., the risk of PTSD was found to be higher among African Americans, and lower among Asians, in comparison to European Americans (Roberts et al., 2011). Higher levels of PTSD have also been found among Latino populations in the U.S. (Pole et al., 2005).

Differing symptom expression has been found among racial and ethnic minority groups. With depression, differences have been found for somatic symptoms, with Asian and Latino children experiencing higher levels than other ethnic minority groups (Choi & Park, 2006). There is even some suggestion that the acceptable physical symptoms may differ by ethnicity, with Latinos being more likely to endorse constipation and diarrhea, as compared to other physical complaints, when suffering from depression (Choi & Park, 2006).

Further differences by race and ethnicity when experiencing depression include: African American children have been found to experience higher levels of anger and aggression; Latino children experience more decreased energy, crying, and low self esteem; and Asian children experience more overall sad mood (Choi & Park, 2006).

When experiencing anxiety, different symptom expression has also been observed across racial and ethnic minority children. Similar to depression, Latino children more often experience somatic symptoms in relation to anxiety (Pina & Silverman, 2004). Some theorize that such symptom expression is more acceptable in Latino cultures, especially for males who often internalize the "Machismo" concept which stresses the importance of being a strong male (Pina & Silverman, 2004), as well as being more acceptable in Asian cultures, for which psychological illness carries with it cultural stigma (Chen et al., 1998).

Mechanisms for differences among racial and ethnic groups in trauma exposure and symptoms. An additional component to understanding how race and ethnicity may impact trauma exposure and symptoms is to understand the possible contributing causes of differences. Potential mechanisms suggested by the literature include biological differences among groups (Murakami et al., 1999), differences in historical backgrounds (Al-Issa & Tousignant, 1997), unique family processes (Anderson & Mayes, 2010), and differing treatment seeking behaviors (Roberts, Gilman, Breslau, Breslau, & Koenen, 2011).

Some literature suggests that racial or ethnic minority groups differ biologically, which may lead to differences in psychological expression. For example, there is some evidence that certain alleles that have been linked to anxiety traits and depression appear in different frequencies among Japanese, African American, and European American adults (Murakami et al., 1999; Katsuragi et al., 1999). Additional biological differences have been suggested concerning the onset of puberty and the linkage to depression with early

maturation; early puberty is associated with positive feelings in African American girls but negative feelings in Latina girls (Anderson & Mayes, 2010; Nadeem & Graham, 2005). Finally, physiological arousal differences have been suggested based on race and ethnicity, with Latina girls reporting higher physiological anxiety than African American girls, and African American boys reporting higher physiological anxiety than European American boys (McLauglin et al., 2007). In contrast, another study compared arousal rates while performing a behavioral task. European American children demonstrated higher pulse rates and blood pressure as compared to their African American counterparts (Beidel et al., 1994). Understanding the biological differences between races and ethnicities—and how such differences may inform differences in behavior—is still in its infancy stage, especially in studying children, but the literature thus far suggests there are many mechanisms that have yet to be fully understood.

Historical background may also lead to differences in child reaction to trauma. Persons of a race or ethnicity with a history of oppression or genocide may live with the effects of such trauma exposure, even though it did not happen to them as individuals but instead to their ancestors. This concept and its effect has yet to be fully explored, but has been studied most in depth with African Americans, Jewish Holocaust survivors, and indigenous people of North America (Brown, 2008). For African Americans, the involuntary migration to the United States—combined with legalized slavery, discrimination, and racism—created an environment of traumatization and an increased vulnerability to further trauma (Pole et al., 2008). While it is important to note that some persons included in the African American category came more recently to the United States as immigrants from Africa and the Caribbean, these immigrants also face the racial inequality and ongoing

discrimination which was legalized up until the 1960s and that continues through various mechanisms today (Pole et al., 2008).

Another contributor to differences in racial and ethnic minority reaction to trauma may be differences in family processes, which can serve both as a vulnerability or protective factor depending on the culture and the type of trauma. Within the African American community, the family structure often extends beyond the nuclear family to extended members such as grandparents and cousins, as well as to non-related persons who are considered family members (Carswell & Carswell, 2008; Hatchett, Cochran, & Jackson, 1991). These kin members provide support to family members in need, often adopting rejected and orphaned members, particularly children and the elderly (Hatchett, Cochran, & Jackson, 1991). As such, strong familial ties serve to protect and buffer the negative affects of trauma.

Current research is limited as to how such processes may play out in the various types of trauma, but there is some literature that explores family structure and physical abuse. For example, in Latino cultures the concept of Machismo is an important value for males. It is defined as strong identification and adherence to rigid gender roles that can include being aggressive, authoritarian, and having a negative attitude towards females (Deyoung & Zigler, 1994). In a family that subscribes strongly to such a belief, the father is considered the head of the family and may inflict as much punishment as he sees fit in order to assure the children's good behavior (Bird & Canino, 1982). Of note, Machismo also instructs one to protect and provide for his family, and instills self-respect in those that believe in it (Torres, 1998). An example of another protective family cultural factor in Latino culture is the value of "Familism." Familism emphasizes family unity and a sense of obligation to provide emotional support and care for all of its members. It emphasizes the family over the

individual's needs (Cuellar, Arnold, & Gonzalez, 1995). In the context of physical abuse, Familism can be a protective factor counteracting the Machismo ideal. However, Familism can also be a source of vulnerability, because a family that is less focused on the individual may provide less nurturing to each individual child (Ferrari, 2002).

An additional difference in racial and ethnic reaction to trauma may lie in treatment utilization, or whether members of a culture seek out and use professional services for psychological disturbances. Reasons for racial and ethnic minority groups underutilization of services include culturally associated stigma (Zayfert, 2008), the lack of culturally sensitive and appropriate treatments (Lester et al., 2010), and the socioeconomic impact of seeking treatment, including cost, lack of transportation, and needed child care (Schruafnagel, Wagner, Miranda, & Roy-Byrne, 2006).

While the literature suggests definitive differences in child trauma experience, reaction, and treatment overall among children from different races and ethnicities, it is important to recognize that often the true reason for differences can be hard to discern in the face of the large heterogeneity among racial and ethnic minorities, including differences in socioeconomic status, urban/rural location, immigration status, refugee/immigrant or native experience, and acculturation level (Pole et al., 2008). For this reason, exploration in this study went beyond race and ethnicity, and took into account cultural factors through examining country of birth, primary language spoken at home, and refugee/immigrant status.

Cultural factors. Beyond ethnic identity, children's cultural background serves as the backdrop to frame interpretations of what they experience. The cultural background includes how the child's culture defines trauma. It also incorporates common symptoms that are typically seen within the child's culture, including culture-bound syndromes that may exist within his or her culture. Furthermore, the cultural background includes cultural factors

such as level of acculturation and experiences that may be culturally related, such as being a refugee/immigrant.

Cultural definition of trauma. Some have suggested that what is considered "trauma" in itself is a culturally bound decision (Lewis & Ippin, 2004). For example, the practices of circumcision and caning may seem like traumatizing events according to certain cultural ideals. However, within the frameworks in which they occur, these children do not necessarily experience the event as traumatic, nor suffer any negative consequences as a result (Lewis & Ippin, 2004). Different trauma definitions were demonstrated in a qualitative study of eight Sudanese Refuge children living in the United States. Some of the children defined trauma as "missing anything of value of self" or "something that is a depressing feeling" (Bolea, Grant, Burgess, & Plasa, 2003). Such a definition differs remarkably from a Western definition of trauma, which typically defines trauma as "a disordered psychic or behavioral state resulting from severe mental or emotional or physical injury" (Merriam-Webster, 2010). The Western definition has been used in the creation of measures of trauma, but the validity of such measures to cultures which define trauma differently have yet to be explored. For example, the category of PTSD has been considered by some as a culture-bound designation which can be difficult to apply to other cultures. The specific diagnostic category of PTSD often does not have equivalent terms in language description or in symptoms experienced (Silove & Bryant, 2006). It is possible that using the PTSD designation may in fact impede traditional healing practices, because it may shift the emphasis from normal coping to abnormal experiences that need treatment (Silove & Bryant, 2006).

How culture can impact symptoms of trauma. Many factors shape responses and resiliencies to children's trauma, including attachment (Lewis & Ippin, 2004), self-control

(Lambert, Weisz, & Knight, 1989), parenting practices (Nader, 2009), national cultural features (Nader, 2009) and past history of trauma (Herman, 1992).

Attachment. Early attachment has been demonstrated to shape responses and resiliencies to trauma. The availability of the caregiver and the underlying attachment system can be activated or depressed in the face of trauma by both parents and children (Lewis & Ippin, 2004). Additionally, caregivers' or other attachment figures' cultural identity—and their culturally dictated role regarding whether to advocate for their children—will impact the children's trauma experience (Lewis, 1996). However, both attachment style and attachment type differ somewhat based on culture. For example, Israeli, Japanese, and Indonesian attachment practices have been noted to differ from North American practices (Nader, 2009; Lewis & Ippin, 2004). Culture can also influence rapport between interviewer and interviewee, willingness to report, and what is revealed in the report by the attachment figures (Mezulis, Abramson, Hyder, 2005). Culturally acceptable ways of expression of depression and anxiety can range widely, from being silent concerning levels of emotional pain to exaggerated emotionality (Boehnlein, 2001; Laria & Lewis-Fernandez, 2006). Further, some cultures such as Asian and Middle Eastern countries may attach shame to emotional sharing. As a result, child trauma survivors that express such feelings may be rejected by their primary attachment figures and stigmatized by others in the community (Kinzie, 1993; Shiang, 2000). When stigma is associated with the sharing of mental health problems, effects of trauma may be under-reported and trauma symptoms may be untreated. In addition, many persons in non-emotional sharing cultures may express distress in physical symptoms (Shiang, 2000).

Issues of self-control can also vary by culture and may lead to different expression of symptoms in children. For example, cultures that require controlled behaviors from its

members–like Kenya and Thailand–will tend to produce children who demonstrate more over-controlled symptoms such as depression, anxiety, fears, and physical complaints (Lambert, Weisz, & Knight, 1989; Mash & Dozois, 2003). By contrast, cultures that do not require over-controlled behavior–like the United States–will have more children exhibiting under-controlled symptoms such as disobedience and cruelty to others (Weisz, Sigman, Weiss, & Mosk, 1993).

Additionally, culture affects parenting practices. How parents choose to reward or punish various behaviors is guided by the culture in which they are embedded. These patterns of behavior will then influence how, and to what extent, children will manifest distress, as well as what is allowable in their household (Liu & Tekeuchi, 2001). Reporting patterns may also differ for parents of different cultures. Whether parents tend to focus on externalizing issues with their children, or whether they are willing to recognize and report problems faced by their children, may be dependent on the shame element that exists within that culture (Lau & Takeuchi, 2001).

Certain national culture features are other factors that can profoundly impact the sanctioned reaction to trauma, the interpretation of traumatic events, and the support available (Nader, 2009). These include power distance (the extent to which powerful and powerless members of the culture accept the inequality of the power distribution), individualism/collectivism (taking care of oneself and one's immediate family versus an expectation that the community helps to take care of its individuals), masculinity/femininity (how much a culture's dominant values focus on masculine traits such as assertiveness, resource allocation, and a lack of caring for others, versus feminine traits such as social goals, quality of life, and relationships), uncertainty/avoidance (wanting to avoid unpredictability), gender behavior expectations, time orientation (long-term future planning

versus short-term focus), and emotional expression (what is accepted or taboo to reveal) (Nader, 2007).

Some cultural groups may have experienced a long past history of trauma which is then transmitted through the generations. Other cultural groups may have a history of repeated exposure to trauma. Specifically, Refugee/Immigrant children may have a long history of traumatic events, thus making it important to look beyond just the current trauma being reported (Herman, 1992). Refugee/Immigrant children themselves may not have experienced direct trauma, but vicariously have been traumatized by parental accounts of past events. For example, in one study concerning Guatemalan children in a Refugee/Immigrant camp, the children told stories and drew pictures of torture and war, despite having never had direct exposure themselves (Miller, 1996).

Culture bound syndromes. The effects of trauma in other cultures may have no exact Western equivalent but instead fit into specific culturally defined categories. Such categories have been labeled “cultural bound syndromes” or “cultural related specific syndromes,” and are defined as mental or psychiatric conditions that are closely related to cultural factors (Tseng, 2006). The DSM-IV identifies 25 such syndromes identified in various cultures around the world, along with a brief description of the symptoms falling within each category. Despite the syndrome identification within the DSM-IV, there are few if any empirical studies that have attempted to identify any of these syndromes among traumatized children. Based on the symptom descriptions, it appears that many may be natural results of a traumatizing event. For example “Susto” or “fright” or “loss soul” is a folk illness found among some Latino groups and persons in Mexico, Central, and South America. It is an illness believed to form from a frightening occurrence that has led to the soul departing the body, leaving the person sick and unhappy. Persons with Susto may suffer from appetite and

sleep problems, sadness, low motivation, low self-worth, and a variety of somatic complaints. Different constellation of such symptoms can be found to resemble PTSD. Like PTSD, Susto can have delayed onset (Castro & Eroza, 1998) and is caused from traumatizing events such as accidents, witnessing a death, or witnessing the devil (Weller, Baer, de Alba Garcia, & Rocha, 2008). Some researchers have even found that the belief in Susto can make Latino Americans' more susceptible to suffering from PTSD (McFarlane et al., 2005).

There have been few studies comparing PTSD to Susto or assessing both simultaneously. In one of the few studies, researchers studied Mayan Refugee/Immigrants and the prevalence of ethno-medical syndromes. The study found 59% of adults and 48.4% of children experienced Susto and that these symptoms were significantly associated with posttraumatic stress symptoms, depression, and anxiety (Smith, Sabin, Berlin, & Nackerud, 2009). In this cross-sectional study, measures were created specifically to evaluate the various research questions posed. As such, there was limited psychometric data provided, and the validity and strength of results is questionable. In another study, conducted in Australia, Latino Refugee women who were found to be suffering from Susto had also undergone torture or other trauma (Allotey, 1998). This sample was extremely small, and no formal measures evaluating the trauma or the Susto were utilized. In fact, the women presented as self-diagnosed (Allotey, 1998). Despite these severe limitations, both studies serve to suggest a possible link between trauma and Susto, and it is an area that should be further explored.

An additional cultural syndrome found within Latino populations is called "Ataques de Nervios." This is defined as nervous attacks induced by intense stress occurrences, which lead to anger and grief (Laria & Lewis-Fernandez, 2006). Symptoms include fainting, shaking, heart palpitations, and shouting (Guarnaccia et al., 1996). This disorder has also been compared with and linked to PTSD, though there are few formal studies that explore such a relationship (Guarnaccia, 1993).

According to Tseng (2001), culture can play a role in psychiatric symptoms through six common pathways. These include: pathogenic effect (culture leading to the forming of the disorder), psycho selective effect (culture choosing and accepting specific behavior patterns to deal with stressors), psycho plastic effect (culture changing how a disorder is expressed), path elaborating effect (culture grouping specific mental symptoms into a unique category), psycho facilitating effect (culture causing an increase of frequency of symptoms), and psycho reactive effect (culture molding how its members respond to the clinical state). By understanding the different possible methods by which culture can shape and define psychiatric disorders, it becomes clearer that a greater understanding of how culture and trauma interact is needed, which is one of the goals of this study.

Level of acculturation. Acculturation can be understood as how ethnic minority individuals who have moved to a new country learn to adapt and incorporate the dominant culture into their core selves (Berry, Trimble, & Olmedo, 1986). Acculturation is an ongoing and multidimensional process that occurs when members of different cultures come in continuous contact over a long period of time (Organista, Marin, & Chun, 2010). This process results in changes in the original cultural pattern, both externally (language, expression of self) and sometimes internally (values, customs, beliefs) (Organista, et al., 2010). One model of acculturation put forth by Canadian psychologist Berry (2003) suggests that all individuals' acculturation can be classified into one of four different strategies: Assimilation, Separation, Marginalization, and Integration. In both Assimilation and Separation, a person attempts to choose one culture and ignore as much as possible the other. Assimilation occurs when the person tries to de-emphasize the original culture, and instead tries to interact, and identify primarily with the new culture. By contrast, Separation occurs when the person tries to maintain his or her culture of origin purely, avoiding interaction with

and learning about the other culture. In Marginalization, the person does not try to preserve his or her culture of origin nor learn about the other culture. Finally, in Integration the person preserves his or her own culture but also participates in the other culture (Berry, 2003; Organista et al., 2010). According to Berry, among these different approaches, Integration will lead to the lowest level of acculturation stress while Marginalization will lead to the highest levels of stress (Berry, 2003).

In considering trauma in this context, children's traumatic experiences may be amplified by acculturation stress that they experience. Acculturative stress can include stressors such as problems with language, perceived or actual discrimination by those from the dominant culture, and perceived cultural discordancy (Gil, Vega, & Dimas, 1994).

Risk factors for producing acculturative stress include lack of language competency (Rodriguez, Myers, Mira, Flores, & Garcia-Hernandez, 2002), emigrating after 12 years of age (Mena, Padilla, & Maldonado, 1987), generational status, persons who are visibly different from the majority—such as by color of skin or language (Organista et al., 2010)—and persons who were forced to migrate to the new culture (Organista et al., 2010). High levels of acculturative stress can lead to psychological symptoms such as depression, anxiety, and becoming alienated from peers (Sue & Sue, 2003). Some research further suggests that those low in acculturation are less resilient in the face of trauma, as they are unable to use the host culture as a source of help (Webster et al., 1995; Perilla et al., 2002).

Various instruments exist to measure acculturation. Generally, such instruments are self-report measures that include questions about attitudes, norms, and behaviors (Organista, et al., 2010). Included in a robust measure of acculturation are questions concerning language use and preference, media usage, ethnicity of friends, food consumption habits, cultural values, and many more areas of living (Zane & Mak, 2003). Scales differ between those that

take a unidirectional approach (where responses range from culture of origin to the new culture) and scales that take a bidirectional approach (in which an individual does not have to "lose" one culture in favor of the other) (Marin & Gamba, 1996; Organista, et al., 2010). While currently the bidirectional approach is preferred by most researchers, the unidirectional approach is still in use (Organista et al., 2010). The most recurrent factor used in acculturation measures overall asks about language ability, preference, and use (Zane & Mak, 2003). Another commonly used marker of acculturation is if the child was born in the United States, sometimes referred to as nativity (Schwartz, et al., 2010)

As the concept of acculturation recognizes, even if a child speaks English, was born in the United States, and resides in the United States, he or she may not necessarily fit into the cultural norms prescribed by the country. Despite the fact that the United States is composed of multiple cultures, there is a bias within its boundaries towards a European American framework and reference point. Some children who are from other cultures but have lived in this country for long periods of time, or whose families have been present for multiple generations, may have adjusted to these norms and identify more with the customs typically found within this group, while others may not.

Refugee/Immigrant status. Children become refugees when they have been exposed to war or political violence, and have been forced or voluntary displaced from their homes (The National Child Traumatic Stress Network, n.d.). Child refugee trauma often leads to high levels of PTSD, depression, anxiety, grief, and other psychiatric disorders (Masinda & Muhesi, 2004; Nader et al., 1993). Some researchers estimate that the prevalence rates of PTSD in refugees are double the rate of non-refugees (Giaconia et al., 1995). Reasons for this include the combination of exposure to war and violence, losses suffered as a result of leaving the home country, and adjustment issues once entering a new country (Hodes, 2002;

Sack et al., 1997). Due to such high levels of PTSD in this population, some researchers suggest the diagnosis is inadequate in fully capturing the refugee experience (Eisenbruch et al., 1991). Instead, these researchers argue for the use of a cultural bereavement model, which can more fully capture the torment of the refugee experience. Despite this suggestion, to date the idea has not been embraced, and instead the PTSD criteria are the most widely used.

PTSD in refugee children has been measured in a variety of cultures including Tibet (Servan-Schreiber et al., 1998); Cambodia (Kinzie et al., 1989), Lebanon (Saigh, 1991), Rwanda (Dyregrov et al., 2000) and others. In addition to experiencing PTSD, refugee children from around the world have been shown to experience depression, anxiety, and grief. Depression has been reported at rates ranging from 11.5% in Tibetan refugee children (Servan-Schreiber et al., 1998) to 47% in Bosnian refugee children (Papageorgiou et al., 2000). Depression has been measured with various instruments, which also may account at least in part for the differing rates. Anxiety has been reported in the refugee population at rates ranging from 11% of Vietnamese child refugee (Felsman et al., 1990) to 23% of Bosnian child refugee (Papageorgiou et al., 2000).

Beyond anxiety and depression, grief reactions are a large part of the refugee's experiences, because grieving often includes the loss of family members and of their homeland. Despite the large numbers of children who suffer different types of bereavement, grief reactions have been largely ignored by the literature (Ehntholt & Yule, 2006). In studies that have measured grief rates, ranges of up to 98% of the sample measured have been found all over the world, including refugee children from Kuwait (Nader et al., 1993) and from Bosnia (Smith, Perrin, Yule, Hacam, & Stuvland, 2002).

The literature also suggests that the length of time children are active refugees (thus having no home country) may be related to incidence of PTSD. In a study involving Croatian adolescent refugees, higher incidences of PTSD corresponded to the length of time that the children were active refugee (Ajdukovic, 1998), and this has also been mentioned as a potential factor in other studies (Smith et al., 2002).

Children's type of refugees experience can also affect the incidence of PTSD. Highest levels of PTSD have been found in those who fled from a country, followed by those persons living in refugee camps, with lesser levels occurring for those who have been relocated into a new country (Nader et al., 1993). Even for those children who are resettled, PTSD can still occur and profoundly affect them. In one study of Asian refugee children resettled in the United States, PTSD features prevented successful integration into their new environment (Fox, Cowell, & Montgomery, 1994).

Summary

Children's reaction to trauma can be understood by utilizing an ecological framework. Through such a model, the interactions of children's microsystems, exosystems, and macrosystems can inform what symptoms they may experience and how they recover from trauma.

The symptoms produced from childhood trauma can impact all domains of children's inner worlds, including cognitive, emotional, and behavioral functioning (Pynoos & Nader, 1993). Symptoms the children may experience can range from anxiety, depression, thought disturbances, concentration disruption, hyper-arousal, sleep problems, and beyond (Eth, 2001; Stien & Kendall, 2004). When left untreated, trauma symptoms can impede children's normal development and lead to a negative trajectory into their adult lives (Grych et al., 2000).

Factors identified by the literature that may impact effects of trauma include the type of trauma faced, the level of exposure, and the age and the gender of the children.

Additional factors that have not been explored in as much depth, but also may influence trauma symptoms and recovery, include race, ethnicity, and cultural factors.

Statement of the Problem

Child traumatic stress affects the welfare and healthy development of children from all races, ethnicities, and cultures. The majority of children that experience trauma will not suffer long-term consequences, nor necessarily need treatment. However, some children will suffer effects of trauma exposure, resulting in a variety of physiological, developmental, and psychological consequences (Catherall, 2004). Such effects can range from mild anxiety symptoms to diagnosed PTSD to delayed cognitive development and beyond (Cook-Cottone, 2004). When trauma symptoms are not identified and treated, children's normal developmental trajectories can be profoundly disrupted, possibly leaving them with permanent impairments (Grych et al., 2000).

Despite the importance of the topic, the literature is in the early stages of understanding children's responses to trauma (Balaban, 2009), and in particular whether children of differing races, ethnicities, and cultural factors have different symptoms from trauma and different reactions to treatments (Hinshaw & Nigg, 1999). To date the literature has focused primarily on the effects of variables such as severity of exposure (Goenijian et al., 2001; Lee et al., 2004), age of the child (Green et al., 1991; Scheering et al., 2003), and gender of the child (Breslau et al., 1997; Ostrov & Keating, 2004) in differentiating symptoms. However, race, ethnicity, and cultural factors are variables that may also impact symptoms and recovery. By not taking into account the potential impact of these factors in

children's reactions and treatments, we are doing a disservice to all children impacted by a traumatic event. We also may be missing a critical piece in understanding what symptoms racially, ethnically, and culturally diverse children may show and the extent to which their symptoms respond to treatment.

There is some evidence that race and ethnicity may play a role in trauma symptoms and recovery. Evidence of a potential interaction of race, ethnicity, and trauma includes the possibility that some races and ethnicities may be at a higher risk of experiencing certain types of trauma (Roberts et al., 2011). Additionally, the symptoms experienced after trauma may differ by racial or ethnic group, with some racial or ethnic groups such as Latino and African American children experiencing a different constellation of symptoms, for example more somatic symptoms for Latino children (Choi & Park, 2006; Pina & Silverman, 2004). Furthermore, evidence exists suggesting differences in treatment by race and ethnicity, including differences in treatment retention (Pole et al. 2008) and treatment response (Triffleman & Pole, 2010).

In addition to a potential influence of race and ethnicity on child trauma, there is some evidence that cultural factors may also have an impact. Culture may impact the definition of trauma, interpretation of events, what the culturally acceptable symptoms and syndromes are and the treatment methods. Culture also can influence attachment style, parenting practices, self-control, and other embedded schemas that aid the individual in synthesizing and healing from trauma. Furthermore, for children whose families have moved to a new country, the level of acculturation that children have in relation to their dominant culture can influence how different or overlapping their symptoms and treatment may be from their peer group. Level of acculturation may also add an additional layer of stress that children must deal with when attempting to recover from trauma. Many different elements

can serve to inform elements of acculturation, including country of birth and language choice.

Finally, whether children are refugees can dramatically influence the symptoms they present with and their responses to treatment. Child refugee trauma is a complex mix of experiencing violence, displacement from home, and forced adaptation to a new environment. For these reasons, child refugees suffer in different ways than children experiencing other traumas, sometimes exhibiting PTSD symptoms similar to soldiers of war and grief symptoms comparable to those who have suffered great losses (Masinda & Muhesi, 2004; Nader et al., 1993).

The present study used the NCTSN dataset in an effort to further expand our understanding of the possible roles of race, ethnicity, and cultural factors in order to better diagnose and treat children who have experienced trauma from all backgrounds. This study examined the role of race, ethnicity, and cultural factors in a child trauma population on (1) scores on clinical scales, functional problems, clinical problems, and clinical categorization at baseline; (2) changes in scores on clinical scales and functional problems after a short period of treatment; and (3) the clinical categorization at three month (or first recorded) follow up. The project specifically focused on children who had experienced at least one trauma and who were treated in clinics across the United States.

Hypotheses

The primary hypotheses were:

1) Scores on clinical scales, functional problems, clinical problems, and clinical categorization at baseline will differ by children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or

not they were born in the United States, used English as the primary language spoken at home, and were refugee/immigrants.

2) Change in scores on clinical scales, functional problems, and the clinical categorization at three month (or first recorded) follow up will differ by children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, had English as the primary language spoken at home, and were refugee/immigrants.

Method

Participants

Participants were drawn from the National Child Traumatic Stress Network (NCTSN) Core Data Set (CDS). The data were collected as part of a quality improvement initiative. The NCTSN was created through a Congressional initiative in 2000 to respond to the needs of children and their families who have been exposed to trauma. The data for the current study were collected between 2004-2010 and come from the collaborative efforts of 56 research and treatment centers located across the United States. The NCTSN is funded by the Center for Mental Health Services, Substance Abuse and Mental Health Services Administration. The sample includes children and adolescents between the ages of 0-21 who have presented to an NCTSN center for assessment and treatment services. The inclusion criteria for the present study were: children and adolescents between 0-21 years of age, with at least 1 trauma reported, and with complete data on the ten outcome measures examined in this study. Case-wise deletions were performed for participants who fell outside of these parameters.

The sample for this study included 10,115 children and adolescents with Baseline data. Age and gender of participants are reported in Table 1. Approximately 53.1% of the sample were female, and most were between 6-12 years of age.

Table 1.

Age and Gender Characteristics of Full Sample at Baseline

Age Group	Male	Female	Total
0-5	571	581	1152
6-12	2301	2005	4306
13-21	1356	2306	3662

Table 2 shows the racial characteristics of the sample. Over 75% were either White/Caucasian or Black/African American.

Table 2.

Racial Characteristics of Full Sample

Race	N = 10,115	Percentage
White/Caucasian	5620	55.6
Black/African American	2970	29.4
Asian	125	1.2
American Indian/Alaska Native	295	2.9
Unknown	1030	10.2

Furthermore, 30.3% of the sample identified as Latino in ethnicity. The breakdown of the racial groups by ethnicity can be seen in Figure 1.

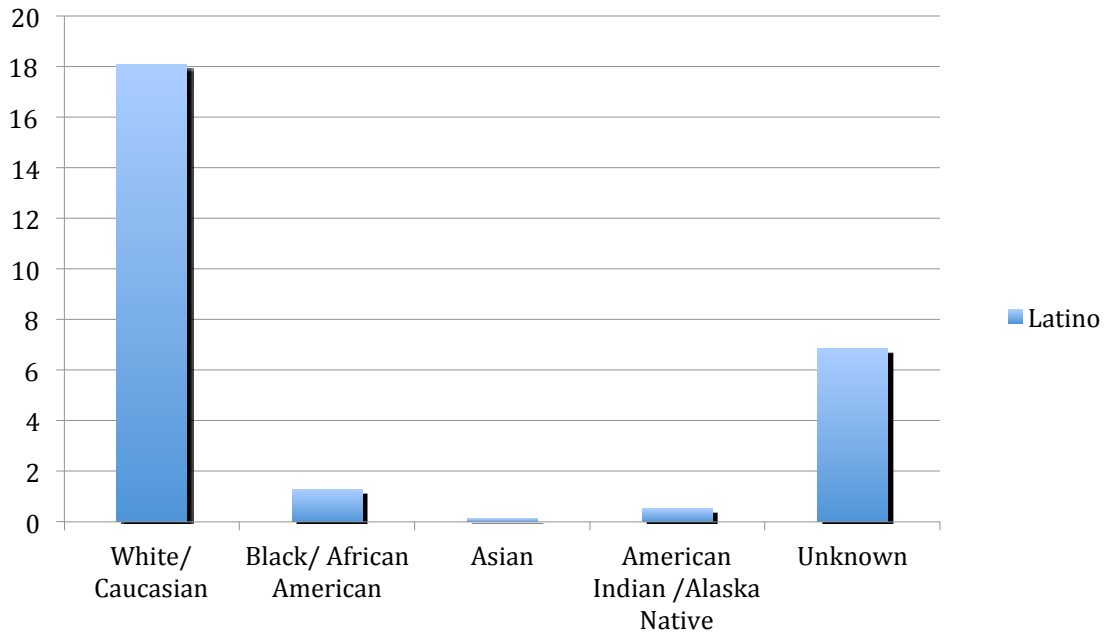

Figure 1. Percentage of Latino Children from Specific Racial Groups of Full Sample, *N* = 10,115

Other demographic characteristics of the sample relevant to this study included birth in the United States, English as the primary language spoken at home, and refugee/immigrant status. Percentages do not always add to 100% due to missing data. As shown in Table 3, few participants were refugee/immigrants or were born outside the United States, but over 15% of participants spoke a language other than English as their primary language at home. These groups were not mutually exclusive.

Table 3.

Additional Demographic Characteristics

Characteristic	Frequency	Percentage
US Born	8225	81.3
Non US Born	593	5.9
English in Home	8561	84.6
Non English in Home	1554	15.4
Refugee/Immigrant	306	3.0
Non Refugee/Immigrant	8365	82.7

Measures

A series of questions and standardized measures were administered to all participants as part of standard clinical practice by clinical staff prior to the start of treatment (baseline). For the purposes of this study, a subset of questions and measures were selected that were relevant to the research questions.

Demographic questionnaire. Demographic information included participant's age, gender, race, and ethnicity, as well as other information.

Cultural factors. The cultural factors used in this study were selected based on the empirical literature and their availability within the dataset and include the following:

Birth in the United States. The dichotomous variable asked whether the children's country of birth was the United States. It was referred to as "U.S. born."

English as the primary language spoken in the home. The dichotomous variable asked whether the children's primary language spoken at home was English. It was referred to as "Primary English in home."

Refugee/Immigrant status. The dichotomous variable asked whether the children were refugee, asylum seekers or immigrants with a history of exposure to community violence. It was referred to as "Refugee/Immigrant."

Trauma type history questionnaire. An adapted version of the UCLA PTSD Reaction Index was used to assess the trauma history profiles of youth in the current sample. Questions included an assessment of whether participants experienced 19 different types of trauma with an additional question to assess any other trauma not previously endorsed. The sum of all trauma types experienced was calculated and then used as an independent variable named "number of trauma types." Specific details about each trauma type endorsed were used in the descriptive analysis section.

Treatment questionnaire. Clinicians were asked to identify which trauma type was the primary reason for treatment service. Additionally, services used 30 days prior to entry as well as during the course of treatment were identified by clinicians in consultation with relevant collaterals. Service utilization included 19 different variables representing an array of child services and systems, including: 1) inpatient psychiatric unit or a hospital for mental health problems; 2) residential treatment center (a self-contained treatment facility where the child lives and goes to school); 3) detention center, training school, jail or prison; 4) group home (a group home residence in a community setting); 5) treatment foster care (placement with foster parents who receive special training and supervision to help children with problems); 6) probation officer or court counselor; 7) day treatment program (a day program that includes a focus on therapy and may also provide education while the child is there); 8) case management or care coordination (someone who helps the child get the kinds of services s/he needs); 9) in-home counseling (services, therapy, or treatment provided in a child's home); 10) outpatient therapy other than at this clinic (from psychologist, social worker,

therapist, or other counselor); 11) outpatient treatment from a psychiatrist; 12) primary care physician/pediatrician for symptoms related to trauma or emotional/behavioral problems (excluding emergency room); 13) school counselor, school psychologist, or school social worker (for behavioral or emotional problems); 14) special class or special school (for all or part of the day); 15) child welfare or department of social services (includes any types of contact); 16) foster care (placement in kinship or non-relative foster care); 17) therapeutic recreation services or mentor; 18) hospital emergency room (for problems related to trauma or emotional or behavioral problems); and 19) self-help groups (e.g., AA, NA).

The Child Behavior Checklist (CBCL). The Child Behavior Checklist (CBCL) 1-5 and 6-18 is completed by a parent or caregiver who knows the child well. The CBCL was developed by Achenbach and colleagues as a dimensional evaluation of psychopathology in order to identify at-risk children (Achenbach, 1992; Achenbach & Rescorla, 2001). The CBCL is used as a screening tool to indicate the likelihood of the presence of a disorder, but does not map onto DSM-IV diagnoses (Hartman et al., 1999). This widely used measure consists of 118 items scored on a 3-point scale ranging from 0 (not true) to 2 (often true) and yields scores on two broad band scales Internalizing and Externalizing , as well as scores on DSM-IV oriented scales, and empirically based syndrome scales that reflect emotional and behavioral problems and symptoms. The reliability and validity of the measure is considered good with internal consistency between .63-.97 and test/re-test reliability over an eight-day period of .80 (Achenbach, 1991). The measure demonstrates strong construct validity and acceptable criterion validity. It is psychometrically mature and has been used in countless peer reviewed articles. The 2001 version is based on new national norms collected between 1999-2000 (Achenbach & Rescorla, 2001).

This study used the Internalizing and Externalizing T-scores as dependent variables that corresponded to children's symptoms; these scores are standardized to the child's gender and age. These variables were called CBCL Externalizing and CBCL Internalizing.

UCLA PTSD Reaction Index (UCLA PTSD RI). The UCLA PTSD RI is a self-report Likert type scale that assesses posttraumatic symptoms and PTSD in children (Pynoos et al., 1998a). It was developed for children of ages 6 to 17 and takes approximately 20-30 minutes to complete. The measure includes 22 statements that directly map onto the DSM-IV PTSD criteria. The children are asked whether they have experienced each of these symptoms "none", "little", "some", "much", or "most" days during the past month. To score the measure, each response receives a value and the total values are added together to create an overall PTSD severity score. A score equaling 38 or more is considered equivalent to a likelihood of having PTSD. For this study, the overall PTSD raw severity score was used as a dependent variable representing some of the participants' symptoms of trauma. The variable was named "PTSD score".

The measure's internal consistency is .69, the inter-rater reliability is 0.88, and the test re-test reliability is .84 over 1 week (Pynoos et al., 1998; Roussos et al., 2005). The UCLA PTSD RI has been shown to have good convergent validity with other measures of PTSD, such as .70 with the Schizophrenia for School-Age Children PTSD module (Steinberg et al., 2004) and .82 with the Child and Adolescent Version of the Clinician Administered PTSD Scale (Rodriguez et al., 2001).

Despite the wide use of the measure, normative data are not available (Steinberg et al., 2004).

Trauma Symptom Checklist for Children-Alternative (TSCC-A). The TSCC-A is a 54 item, Likert type scale that assesses distress and posttraumatic symptoms (Sadowski &

Friedrich, 2000). Children are presented with a variety of different statements and asked to endorse if the statement “never”, “sometimes”, “lots of times”, or “almost all the time” applies to them. The measure was originally developed for children ages seven to sixteen. The overall reliability and consistency is good (Sadowski & Friedrich, 2000). The TSCC-A has demonstrated internal consistency of .77-.90 for its subscales and .89 overall (Briere, 1996). It also has been shown to have convergent validity of .75-.82 with other measures of PTSD (Balaban, 2009). The measure was originally standardized on 3,000 ethnically and economically diverse children ages 7 to 16 with no history of trauma (Ohan et al., 2002). The measure has also been validated for use in children age 17 (Briere, 1996; Sadowski & Friedrich, 2000).

The TSCC- Alternate version, which was used in this study, includes five clinical scales of Anger, Depression, Anxiety, Posttraumatic Stress, and Dissociation. The Dissociation scale is comprised of two subscales: “overt dissociation” and “fantasy dissociation.” This study used the five subscales as dependent variables to measure participants’ symptoms. These were named TSCC-A Anger, TSCC-A Depression, TSCC-A Anxiety, TSCC-A PTS and TSCC-A Dissociation (this included the Dissociation and Fantasy subscales).

Functional problem score. A measure was developed for the NCTSN to assess commonly reported functional impairments and problems. Clinicians obtained relevant information from caregivers and other collaterals on 14 problem and functional impairments over the past month. These problems included: (1) Academic problems (e.g., problems with school work or grades); (2) Behavior problems in school or daycare (e.g., getting into trouble, detention, suspension, expulsion); (3) Problems with skipping school or daycare (e.g., where he /she skipped at least four days in the past month, or skipped parts of the day

on at least half of the school days); (4) Behavior problems at home or community (e.g., violent or aggressive behavior; breaking rules, fighting, destroying property, or other dangerous or illegal behavior): (5) Suicidality (e.g., thinking about killing himself/herself or attempting to do so); (6) Other self-injurious behaviors (e.g., cutting him/herself, pulling out his/her own hair; (7) Developmentally inappropriate sexualized behaviors (e.g., saying or doing things about sex that children his/her age do not usually know); (8) Alcohol use; (9) Substance use (e.g., use of illicit drugs or misuse of prescription medication); (10) Attachment problems (e.g., difficulty forming and maintaining trusting relationships with other people); (11) Criminal activity (e.g., activities that have resulted in being stopped by the police or arrested); (12) Running away from home (e.g., staying away for at least one night);, (13) Prostitution (e.g., exchanging sex for money, drugs or other resources); and (14) Child has other medical problems or disabilities (e.g., chronic or recurrent condition that affects the child's ability to function).

The clinician rated that each problem as either "not a problem", "somewhat/sometimes a problem", "very much/very often a problem", or "unknown." If the clinician indicated that the problem was either "somewhat/sometimes a problem" or "very much/very often a problem" the response was coded as "1." This study used the total problem score (sum of all 14 problems coded as a "1") as a dependent variable to measure the participant's functioning in multiple domains (home, school and community). The variable was called "Functional problems."

Clinical problem score. A form was developed by the NCTSN to clinically evaluate children and adolescents on an array of common DSM-IV diagnoses, symptoms, and problems. Clinicians rated each client on 20 symptoms, problems, and diagnoses including: (1) Acute stress disorder, (2) Post traumatic stress disorder, (3)

Traumatic/complicated grief, (4) Dissociation, (5) Somatization, (6) Generalized anxiety, (7) Separation disorder, (8) Panic disorder, (9) Phobic disorder, (10) Obsessive compulsive disorder, (11) Depression, (12) Attachment problems, (13) Sexual behavioral problems, (14) Oppositional defiant disorder, (15) Conduct disorder, (16) General behavioral problems, (17) Attention deficit hyperactivity disorder, (18) Suicidality, (19) Substance abuse, and (20) Sleep disorder. For each symptom and disorder the clinician could check either "no", "probable", or "definite" to indicate that the child has or exhibits the problem. If the clinician indicated "probable" or "definite: then the response was coded as "1". The total for all 20 clinical problems were then tallied resulting in the participant's total clinical problem score. This study used the total clinical problem score as a dependent variable to further indicate the participant's level of functioning. The variable was called "Clinical problems."

At three month (or first recorded) follow up. According to the NCTSN protocol, the first follow up measures were to be given after three months of treatment. However, due to unavoidable circumstances, many of the sample did not receive follow up at three months. Some stopped treatment or attended sporadically or in a pattern that led to the first follow up being far later. Thus the follow up point that was used was labeled as three month (or first recorded) follow up.

Procedure

Children and youth who presented for mental health services at one of 56 NCTSN centers were assessed at those sites for participation in the Core Data Set. Criteria for inclusion in the present study included factors such as age, presentation for assessment and treatment services, and exposure to at least one reported lifetime traumatic event. Caregivers

completed the Child Behavior Checklist based on their knowledge and impressions of the child. The child completed the UCLA-PTSD RI and the TSCC-A. If needed, the treating clinician provided additional support for the collection of this information (e.g., clinical interviews for children and caregivers with reading difficulties). The treating clinician also completed the demographic, clinical evaluation, services, treatment, and trauma history profile forms using information collected during the intake and assessment sessions during the course of treatment.

Clinical staff entered the data into a web-based data collection system – Inform. Measures were administered again at the end of treatment and/or every 3 months until the end of treatment. The Core Data Set was used to standardize the process of data collection across all participating NCTSN treatment centers.

Data Analysis

All data analyses were performed using PASW-20 software (SPSS), using hierarchical regression (for both hypothesis 1 and 2), and logistic regression (for both hypothesis 1 and 2). Bonferroni corrections were made to minimize Type I errors; thus, alpha = .005 was necessary to achieve alpha = .05. Descriptive statistics were used to further characterize the participants. Additional details of data analyses are explained in the Results section.

Results

Results will be organized in the following way. First, descriptive information about the participants and the traumas they experienced will be presented in a series of Figures and Tables. These will be shown for Baseline and for 3-month (or first recorded) follow-up and, as appropriate, will display findings according to ethnicity, race, US/non US born, language

at home, and refugee/immigrant status. Next correlation tables will be presented for all independent and dependent variables.

The third section will include results from testing hypothesis one. This will include hierarchical regression results on baseline data with predictors: children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, used English as the primary language spoken at home, and were refugee/immigrants with dependent variables being used from all clinical scales, the functional problems total, and the clinical problem total. Post hoc ANOVA results will be presented where indicated.

The fourth section will include logistic regression results on baseline data, specifically examining whether the above predictors would make children more or less likely to fall into the clinical range for CBCL Externalizing, CBCL Internalizing, and The UCLA PTSD Reaction Index.

The next section of the results will include hierarchical regression results on three month (or first recorded) follow-up data with predictors: children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, used English as the primary language spoken at home, and were refugee/immigrants with dependent variables being used as the change scores from baseline for all clinical scales and the Functional problems number. Post hoc ANOVA results will be presented where indicated.

The final section will include logistic regression results at the three month (or first recorded) follow up data, specifically examining whether the above predictors would make children more or less likely to fall into the clinical range at three month (or first recorded)

follow up for CBCL Externalizing, CBCL Internalizing, and The UCLA PTSD Reaction Index.

Trauma Characteristics

All children in the study experienced at least one trauma, while 74.3% of the children in the total sample experienced two or more trauma types, with many children experiencing even more as shown in Figure 2.

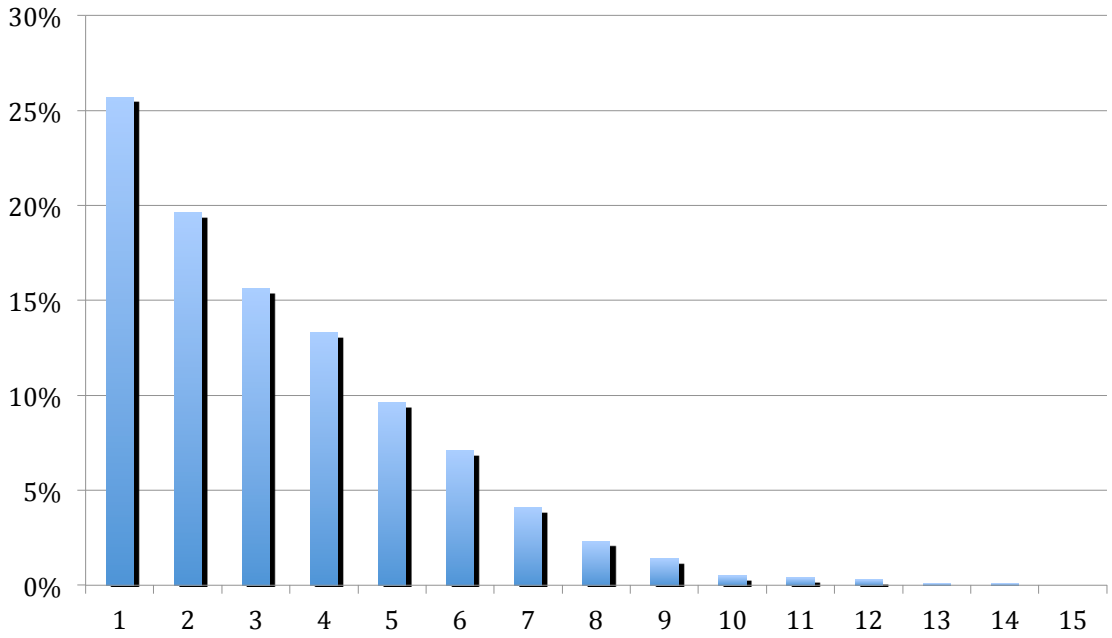

Figure 2. Percentage of Children from Full Sample Presenting with 1-15 Total Trauma Types

These children experienced a wide range of traumas, with the largest percentages experiencing traumatic loss (48.1%), domestic violence (45.6%) or an impaired caregiver (36.5%), as shown in Figure 3. Additionally, traumatic loss (14.6%) and domestic violence (13.1%) were the most often clinician-identified primary trauma being addressed in treatment, as shown in Figure 3.

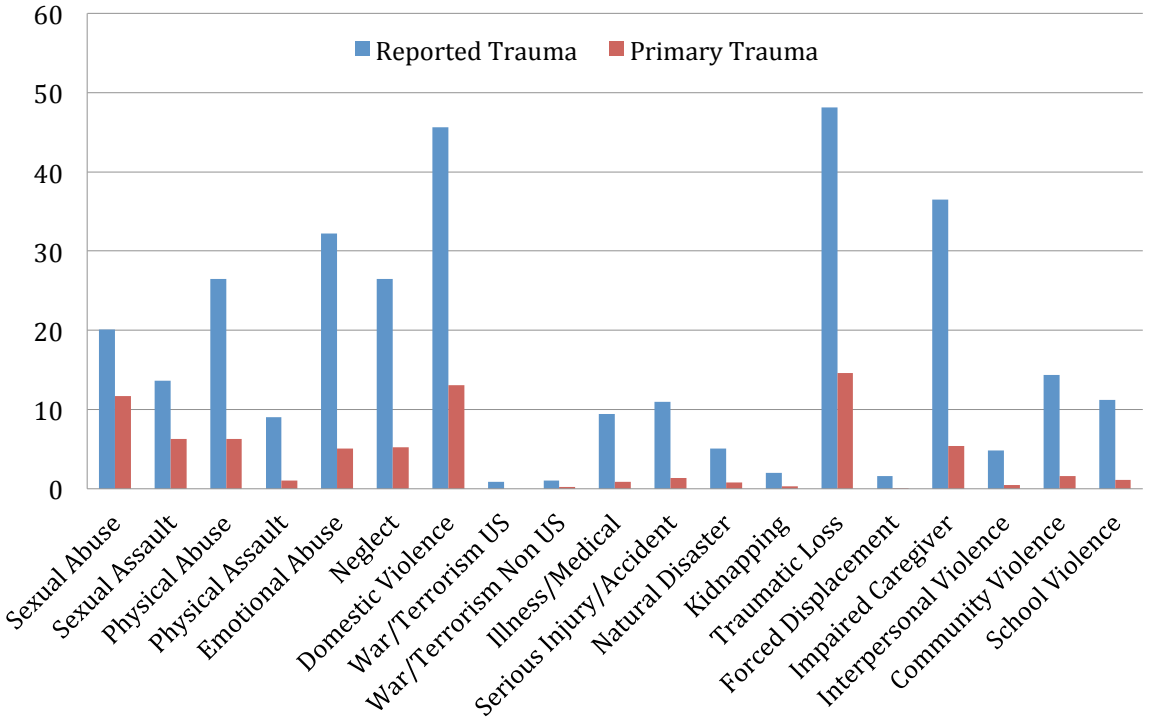

Figure 3. Percentages of Frequency of Reported Trauma and Primary Trauma Focused on in Treatment

The primary trauma presenting for treatment by children's age group at time of treatment is shown in Figure 4.

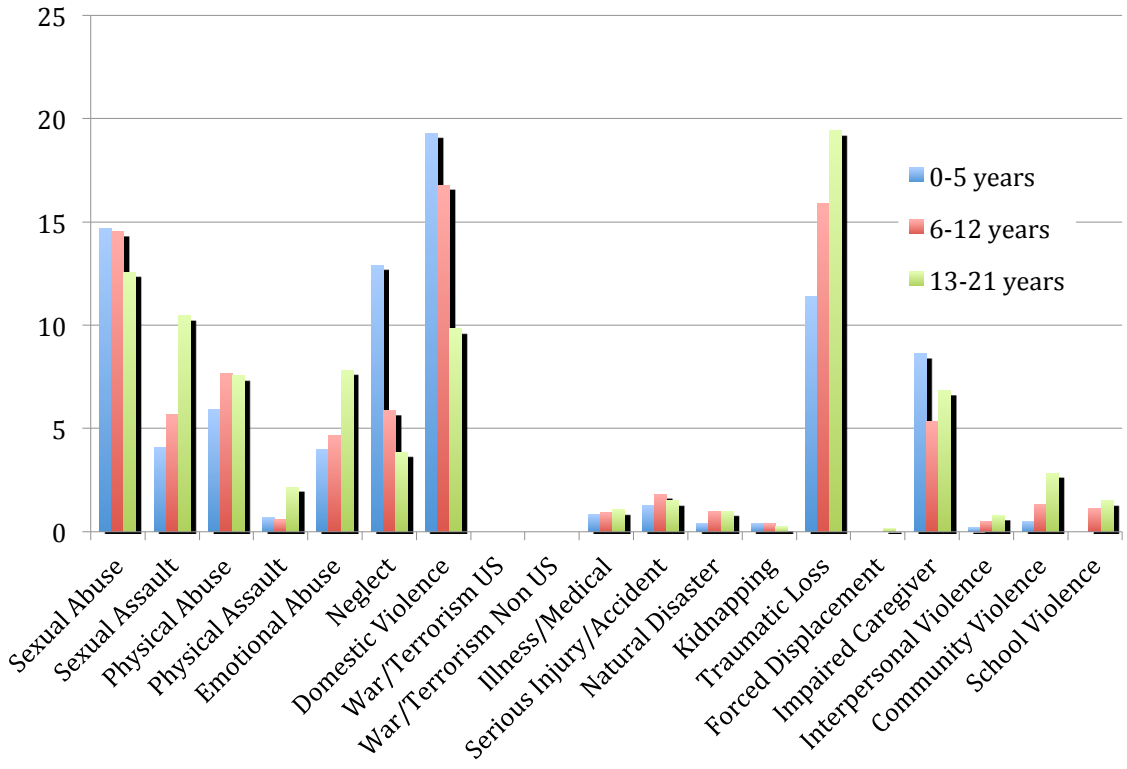

Figure 4. Percentages of Frequency of Trauma Experienced by Age Group at Baseline

Baseline Functioning

Outcome measures. The means and standard deviations of the outcome measures at Baseline are shown in Table 4. The differing number of participants for each measure is indicative of numerous participants missing data for various measures.

Table 4.

Means and Standard Deviations of Dependent Variables at Baseline

Variable	*N*	***M***	***SD***
CBCL Externalizing	8047	62.39	11.69
CBCL Internalizing	8047	61.17	11.33
UCLA PTSD RI	7056	26.25	14.90
TSCC-A Anger	5970	50.00	11.13
TSCC-A Depression	5970	50.74	12.09
TSCC-A Anxiety	5970	51.87	12.90
TSCC-A PTS	5970	51.96	11.58
TSCC-A Dissociation	5970	52.00	11.78
Functional problems	7502	3.07	2.20
Clinical problems	10,115	3.89	3.09

Table 5 shows the children who fell into the normal, clinical, and subclinical range on each of the dependent measures at Baseline for which such categories are available.

Table 5.

Percentage of US Born English Speaking, Non-US Born, Non-English Speaking, and Refugee/Immigrant Children at Normal, Subclinical, and Clinical Levels on Dependent Variables at Baseline

	US Born English Speaking	Non-US Born	Non-English Speaking	Refugee/Immigrant
	%	%	%	%
CBCL Externalizing				
Normal	38	43	55	34
Sub-Clinical	12	17	16	19
Clinical	50	40	39	47
CBCL Internalizing				
Normal	42	25	33	25
Sub-Clinical	13	18	12	18
Clinical	45	57	55	57
UCLA PTSD RI				
Normal	51.3	41.3	43.3	45.1
Sub-Clinical	31.1	36.1	38.1	32.4
Clinical	17.6	22.6	18.6	22.5
TSCC-A Anger				
Normal	78.8	82	79	79
Sub-Clinical	7.2	4	6	6
Clinical	14	14	15	15
TSCC-A Depression				
Normal	71	76	79	76
Sub-Clinical	7	7	6	9
Clinical	22	17	15	15
TSCC-A Anxiety				
Normal	74.9	76	75	75
Sub-Clinical	8.1	8	8	9
Clinical	17	16	17	16
TSCC-A Post Traumatic Stress				
Normal	72	74	73	69
Sub-Clinical	12	11	11	15
Clinical	16	15	16	16
TSCC-A Dissociation				
Normal	76	76	79	78
Sub-Clinical	8	10	8	11
Clinical	16	14	13	11

Table 6.

Percentage of US Born English Speaking, Non-US Born, Non-English Speaking, and Refugee/Immigrant Children at Normal, Subclinical, and Clinical Levels on Dependent Variables At Three Months (Or First Recorded) Follow Up

	US Born English Speaking	Non-US Born	Non-English Speaking	Refugee/Immigrant
	%	%	%	%
CBCL Externalizing				
Normal	49.8	53.4	61	48.8
Sub-Clinical	12.6	14.1	11.11	13.8
Clinical	37.6	32.5	27.9	37.5
CBCL Internalizing				
Normal	66.5	60.2	63.8	61.25
Sub-Clinical	16	17.3	15	20
Clinical	17.5	22.5	21.2	18.75
UCLA PTSD RI				
Normal	39.8	45.5	48	45
Sub-Clinical	45.6	40.7	38.5	42.9
Clinical	14.5	13.9	13.6	12.1

Descriptive measures. At baseline, treating clinicians reported and diagnosed a variety of disorders and behavioral problems currently exhibited by the children. The two separate reports included a report of functional problems and a report of clinical problems. The problems included issues such as academic problems, substance abuse, and behavior problems in specific settings.

Report of functional problems. The various percentages of frequency of functional problems at Baseline can be seen in Figure 5 specifically for U.S. born English speakers, and for non U.S. Born, non English speakers at home, and refugee/immigrant subgroups.

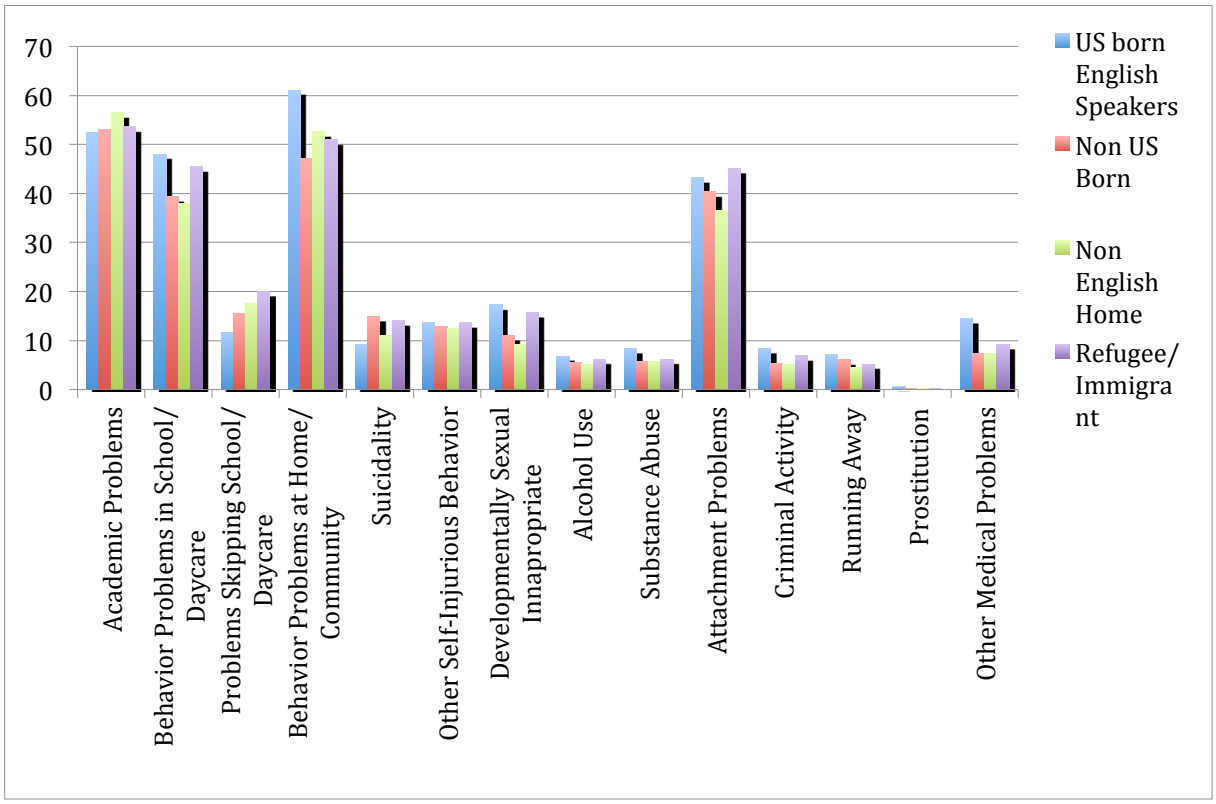

Figure 5. Baseline Percentages of Frequency of Functional Problems for U.S. Born English Speakers, and for Non U.S. Born, Non English Speakers at Home, and Refugee/Immigrant Subgroups

Clinical problems. The various distributions of clinical problems can be seen in Figure 6 specifically for U.S. Born English Speakers, and for Non U.S. Born, Non English Speakers at Home, and Refugee/Immigrant Subgroups.

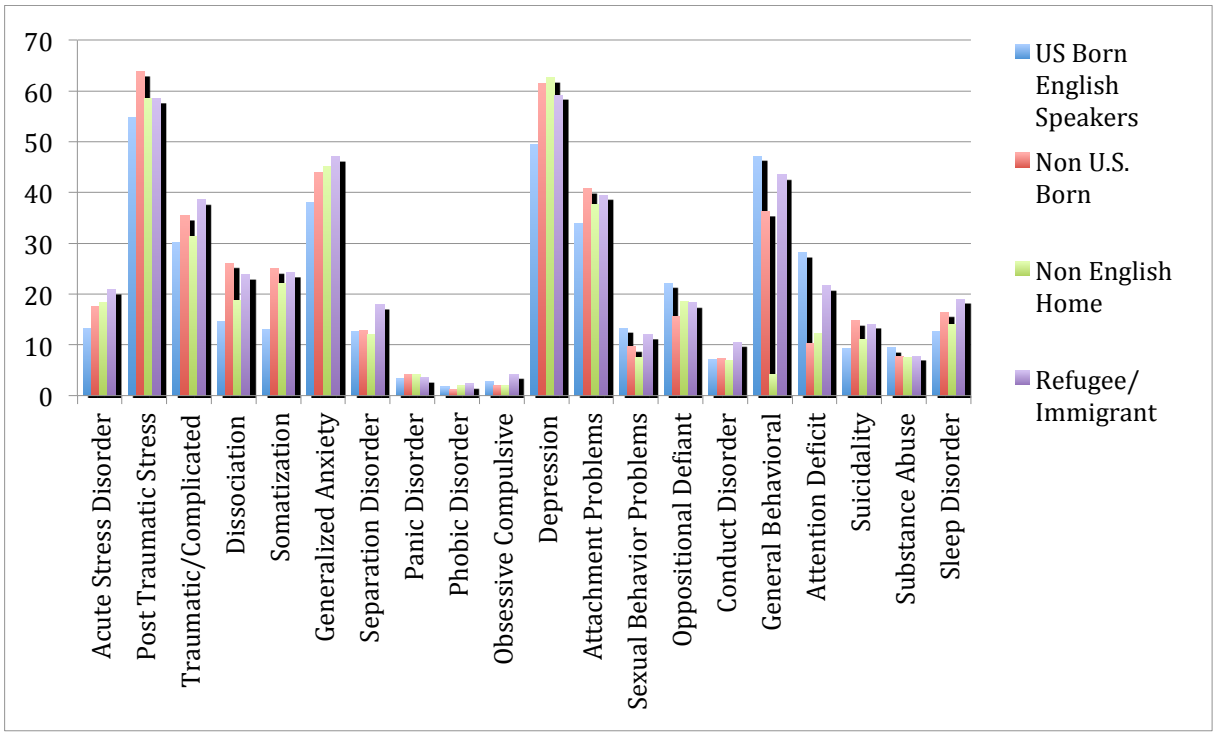

Figure 6. Baseline Percentages of Frequency of Clinical Problems and Symptoms of U.S. Born English Speakers, and for Non U.S. Born, Non English Speakers at Home, and Refugee/Immigrant Subgroups

Hierarchical Linear Regression

Correlation of study variables are seen in Tables 7- 9 .

Table 7.

Correlation of Independent Variables Age, Gender, Number of Trauma Types, Race, and Dependent Variable

	Age	Gender	Trauma Type Number	Indian/ Native American	Asian	Black/ African American	White/ Cauca-sian
Age	1	*					
Gender	.126**	1					
Trauma Type Number	.206**	.060**	1				
Indian/Native American	-.011	.032**	.080**	1			
Asian	.023*	.010	-.004	-.003	1		
Black/African American	-.028**	-.031**	-.065**	-.060**	-.054**	1	
White/Caucasian	.007	.017	.130**	-.089**	-.071**	-.586**	1
Unknown Race	.007	.027**	-.027**	-.054**	-.035**	-.209**	-.364**
Ethnicity	.073**	.016	-.013	-.049**	-.048**	-.377**	.050**
US Born	-.126**	-.030**	-.016	.030**	-.067**	.119**	-.028**
English	-.077**	-.010	.038**	.056**	-.029**	.250**	-.112**
Refugee/Immigrant	.048**	-.006	.051**	-.003	.041**	-.040**	.013
CBCL Externalizing	.031**	-.070**	.145**	-.015	-.023*	.014	.017
CBCL Internalizing	.111**	-.005	.147**	-.019	.008	-.093**	.079**
UCLA PTSD RI	.027*	.157**	.181**	.029*	-.004	-.006	.015
TSCC-A: Anger	.031*	.035**	.132**	.019	-.002	.046**	.002
TSCC-A: Anxiety	-.058**	.018	.126**	.006	.019	-.061**	.063**
TSCC-A: Depression	.055**	.021	.143**	.021	.017	-.034**	.040**
TSCC-A: Dissociation	.009	.032*	.127**	.008	.000	.012	.012
TSCC-A: Post Traumatic Stress	-.015	.023	.158**	.015	.014	-.040**	.046**
Total Functional Problem	.255**	-.042**	.266**	.026*	-.029*	.018	.006
Total Clinical Problem	.197**	.003	.329**	.051**	-.003	-.061**	.082**

** Correlation is significant at the 0.01 level * Correlation is significant at the 0.05 level

Table 8.

Correlation of Independent Variables Ethnicity, US Born, English Speaking at Home, Refugee/Immigrant, and Dependent Variables

	Ethnicity	US Born	English	Refugee/Immigrant
Age	.073**	-.126**	-.077**	.048**
Gender	.016	-.030**	-.010	-.006
Trauma Number	-.013	-.016	.038**	.051**
Indian/Native American	-.049**	.030**	.056**	-.003
Asian	-.048**	-.067**	-.029**	.041**
Black/African American	-.377**	.119**	.250**	-.040**
White/Caucasian	.050**	-.028**	-.112**	.013
Unknown Race	.286**	-.093**	-.190**	.025*
Ethnicity	1	-.245**	-.576**	.067**
US Born	-.245**	1	.388**	-.260**
English	-.576**	.388**	1	-.137**
Refugee/Immigrant	.067**	-.260**	-.137**	1
CBCL Externalizing	-.086**	.021	.071**	.004
CBCL Internalizing	.069**	-.062**	-.072**	.028*
UCLA PTSD RI	-.013	.022	.037**	.017
TSCC-A: Anger	-.056**	.047**	.060**	.004
TSCC-A: Anxiety	.044**	-.010	-.035**	.019
TSCC-A: Depression	.006	-.018	.001	.021
TSCC-A: Dissociation	-.035*	.022	.035**	-.007
TSCC-A: Post Traumatic Stress	.013	.015	-.004	.025
Total Functional Problems	-.057**	.061**	.094**	-.013
Total Clinical Problems	.063**	-.028**	-.063**	.055**

** Correlation is significant at the 0.01 level * Correlation is significant at the 0.05 level

Table 9.

Correlation of Dependent Variables

	CBCL Externalizing	CBCL Internalizing	UCLA PTSD RI	TSCC-A: Anger	TSCC-A: Anxiety	TSCC-A: Depression	TSCC-A: Dissociation	TSCC-A: Post Traumatic Stress	Functional Problems	Clinical Problems
CBCL Externalizing	1									
CBCL Internalizing	.543**	1								
UCLA PTSD RI	.143**	.256**	1							
TSCC-A: Anger	.347**	.199**	.538**	1						
TSCC-A: Anxiety	.087**	.237**	.682**	.508**	1					
TSCC-A: Depression	.176**	.260**	.665**	.634**	.718**	1				
TSCC-A: Dissociation	.171**	.198**	.650**	.600**	.673**	.689**	1			
TSCC-A: Post Traumatic Stres	.094**	.228**	.743**	.532**	.802**	.715**	.709**	1		
Total Functional Problems	.482**	.290**	.207**	.301**	.111**	.237**	.186**	.138**	1	
Total Clinical Problems	.229**	.253**	.208**	.192**	.173**	.223**	.167**	.192**	.417**	1

** Correlation is significant at the 0.01 level * Correlation is significant at the 0.05 level

Hypothesis 1 predicted that scores on clinical scales, functional problems, clinical problems, and clinical categorization at Baseline would differ by children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, used English as the primary language spoken at home, and were refugee/immigrants. This hypothesis was tested in a series of hierarchical multiple regressions. These regressions were conducted upon the following dependent variables at Baseline: CBCL Externalizing Score, CBCL Internalizing Score, UCLA PTSD RI Severity Raw Total Score, TSCC-A Anger, TSCC-A Depression, TSCC-A Anxiety, TSCC-A Posttraumatic Stress, TSCC-A Dissociation, Total Functional Problem Score, and Total Clinical Problem Score. Ten hierarchical regressions were conducted. For all hierarchical regressions, it was predicted that the outcome scores would differ by the following independent variables: gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status. For all regressions the order of the steps was the same. At step one gender-males and age were entered into the model. At step two, number of trauma types was entered into the model. At step three, race was entered. At step four, ethnicity was entered into the model, and finally, at step five the set of U.S. born, English as primary language spoken at home, and refugee/immigrant status were entered into the model. For the race step, the racial group with the highest number of participants was set as the standard against which the other races were compared; the White/Caucasian group was thus the standard. Follow-up post hoc tests were used to further examine race if it was significant in the model. The order of entry was based on the trauma literature. Age, gender, and number of trauma types are well known to influence response to trauma; the race, ethnicity, and cultural factors were held to the end to

see if they added significant variance after these were accounted for. A Bonferroni correction for 10 tests was made at the level of the initial test of the model. Thus, to consider each outcome variable, the *p* level for the full model had to be $p = .005$ or less to proceed with that analysis. The final model is shown for each.

Hierarchical regression CBCL Externalizing. For the model predicting CBCL Externalizing, reported in Table 10, the overall model was significant (F (11, 5931) = 23.889, $p < .0001$, Adjusted $R^2 = .041$).

Table 10.

Hierarchical Regression Analysis Summary for Variables Predicting Children's CBCL Externalizing T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.005*		
Gender-male	1.631	0.298	0.070			0.005*
Age	0.038	0.036	0.014			0.000
Step 2				.036*	.031*	
Number of trauma types	0.916	0.069	0.174			0.029*
Step 3				.038*	.003*	
Black/African American	-0.172	0.353	-0.007			0.000
Asian	-1.880	1.488	-0.016			0.000
American Indian/Alaskan	-1.754	0.794	-0.028			0.001
Unknown race	-0.727	0.597	-0.017			0.000
Step 4				.041*	.003*	
Ethnicity-Latino	-1.393	0.432	-0.056			0.002*
Step 5				.041*	.000	
U.S. Born	-0.699	0.725	-0.013			0.000
English in home	0.612	0.534	0.019			0.000
Refugee/Immigrant	0.133	0.899	0.002			0.000

*$p < .005$

In the first step the contribution of gender was significant, Adjusted $R^2 = .005$, $p < .0001$. In the second step the contribution of number of trauma types was significant, Adjusted $R^2 = .036$, $p < .0001$, In the third step the addition of the four racial groups Black/African American, Asian, American Indian/Alaskan Native, and unknown race was significant, Adjusted $R^2 = .038$, $p < .0034$. None of these racial categories individually was significantly different from the standard group (White/Caucasian). Due to the overall significance of the race step we performed a follow up post hoc test. A one way ANOVA was used to test for differences in externalizing T-scores among the racial groups.

Externalizing T-scores did not differ significantly across the five different racial groups, F (5, 8046) = 2.681, p = .020.

In the fourth step Ethnicity/Latino was significant, Adjusted R^2 =.041, p < .0001. In the final step the block of U.S. born, English as primary language spoken at home, and Refugee/Immigrant status did not account for additional variance in the full model. Overall, the full regression equation explained 4.1% of the variance in CBCL Externalizing scores at Baseline.

These results suggest that children's CBCL Externalizing scores are predicted by number of trauma types (more trauma types is associated with higher [worse] externalizing scores), gender (being male is associated with higher externalizing scores), ethnicity (being non-Latino is associated with higher externalizing scores), and finally race. Post hoc examination of race indicated that no significant differences exist between the five racial groups.

Hierarchical regression CBCL Internalizing. For the model predicting CBCL Internalizing, reported in Table 11, the overall model was significant (F (11, 5361) = 31.601, p < .0001, Adjusted R^2 = .059).

Table 11.

Hierarchical Regression Analysis Summary for Variables Predicting Children's CBCL Internalizing T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.014*		
Gender-male	0.455	0.289	.020			.000
Age	0.245	0.034	.093			.008*
Step 2				.035*	.021*	
Number of trauma types	0.781	0.067	.153			.023*
Step 3				.044*	.009*	
Black/African American	-1.721	0.342	-.069			.004*
Asian	1.308	1.439	.012			.000
American Indian/Alaskan	-1.903	0.768	-.032			.000
Unknown race	-0.442	0.577	-.011			.000
Step 4				.046*	.002*	
Ethnicity-Latino	0.407	0.418	.017			.000
Step 5				.049*	.004*	
U.S. Born	-1.425	0.701	-.028			.001
English in home	-1.695	0.516	-.054			.002*
Refugee/Immigrant	1.084	0.870	.016			.000

*p < .005

In the first step age alone was significant Adjusted R^2 = .014, p < .0001. In the second step the contribution of number of trauma types was significant, Adjusted R^2 =.035, p < .0001. In the third step the addition of the four racial groups Black/African American, Asian, American Indian/Alaskan Native, and unknown race was significant, Adjusted R^2 = .044, p < .0001. However, only the Black/African American group contributed to the model, accounting for .4% of the variance. Due to the overall significance of the race step we performed a follow up post hoc test. A one way ANOVA was used to test for differences in

internalizing T-scores among the racial groups. Internalizing T-scores did differ significantly across the five different racial groups, F (5, 8041) = 15.410, p = .0001.

Post hoc comparisons revealed significant differences between African American/Blacks and Caucasian/Whites on internalizing T-scores with a mean difference of -2.594, p = .0001 (Caucasian/Whites having higher/worse internalizing scores), and African American/Black and the "race unknown" racial group with a mean difference on internalizing T-scores of -1.941, p =.0001 ("race unknown" racial group having higher/worse internalizing scores).

In the fourth step Ethnicity/Latino was significant, Adjusted R^2 =.046, p < .0002. In the final step the block of U.S. born, English as primary language spoken at home, and refugee/immigrant status was significant, Adjusted R^2 =.049, p < .0001; only English as primary language spoken at home contributed to the model, accounting for .2% of the variance.

These results suggest that children's CBCL Internalizing scores are predicted most strongly by number of trauma types (more trauma types is associated with higher [worse] internalizing scores), age (the older the age the more internalizing), race (being Black/African American is associated with lower internalizing scores than being White/Caucasian or being of unknown race), English as the primary language spoken at home (speaking English at home is associated with lower internalizing scores), and ethnicity (being Latino is associated with higher internalizing scores).

Hierarchical regression UCLA PTSD RI raw score. For the model predicting UCLA PTSD RI Raw score, reported in Table 12, the overall model was significant (F (11, 5361) = 31.601, p < .0001, Adjusted R^2 = .059).

Table 12.

Hierarchical Regression Analysis Summary for Variables Predicting Children's Total UCLA PTSD RI Raw Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.028*		
Gender-male	-4.679	0.403	-.156			.024*
Age	-0.166	0.065	-.035			.001
Step 2				.057*	.030*	
Number of trauma types	1.098	0.087	.173			.028*
Step 3				.058*	.002	
Black/African American	0.824	0.493	.025			.000
Asian	0.621	1.635	.005			.000
American Indian/Alaskan	0.488	1.129	.006			.000
Unknown race	1.530	0.702	.031			.001
Step 4				.058*	.000	
Ethnicity-Latino	0.004	0.560	.000			.000
Step 5				.059*	.001	
U.S. Born	0.623	0.786	.012			.000
English in home	1.205	0.634	.034			.001
Refugee/Immigrant	1.029	1.037	.014			.000

*p < .005.

In the first step gender alone was significant, Adjusted R^2 = .028, p < .0001. In the second step the contribution of number of trauma types was significant, ΔR^2 = .002, p < .0001. In the third step the addition of the four racial groups did not account for additional variance in the full model. In the fourth step Ethnicity/Latino did not account for additional variance in the full model . In the final step, the block of U.S. born, English as primary language spoken at home, and refugee/immigrant status did not account for additional variance in the full model. Overall, the full regression equation explained 5.9% of the variance of Children's Total UCLA PTSD RI scores at Baseline.

These results suggest that children's Total UCLA Post Traumatic Stress RI Raw scores are predicted most strongly by the number of trauma types experienced (more trauma types is associated with higher [worse] scores), and then by gender (being female is associated with higher scores).

Hierarchical regression TSCC-A Anger score. For the model predicting TSCC-A Anger score reported in Table 13, the overall model was significant *(F (*11, 4517) = 11.199, *p* < .0001, Adjusted R^2 = .024).

Table 13.

Hierarchical Regression Analysis Summary for Variables Predicting Children's TSCC-A Anger T- Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.001		
Gender-male	-0.818	0.335	-0.036			.001
Age	-0.022	0.066	-0.005			.000
Step 2				.016*	.015*	
Number of trauma types	0.591	0.074	0.121			.014*
Step 3				.021*	.006*	
Black/African American	1.420	0.405	0.057			.003*
Asian	1.873	1.439	0.019			.000
American Indian/Alaskan	0.864	0.975	0.013			.000
Unknown race	-0.063	0.610	-0.002			.000
Step 4				.022*	.001	
Ethnicity-Latino	-0.151	0.469	-0.006			.000
Step 5				.024*	.003	
U.S. Born	1.479	0.695	0.035			.001
English in home	1.112	0.542	0.040			.001
Refugee/Immigrant	0.595	0.920	0.010			.000

*p < .005.

In the first step the block of gender and age was not significant, Adjusted R^2 = .002, p < .0124. In the second step, the contribution of number of trauma types was significant and explained 1.5% of the variance, Adjusted R^2 =.016, p < .0001. In the third step the addition of all four racial groups including Black/African American, Asian, American Indian/Alaskan Native, and unknown race was significant, Adjusted R^2 = .021, p < .0001. However, only the Black/African American group contributed significantly to the model, accounting for .3% of the variance. None of the other racial categories individually were significant. Due to the overall significance of the race step we performed a follow up post hoc test. A one way ANOVA was used to test for differences in Anger T-scores among the racial groups. Anger T-scores did not differ significantly across the five different racial groups, F (5, 5964) = 2.053, p = .06821.

In the fourth step Ethnicity/Latino did not account for additional variance in the full model, and there was no significant change in R^2. In the final step, the block of U.S. born, English as primary language spoken at home, and refugee/immigrant status did not account for additional variance in the full model and there was no significant change in R^2. Overall, the full regression equation explained 2.4% of the variance of the TSCC-A Anger T- Score.

These results suggest that children's TSCC-A Anger scores are predicted by the number of trauma types the child has experienced (more trauma types is associated with higher TSCC-A Anger scores).

Hierarchical regression TSCC-A Depression score. For the model predicting TSCC-A Depression Scores, reported in Table 14, the overall model was significant (F (11, 4517) = 9.354, p < .0001, R^2 = .020.)

Table 14.

Hierarchical Regression Analysis Summary for Variables Predicting Children's TSCC-A Depression T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.003*		
Gender-male	-0.434	0.364	-.018			.000
Age	0.122	0.071	.026			.001
Step 2				.020*	.017*	
Number of trauma types	0.700	.0.080	.132			.017*
Step 3				.020*	.001	
Black/African American	0.003	0.440	.000			.000
Asian	2.814	1.565	.027			.001
American Indian/Alaskan	0.730	1.060	.010			.000
Unknown race	0.650	0.664	.016			.000
Step 4				.020*	.000	
Ethnicity-Latino	-0.156	0.510	-.006			.000
Step 5				.020*	.000	
U.S. Born	-0.749	0.756	-.016			.000
English in home	0.390	0.590	.013			.000
Refugee/Immigrant	0.631	1.001	.010			.000

*$p < .005$.

In the first step the block of gender and age was significant, Adjusted $R^2 = .003$, $p < .0004$. Neither gender nor age was significant alone, however. In the second step, the contribution of number of trauma types was significant and explained 1.7% of additional variance, Adjusted $R^2 = .020$, $p < .0001$. In the third, fourth, and fifth steps, the addition of race, ethnicity/Latino, and cultural factors did not account for additional variance in the full model and there was no further significant change in R^2. Overall, the full regression equation explained 2.0% of the variance of the TSCC-A Depression T-scores.

These results suggest that children's TSCC-A Depression T-scores are predicted only by the number of trauma types the child has experienced (more trauma types is associated with higher TSCC-A Depression scores).

Hierarchical regression TSCC-A Anxiety score. For the model predicting TSCC-A Anxiety Scores, reported in Table 15, the overall model was significant *(F (*11, 4517) = 11.502, $p < .005$, Adjusted $R^2 = .025$.)

Table 15.

Hierarchical Regression Analysis Summary for Demographic Variables Predicting Children's TSCC-A Anxiety T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.007*		
Gender-male	-0.655	0.388	-0.025			.001
Age	-0.545	0.076	-0.108			.011*
Step 2				.023*	.016*	
Number of trauma types	0.731	0.085	0.129			.016*
Step 3				.025*	.003	
Black/African American	-0.822	0.468	-0.029			.001
Asian	2.679	1.667	0.024			.001
American Indian/Alaskan	-0.489	1.129	-0.006			.000
Unknown race	0.600	0.707	0.013			.000
Step 4				.025*	.000	
Ethnicity-Latino	0.347	0.544	0.013			.000
Step 5				.025*	.000	
U.S. Born	0.329	0.805	0.007			.000
English in home	-0.490	0.628	-0.015			.000
Refugee/Immigrant	1.170	1.066	0.017			.000

*$p < .005$.

In the first step the combination of gender and age was significant, Adjusted R^2 = .007, $p < .0001$; age alone accounted for a significant portion of variance. In the second step the contribution of number of trauma types was significant, explaining an additional 1.6% of the variance, Adjusted R^2 =.023, $p < .0001$. In the third, fourth, and fifth steps, the addition of the four racial categories, Ethnicity/Latino, and the block of cultural factors—U.S. born, English as primary language spoken at home, and refugee/immigrant status—did not account for additional variance in the full model, and there was no significant change in R^2. Overall, the full regression equation explained 2.5% of the variance of the TSCC-A Anxiety T-scores.

These results suggest that children's TSCC-A Anxiety scores are predicted by the number of trauma types experienced (more trauma types is associated with higher scores) and the children's age (younger age is associated with higher TSCC-A Anxiety scores).

Hierarchical regression TSCC-A Post Traumatic Stress score. For the model predicting TSCC-A Post Traumatic Stress scores reported in Table 16, the overall model was significant, (F (11, 4517) = 12.244, $p < .0001$, Adjusted R^2 = .027).

Table 16.

Hierarchical Regression Analysis Summary for Variables Predicting Children's TSCC-A Post Traumatic Stress T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.002*		
Gender-male	-0.642	0.347	-0.028			.001
Age	-0.259	0.068	-0.057			.003
Step 2				.027*	.025*	
Number of trauma types	0.821	0.076	0.162			.024*
Step 3				.027*	.001	
Black/African American	0.031	0.420	0.001			.000
Asian	2.639	1.493	0.026			.001
American Indian/Alaskan	0.000	1.012	0.000			.000
Unknown race	0.473	0.633	0.012			.000
Step 4				.026*	.000	
Ethnicity-Latino	0.142	0.487	0.006			.000
Step 5				.027	.001	
U.S. Born	1.077	0.721	0.025			.000
English in home	-0.081	0.563	-0.003			.000
Refugee/Immigrant	1.202	0.955	0.021			.000

*$p < .005$.

In the first step age and gender were not significant , Adjusted $R^2 = .002$, $p = .0079$. In the second step the contribution of number of trauma types was significant, explaining an additional 2.5% of the variance, Adjusted $R^2 = .027$, $p < .0001$. In the third, fourth, and fifth steps, the addition of the four racial categories, Ethnicity/Latino, and the block of cultural factors did not account for additional variance in the full model, and there was no significant change in R^2.

Overall, the full regression equation explained 2.7% of the variance of the TSCC-A Post Traumatic Stress T-scores. These results suggest that children's TSCC-A Post Traumatic Stress scores are predicted only by the number of trauma types experienced (more trauma types is associated with higher scores).

Hierarchical regression TSCC-A Dissociation score. For the model predicting TSCC-A Dissociation Scores, reported in Table 17, the overall model was significant (F (11, 4517) = 9,097, $p < .0001$, Adjusted $R^2 = .019$).

Table 17.

Hierarchical Regression Analysis Summary for Variables Predicting Children's TSCC-A Dissociation T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.002*		
Gender-male	-1.019	0.352	-0.043			.002*
Age	-0.088	0.069	-0.019			.000
Step 2				.019*	.017*	
Number of trauma types	0.687	0.077	0.134			.017*
Step 3				.019*	.001	
Black/African American	0.613	0.426	0.023			.000
Asian	0.764	1.515	0.008			.000
American Indian/Alaskan	-0.040	1.026	-0.001			.000
Unknown race	-0.199	0.642	-0.005			.000
Step 4				.019*	.000	
Ethnicity-Latino	0.000	0.494	0.000			.000
Step 5				.019*	.001	
U.S. Born	0.673	0.732	0.015			.000
English in home	0.478	0.571	0.016			.000
Refugee/Immigrant	-0.310	0.969	-0.005			.000

*$p < .005$.

In the first step the combination of age and gender was significant, Adjusted R^2 = .002, p = .0033, with gender-male accounting for the variance. In the second step the contribution of number of trauma types was significant explaining an additional 1.7% of the variance, Adjusted R^2 =.019, p < .0001. In the third, fourth, and fifth steps, the addition of the four racial categories, Ethnicity/Latino, and the block of U.S. born, English as primary language spoken at home, and refugee/immigrant status did not account for additional variance in the full model, and there was no significant change in R^2.

Overall, the full regression equation explained 1.9% of the variance of the TSCC-A Dissociation T-scores. These results suggest that children's TSCC-A Dissociation T-scores are predicted by the number of trauma types experienced (more trauma types is associated with higher scores) and the children's gender (being female is associated with higher TSCC-A Dissociation scores).

Hierarchical regression total functional problem score. For the model predicting total functional problem scores reported in Table 18, the overall model was significant, (F *(*11, 6387) = 97.657, p < .005, *Adjusted* R^2 = .143).

Table 18.

Hierarchical Regression Analysis Summary for Demographic Variables Predicting Children's Total Functional Problem Scores

Variable	B	SEB	*B*	*Adjusted* R^2	Δ R^2	sr^2
Step 1				.073*		
Gender-male	0.309	0.052	0.70			.005*.051*
Age	0.124	0.006	0.236			
Step 2				.131*	.058*	
Number of trauma types	0.231	0.012	0.236			.052*
Step 3				.133*	.003*	
Black/African	0.098	0.063	0.020			.000
American	-0.505	0.220	-0.027			.001
Asian	0.151	0.145	0.012			.000
American	0.208	0.097	0.027			.001
Indian/Alaskan						
Unknown race						
Step 4				.135*	.002*	
Ethnicity-Latino	0.029	0.073	0.006			.000
Step 5				.143*	.008*	
U.S. Born	0.553	0.113	0.064			.003*
English in home	0.342	0.080	0.062			.002*
Refugee/Immigrant	-0.119	0.136	-0.010			.000

*p < .005.

In the first step gender and age were significant, Adjusted R^2 = .073, p = .0001. In the second step the contribution of number of trauma types was significant explaining an additional 5.8% of the variance, Adjusted R^2 =.131, p < .0001. In the third step the addition of the four racial categories of Black/African American, Asian, American Indian/Alaskan Native, and unknown race was significant, Adjusted R^2 = .133, p < .0002. Due to the overall significance of the race step we performed a follow up post hoc test. A one way ANOVA

was used to test for differences in total functional problem scores among the racial groups. Total functional problem scores did not differ significantly across the five different racial groups, F (5, 7496) = 1.101, p = .357.

In the fourth step Ethnicity/Latino was significant, Adjusted R^2 = .135, p < .0008. In the final step, the block of U.S. born, English as primary language spoken at home, and refugee/immigrant status was significant, Adjusted R^2 =.143, p < .0001; being U.S. born and English as primary language spoken at home were significant individually. Overall, the full regression equation explained 14.3% of the variance of the Total Problem scores.

These results suggest that children's Total Functional Problem scores are predicted by the number of trauma types experienced (more trauma types is associated with higher scores), the children's age (older age is associated with more problems), children's gender (being male is associated with more problems), birth in the U.S. (being born in the U.S. is associated with more problems), and English as primary language spoken at home (speaking English as the primary language at home is associated with more problems).

Hierarchical regression total clinical problem score. For the model predicting total clinical problem scores reported in Table 19, the overall model was significant, (*F (*11, 7458) = 7.984, p < .0001, *Adjusted* R^2 = .112).

Table 19.

Hierarchical Regression Analysis Summary for Variables Predicting Children's Total Clinical Problem Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.027*		
Gender-male	0.063	0.066	0.010			.000
Age	0.078	0.008	0.110			.011*
Step 2				.109*	.081*	
Number of trauma types	0.386	0.015	0.292			.080*
Step 3				.110*	.002	
Black/African American	0.047	0.080	0.007			.000
Asian	-0.217	0.289	-0.008			.000
American Indian/Alaskan	0.594	0.180	0.036			.001
Unknown race	0.249	0.124	0.024			.000
Step 4				.110*	.000	
Ethnicity-Latino	-0.188	0.094	-0.030			.000
Step 5				.112*	.002*	
U.S. Born	0.162	0.145	0.014			.000
English in home	-0.416	0.111	-0.054			.002*
Refugee/Immigrant	0.383	0.178	0.024			.001

*p < .005.

In the first step only age was individually significant, Adjusted R^2 = .027, p = .0001. In the second step the contribution of number of trauma types was significant, explaining an additional 8.1% of the variance, Adjusted R^2 =.109, p < .0001. In the third step the addition of the four racial categories of Black/African American, Asian, American Indian/Alaskan Native, and unknown race was not significant. In the fourth step Ethnicity/Latino did not account for additional variance in the full model, and there was no significant change in R^2, Adjusted R^2 = .110, p < .9480. In the final step, the block of U.S. born, English as primary

language spoken at home, and refugee/immigrant status was significant, Adjusted R^2 =.112, p < .0002; only English as primary language spoken at home was significant individually. Overall, the full regression model explained 11.2% of the variance of the Total Clinical Problems scores.

These results suggest that children's Total Clinical Problems scores are predicted by the number of trauma types experienced (more trauma types is associated with higher scores), the children's age (older age is associated with more disorders), and English as primary language spoken at home (speaking English as the primary language at home is associated with less disorders).

Hierarchical Logistic Regression on Children's Presenting Symptoms Being in Clinical Range

A series of Hierarchical Logistic Regressions were conducted to test the second part of hypothesis one, that children's presenting symptoms would be in the clinical range depending on various ecological and trauma specific factors. We tested whether these factors made the children more or less likely to fall into the clinical range for CBCL Externalizing, CBCL Internalizing, and The UCLA PTSD Reaction Index. These analyses are not performed for the TSCC-A scores, as so few children fell into the clinical range at Baseline.

For these analyses, we used all the predictor variables used in the hierarchical regression analysis.

For race, the contrast is with the named group in comparison with the standard group, or White/Caucasian.

Hierarchical logistic regression: CBCL Externalizing at Baseline. A hierarchical logistic regression model was built using gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant

status as predictors for being clinical or non-clinical on the CBCL Externalizing measure. The clinical level is defined by Achenbach et al. (1992) as T-scores above 63. At Baseline, 49.37% of the children were in the clinical range for externalizing. A test of the full model, reported in Table 20, was statistically significant, X^2 (11) = 206.278, $p < .0001$.

Table 20.

Hierarchical Logistic Regression Model predicting children's Clinical/ Non-Clinical Groups from CBCL Externalizing Scores (n =5943)

Prediction of Non-Clinical/Clinical	Chi-square	95% CI for Odds Ratio (OR)	Adjusted OR
Model 1: CBCL Externalizing	206.278***		
Gender (male)		1.059-1.306	1.176**
Age		1.006-1.032	1.019**
Number of trauma types		1.118-1.175	1.146***
Race			
Indian/Native Americans		.641-1.121	.847
Asian		.403-1.169	.686
Black/African American		.851-1.090	.963
Unknown		.714-1.092	.883
Ethnicity		.656-.890	.764**
US Born		.823-1.379	1.066
English as primary language		.934-1.365	1.129
Refugee/Immigrant status		.619-1.171	.852

*$p < .05$, **$p < .001$, ***$p < .0001$.

Gender and age were significant predictors of clinical classification, X^2 (2) = 26.229, $p < .0022$, with boys more likely to fall within the clinical range and with older age children more likely to fall within the clinical range. Number of trauma types was a significant predictor of clinical classification, X^2 (1) = 135.600, $p < .0001$ with children who had more trauma types being more likely to fall within the clinical range. Race was not a significant

predictor of clinical classification. Ethnicity was a significant predictor of clinical classification, X^2 (1) = 25.536, $p < .0001$, with non-Latino children being more likely to fall within the clinical range. The cultural factors were not significant predictors of clinical classification.

The change in odds associated with being in the clinical group for externalizing for males was 1.176, indicating that boys were 18% more likely than girls to be in the clinical range. The change in odds associated with being in the clinical group for externalizing for age was 1.019, indicating that older children were 2% more likely to be in the clinical group than younger children. The change in odds associated with being in the clinical group for externalizing for children with more trauma types was 1.146, indicating that the children with more trauma types were 15% more likely than the children with fewer traumas to be in the clinical externalizing group. The change in odds associated with being in the clinical group for the Latino group was .764, indicating that Latino children were 24% less likely to be in the clinical externalizing group.

Hierarchical logistic regression: CBCL Internalizing at Baseline. A hierarchical logistic regression model was built using gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status as predictors for being clinical or non-clinical on the CBCL Internalizing measure.

The clinical level is defined by Achenbach and colleagues (1992) as T-scores above 63. At Baseline, 45.8% of the children were in the clinical range for internalizing. A test of the full model, reported in Table 21, was statistically significant, X^2 (11) = 220.801, $p < .0001$.

Table 21.

Hierarchical Logistic Regression Model predicting children's Clinical/ Non-Clinical Groups from CBCL Internalizing Scores (n = 5943)

Prediction of Non-Clinical/Clinical	Chi-square	95% CI for Odds Ratio (OR)	Adjusted OR
Model 2: CBCL Internalizing	220.801***		
Gender (male)		1.036-1.279	1.151*
Age		1.025-1.051	1.038***
Number of trauma types		1.104-1.160	1.131***
Race			
Indian/Native Americans		.613-1.079	.813
Asian		.980-2.804	1.658
Black/African American		.708-.909	.802**
Unknown		.808-1.230	.997
Ethnicity		.921-1.248	1.072
US Born		.628-1.049	.812
English as primary language		.609-.886	.735**
Refugee/Immigrant status		.830-1.571	1.142

*$p < .05$, **$p < .001$, ***$p < .0001$.

Age and gender were significant predictors of clinical classification, X^2 (2) = 62.181, p <.0001, with males and older children more likely to fall within the clinical range. Number of trauma types was a significant predictor of clinical classification, X^2 (1) = 91.238, p < .0001, with children who experienced more trauma types being more likely to fall within the clinical range. Race was a significant predictor of clinical classification, X^2 (4) = 37.217, p < .0001, with Black/African-American children being less likely to fall within the clinical range as compared with the standard group (white/Caucasian) for internalizing. English speaking at home was a significant predictor of clinical classification, X^2 (3) = 17.606, p <

.001, with English speaking children at home less likely to fall within the clinical range.

The change in odds associated with being in the clinical group for internalizing for males was 1.151, indicating that male children were 51% more likely than females to be in the clinical group for internalizing. The change in odds associated with being in the clinical group for internalizing for age was 1.038, indicating that older children were 4% more likely to be in the clinical range for internalizing. The change in odds associated with being in the clinical group for internalizing for children with higher number of trauma types was 1.131, indicating that these children were 13% more likely than the children with fewer traumas of being in the clinical internalizing group. The change in odds associated with being in the clinical group for internalizing for children in the Black/African-American group was .802, indicating that the children in the Black/African-American group were 20% less likely to be in the clinical internalizing group as compared with the standard (White/Caucasian) group. The change in odds associated with being in the clinical group for internalizing for children who speak English as the primary language at home was .735, indicating that the children who speak English as the primary language at home were 27% less likely to be in the clinical internalizing group.

Hierarchical logistic regression: UCLA PTSD Reaction Index at Baseline. A hierarchical logistic regression model was built using gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status as predictors for being clinical or non-clinical on the UCLA PTSD Reaction Index**.** The clinical level is defined by Pynoos and colleagues (1998) as being a raw score of 38 or higher. At Baseline, 24.6% of the children fell into the clinical range. A test of the full model, reported in Table 22, was statistically significant, X^2 (11) = 184.369, $p <$ .0001.

Table 22.

Hierarchical Logistic Regression Model predicting children's Clinical/ Non-Clinical Groups from UCLA PTSD Reaction Index Scores (n = 5373)

Prediction of Non-Clinical/Clinical	Chi-square	95% CI for Odds Ratio (OR)	Adjusted OR
Model 2:UCLA PTSD Reaction Index	184.369***		
Gender (male)		.503-.655	.574***
Age		.966-1.007	.986
Number of trauma types		1.101-1.161	1.131***
Race			
Indian/Native Americans		.743-1.483	1.050
Asian		.707-1.956	1.176
Black/African American		.986-1.341	1.150
Unknown		.934-1.456	1.166
Ethnicity		.818-1.168	.978
US Born		.743-1.233	.957
English as primary language		.960-1.447	1.178
Refugee/Immigrant status		.850-1.612	1.171

Gender was a significant predictor of clinical classification, X^2 (2) = 84.553, $p <$ .0001, with females more likely to fall within the clinical range. Number of trauma types was a significant predictor of clinical classification, X^2 (1) = 88.566, $p < .0001$, with children with a high number of trauma types being more likely to fall within the clinical range. None of the other independent variables were significant predictors of falling into the clinical group for the UCLA PTSD Reaction Index.

The change in odds associated with being in the clinical group for the UCLA PTSD

RI scores for males was .574, indicating that boys were 43% less likely than girls to be in the clinical range for the UCLA PTSD RI. The change in odds associated with being in the clinical group for UCLA PTSD RI scores for children with more trauma types was 1.131, indicating that children with more trauma types are 13 % more likely than children with fewer traumas to be in the clinical range for the UCLA PTSD RI scores.

Hierarchical Regressions on Change Scores on Clinical Scales and Functional problems between Baseline and At Three Month (Or First Recorded) Follow up

Hypothesis 2 predicted that change in scores on clinical scales and total functional problems, as well as the clinical categorization at three month (or first recorded) follow up, will differ by children's gender, age at treatment, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, had English as the primary language spoken at home, and were refugee/immigrants.

A series of hierarchical regressions were conducted to test this hypothesis using all independent variables as identified as important from the literature. If race was found to be significant in the hierarchical regression, post hoc one-way ANOVAs were conducted to see whether racial groups differed.

The dependent variables in the set of analyses were created by computing the difference between the Baseline scores and the at three month (or first recorded) follow-up scores. These included: CBCL Externalizing Score, CBCL Internalizing Score, UCLA PTSD RI Raw Total Score, TSCC-A Anger Score, TSCC-A Depression Score, TSCC-A Anxiety Score, TSCC-A Posttraumatic Stress Score, TSCC-A Dissociation Score and Total Functional Problem Score. Clinical problems were not examined as this was not measured at follow up. Nine analyses were conducted. To control for multiple tests, each analysis was performed with the Bonferroni correction, at the alpha = 0.05/9 level, or .005.

The independent variables in the regression analyses included all of the following: gender, age at Baseline, number of trauma types, race (Indian/Native American, Asian, Black/African American, unknown) as compared to the standard group (White/Caucasian), ethnicity (Latino), U.S. country of birth, English language spoken at home, and refugee/immigrant status.

At three month (or first recorded) follow-up there was significant improvement on all Dependent variables as reported in Table 23.

Table 23.

One Sample t-Tests of Difference Variables Between Baseline Scores and At Three Month (Or First Recorded) Follow-up Scores

Difference Variable	*n*	Mean Difference	SD	*T*	*p* <
CBCL Externalizing T-score	2786	3.43001	9.0937	19.909	.0001
CBCL Internalizing T-score	2786	3.85930	10.0595	20.250	.0001
UCLA PTSD RI Raw Score	3016	6.32926	13.5959	25.566	.0001
TSCC-A Anger T-score	2359	2.93641	10.3352	13.799	.0001
TSCC-A Depression T-score	2359	4.53201	11.5454	19.065	.0001
TSCC-A Anxiety T-score	2359	4.41501	12.0022	17.866	.0001
TSCC-A Post Traumatic T-score	2359	4.87664	10.9754	21.581	.0001
TSCC-A Dissociation	2358	3.33404	10.7495	15.064	.0001
Total Functional Problems Score	3699	1.06164	3.0556	21.131	.0001

Using all the predictors, the change scores were subjected to hierarchical regressions.

Hierarchical regression Change CBCL Externalizing. For the model predicting CBCL Change Externalizing, the overall model was not significant (F (11, 2507) = 1.755, p < .057.

Hierarchical regression CBCL Change Internalizing. For the model predicting CBCL Change Internalizing, reported in Table 24 , the overall model was significant (F (11, 2496) = 3.019, p < .0001, Adjusted R^2 = .009).

Table 24.

Hierarchical Regression Analysis Summary for Variables Predicting Children's CBCL Change Internalizing T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.004*		
Gender-male	-0.444	0.405	-.022			.000
Age	-.152	0.050	-.062			.004*
Step 2				.004*	.001	
Number of trauma types	-0.089	0.090	-.021			.000
Step 3				.007*	.004	
Black/African American	-.561	0.508	-.023			.000
Asian	-2.262	1.804	-.025			.001
American Indian/Alaskan	-1.113	1.009	-.022			.000
Unknown race	0.461	0.727	.014			.000
Step 4				.009*	.002	
Ethnicity-Latino	0.480	0.569	.023			.000
Step 5				.009*	.001	
U.S. Born	0.246	0.864	.006			.000
English in Home	-1.295	0.676	-.050			.001
Refugee/Immigrant	0.023	1.239	.000			.000

*p < .005

In the first step age alone was significant Adjusted R^2 = .004, p < .0001. In all of the remaining steps, none of the predictors were significant.

These results suggest that change in children's CBCL Internalizing scores at three month (or first recorded) follow up are predicted only by age (the younger the age, the more improvement over three months in internalizing scores).

Hierarchical regression UCLA PTSD RI change raw score. For the model predicting UCLA PTSD RI change raw score, the overall model was not significant (F (11, 2731) = 1.686, $p < .0701$, Adjusted $R^2 = .003$).

Hierarchical regression TSCC-A Anger change T- score. For the model predicting TSCC-A Anger change T- score, the overall model was not significant (F (11, 2147) = 1.103, $p = .3551$, Adjusted $R^2 = .001$).

Hierarchical regression TSCC-A Depression change T- score. For the model predicting TSCC-A Depression change T-score, reported in Table 25, the overall model was significant (F (11, 2136) = 2.451, $p = .0048$, $R^2 = .004$.)

Table 25.

Hierarchical Regression Analysis Summary for Variables Predicting Children's TSCC-A Depression Change T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.002		
Gender-male	-0.008	0.519	.000			.000
Age	-0.289	0.104	-.062			.004*
Step 2				.003	.001	
Number of trauma types	0.226	.0.110	.045			.002
Step 3				.004	.002	
Black/African American	0.633	0.626	.024			.000
Asian	1.874	1.923	.021			.000
American Indian/Alaskan	-0.442	1.429	-.007			.000
Unknown race	1.107	0.934	.028			.001
Step 4				.004	.001	
Ethnicity-Latino	0.213	0.716	.009			.000
Step 5				.009*	.004*	
U.S. Born	1.999	0.997	.050			.002
English in Home	-2.322	0.837	-.082			.004*
Refugee/Immigrant	-.638	1.333	-.011			.000

*$p < .005$.

In the first step four steps none of the variables were significant. This included the block of gender and age, the block of number of trauma types, the block of race, and the block of ethnicity. These factors did not account for variance, and there was no significant changes in R^2. However, the final step of U.S Born, English in Home and refugee/immigrant Status was significant, with English in Home being the only variable within the step that was significant. Children who spoke English at home showed less change. The overall model explained 1.2% of the variance of the TSCC-A Depression change T-scores.

These results suggest that change in children's TSCC-A Depression T-scores at three month (or first recorded) follow up are predicted only by whether the child speaks English in home; children who spoke English at home showed less change in TSCC-A Depression scores.

Hierarchical regression TSCC-A Anxiety change T- scores. For the model predicting TSCC-A Anxiety Scores, reported in Table 26, the overall model was significant *(F (*11, 2147) = 2.809, *p* =.0012, Adjusted R^2 = .009.)

Table 26.

Hierarchical Regression Analysis Summary for Demographic Variables Predicting Children's TSCC-A Anxiety Change T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.004*	.005*	
Gender-male	.439	.535	.018			.000
Age	-.335	.107	-.069			.004*
Step 2				.004*	.001	
Number of trauma types	.155	.113	.030			.001
Step 3				.008*	.005	
Black/African American	-.174	.645	-.006			.000
Asian	2.135	1.981	.024			.001
American Indian/Alaskan	-2.809	1.472	-.041			.002
Unknown race	1.285	.962	.031			.001
Step 4				.008*	.001	
Ethnicity	.370	.738	.015			.000
Step 5				.009*	.003	
U.S. Born	2.318	1.027	.057			.002
English in Home	-1.444	.862	-.050			.001
Refugee/Immigrant	1.215	1.374	.020			.000

*$p < .005$.

In the first step the combination of gender and age was significant, Adjusted $R^2 = .004$, $p < .003$; age alone accounted for a significant portion of variance. In the second, the third, fourth, and fifth steps, the addition of number of trauma types, four racial categories, Ethnicity/Latino, and the block of cultural factors—U.S. born, English as primary language spoken at home, and refugee/immigrant status—did not account for additional variance in the full model, and there was no significant change in R^2. Overall, the full regression equation explained .9% of the variance of changes in the TSCC-A Anxiety T-scores.

These results suggest that change in children's TSCC-A Anxiety scores at three month (or first recorded) follow up is predicted by the children's age (younger age is associated with more improvement in TSCC-A Anxiety scores).

Hierarchical regression TSCC-A Post Traumatic Stress Change T- scores. For the model predicting TSCC-A Post Traumatic Change Scores, reported in Table 27, the overall model was significant *(F (*11, 2147) = 2.701, p =.002, Adjusted $R^2 = .009$.)

Table 27.

Hierarchical Regression Analysis Summary for Demographic Variables Predicting Children's TSCC-A Post Traumatic Stress Change T-Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.000	.001	
Gender-male	-.113	.489	-.005			.000
Age	-.163	.098	-.037			.001
Step 2				.000	.000	
Number of trauma types	.119	.104	.025			.000
Step 3				.006	.008*	
Black/African American	-.282	.591	-.011			.000
Asian	2.590	1.813	.031			.001
American Indian/Alaskan	-3.757	1.348	-.061			.004
Unknown race	1.107	.881	.029			.001
Step 4				.007	.001	
Ethnicity	.765	.675	.033			.001
Step 5				.009	.003	
U.S. Born	2.354	.940	.063			.003
English in Home	-1.134	.789	-.043			.001
Refugee/Immigrant	.422	1.258	.008			.000

*$p < .005$.

In the first step and second steps the addition of age, gender, and number of trauma types was not significant. In the third step the addition of race was significant, Adjusted R^2 = .006 $p < .005$. Due to the overall significance of the race step we performed a follow up post hoc test. A one way ANOVA was used to test for differences in Post Traumatic Stress T-scores among the racial groups. Post Traumatic Stress T-scores did not differ significantly across the five different racial groups, F (5, 2353) = 1.550, p = .171.

In the fifth step, the addition of the block of cultural factors—U.S. born, English as primary language spoken at home, and refugee/immigrant status—did not account for

additional variance in the full model, and there was no significant change in R^2. Overall, the full regression equation explained .9% of the variance of changes in the TSCC-A Post Traumatic Stress T-scores.

These results suggest that change in children's TSCC-A Post Traumatic Stress scores at three month (or first recorded) follow up is predicted by the children's race in the full hierarchical model but that racial groups do not differ in their amount of change.

Hierarchical regression TSCC-A Dissociation Change T- scores. For the model predicting TSCC-A Dissociation Change Scores, the overall model was not significant *(F (*11, 2147) = 1.610, p =.089, Adjusted R^2 = .003.)

Hierarchical regression Total Functional Problem Change Score. For the model predicting Total Problem Change Score, reported in Table 28, the overall model was significant (F (11, 3423) = 7.784, p < .0001, Adjusted R^2 = .021).

Table 28.

Hierarchical Regression Analysis Summary for Demographic Variables Predicting Children's TSCC-A Total Functional Problem Change Scores

Variable	B	SEB	*B*	*Adjusted* R^2	ΔR^2	sr^2
Step 1				.014	.014*	
Gender-male	.047	.105	.008			.000
Age	.079	.013	.110			.001*
Step 2				.019	.005*	
Number of trauma types	.104	.024	.077			.005*
Step 3				.019	.002	
Black/African American	-.008	.129	-.001			.000
Asian	.248	.415	.010			.000
American Indian/Alaskan	-.096	.299	-.005			.000
Unknown race	.346	.191	.034			.001
Step 4				.019	.000	
Ethnicity	.255	.150	.039			.001
Step 5				.021	.003	
U.S. Born	.519	.206	.049			.002
English in Home	.051	.172	.007			.000
Refugee/Immigrant	-.215	.253	-.015			.000

*$p < .005$.

In the first step the contribution of gender and age was significant, Adjusted R^2 = .014, $p < .0001$. In the second step the contribution of number of trauma types was significant, Adjusted R^2 =.019, $p < .0001$. In the third, fourth, and fifth steps the addition of the four racial groups Black/African American, Asian, American Indian/Alaskan Native, and unknown race (with all racial groups in comparison to the standard group, Whites/Caucasians), the addition of Ethnicity/Latino, and the addition of English as primary language spoken at home and refugee/immigrant status were all non-significant. Overall, the

full regression equation explained 2.4% of the variance in the Total Functional Problem change score.

These results suggest that change in children's Total Functional Problem Score are predicted by older age (being older is associated with more improvement in number of problems) and number of trauma types (being in the higher trauma group is associated with more improvement in number of problems).

Hierarchical Logistic Regression of Being in the Clinical Range At Three Month (Or First Recorded) Follow Up

A series of Hierarchical Logistic Regressions were conducted to further test the hypothesis that children's post treatment symptoms would differ depending on various ecological and trauma-specific factors. These included gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status,

We tested whether the variables identified as significant by the literature made the children more or less likely to fall into the clinical range for externalizing, internalizing, and the UCLA-PTSD RI Scale at three month (or first recorded) follow up. These analyses are not performed for the TSCC-A scores, as so few children fell into the clinical range at Baseline.

Hierarchical logistic regression: Clinical range of CBCL Externalizing at three month (or first recorded) follow up. A hierarchical logistic regression model, reported in Table 29 was built using gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status as predictors for being clinical or non-clinical on the CBCL Externalizing measure at three month (or first recorded) follow up. In the follow-up sample 32.32% of the children fell into the clinical

range on externalizing; this compares with 49.7% at baseline. A test of the full model was statistically significant, X^2 (11) = 62.488, $p < .0001$.

Table 29.

Hierarchical Logistic Regression Model Predicting Children's Clinical/ Non-Clinical Groups From Externalizing Change Scores At Three Month (Or First Recorded) Follow Up

Prediction of Non-Clinical/Clinical	Chi-square	95% CI for Odds Ratio (OR)	Adjusted OR
Model 2: CBCL Externalizing	62.488***		
Gender (male)		.919-1.436	1.148
Age		.969-1.024	.996
Number of trauma types		1.108-1.222	1.163***
Race			
Indian/Native Americans		.318-.932	.544
Asian		.146-1.822	.515
Black/African American		.924-1.596	1.214
Unknown		.676-1.524	1.015
Ethnicity		.484-.936	.673
US Born		.496-1.287	.799
English as primary language		.651-1.443	.969
Refugee/Immigrant status		.713-2.554	1.350

Gender and race did not contribute. Number of trauma types was a significant predictor of clinical classification, X^2 (1) = 39.994, $p < .0001$, with the more trauma types a child has experienced the more they are likely to fall within the clinical range at three month (or first recorded) follow up. None of the other predictors including: race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status contributed.

The change in odds associated with being in the clinical group at three month (or first

recorded) follow up for externalizing for children with greater number of trauma types was 1.163,

indicating that the children with more trauma types were 16% more likely than children with less traumas to be in the clinical externalizing group.

Hierarchical logistic regression: Clinical range of CBCL Internalizing at three month (or first recorded) follow up. A hierarchical logistic regression model, reported in Table 30, was built using gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status as predictors for being clinical or non-clinical on the CBCL Internalizing measure at three month (or first recorded) follow up. At this point, 33.05% of the full sample fell into the clinical range; this compares with 45.8% at baseline. A test of the full model (n = 1506) was statistically significant, X^2 (11) = 50.927, p < .0001.

Table 30.

Hierarchical Logistic Regression Model predicting children's Clinical/ Non-Clinical Groups from Internalizing Change Scores At Three Month (Or First Recorded) Follow Up

Prediction of Non-Clinical/Clinical	Chi-square	95% CI for Odds Ratio (OR)	Adjusted OR
Model 2: CBCL Internalizing	50.927***		
Gender (male)		.999-1.577	1.255
Age		.981-1.038	1.009
Number of trauma types		1.100-1.215	1.156***
Race			
Indian/Native Americans		.388-1.137	.664
Asian		.384-3.227	1.113
Black/African American		.647-1.150	.862
Unknown		.636-1.447	.959
Ethnicity		.523-1.022	.731
US Born		.462-1.193	.742
English as primary language		.620-1.383	.926
Refugee/Immigrant status		.807-2.884	1.525

Gender and race did not contribute. Number of trauma types was a significant predictor of clinical classification, X^2 (1) = 41.229, $p < .0001$, with the more trauma types a child has experienced the more they are likely to fall within the clinical range at three month (or first recorded) follow up. None of the other predictors including: race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status contributed.

The change in odds associated with being in the clinical group at three month (or first recorded) follow up for internalizing for children with greater number of trauma types was 1.156,

indicating that the children with more trauma types were 16% more likely than children with fewer trauma types to be in the clinical internalizing group.

Hierarchical logistic regression: Clinical range UCLA PTSD Reaction Index at three month (or first recorded) follow up. A hierarchical logistic regression model was built using gender, age, number of trauma types, race, ethnicity, U.S. born, English as primary language spoken at home, and refugee/immigrant status as predictors for being clinical or non-clinical on the UCLA PTSD Reaction Index post treatment. At three month (or first recorded) follow up, 14.22% fell into the clinical range for the UCLA PTSD Reaction Index; this compares with 24.6% at baseline. A test of the full model was not statistically significant, X^2 (11) = 24.740, $p < .010$, so the contribution of the predictors could not be reliably tested.

Discussion

Past studies involving childhood trauma have identified important variables affecting children's symptoms. The type and severity of traumas experienced are prototypical causal factors in response to trauma, while children's age and gender are also associated with response to trauma. However, few studies have looked at racial, ethnic, and cultural factors to explore how these may be related to children's symptoms and recovery. Racial, ethnic, and cultural factors are markers of the wide diversity in citizens of the United States; these factors influence how our families are structured and what values we find important. More importantly, all persons use these factors as filters to understand the world and their experiences. We were concerned that the current approach to assessment and treatment may have been formulaic and cookie-cutter—an approach that largely ignores the ecological framework of children—thus doing a disservice to some children. We hoped to shed light on

whether, and how, racial, ethnic, and cultural experiences may lead to different trauma symptoms and responses to treatment and, through the study's findings, provide support for a more ecological and individualized approach to children who have experienced trauma. In order to study these racial, ethnic, and cultural factors, we chose factors about children that were available to us in a large dataset of children across the country who were treated for trauma (Briggs, et al., 2012). These factors included racial group, ethnicity, birth in the United States, English as the primary language spoken in the home, and refugee/immigrant status. We must note from the outset that though many of the statistical models were significant, the predictors accounted for only a small amount of the variance in children's symptoms. Thus, the clinical significance of the models is questionable.

Description of the Children

The children in our study were diverse, but the racial and cultural groups were represented in relatively small numbers. The largest racial group represented was White/Caucasian children, comprising over half of the sample, followed by Black/African American children, comprising a little over one-fourth of the overall sample. Other racial groups were minimally represented, with 1.7% of the children being Native American, and .8% of the children being Asian. Of the entire sample, 4.8% of the children were identified as multiracial. A large number of children's race was coded as "unknown;" thus, it was not possible to understand exactly what racial group they might represent. The ethnicity of the children consisted of almost one-third being Latino/Hispanic; other ethnicities were not coded for in the dataset and so could not be represented in the analyses.

The cultural variables specifically examined in this study were present in relatively small numbers. Just 3% of the children were refugee/immigrants, 5.9% were born in a country other than the United States, and 15.4% did not use English as the primary language

at home. Little information was available regarding their socioeconomic status except that two-thirds of the children had public insurance; with so little information, we elected not to include this in analyses.

The children in the study were highly traumatized. As shown in Figure 2, all the children had experienced at least one type of trauma, with most experiencing more. In the full sample, three-fourths of the children experienced two or more trauma types, over half experienced three or more trauma types, and a little over one percent of the children actually experienced ten to fifteen traumas. The count of "trauma types" cannot give the full story of the amount or chronicity of the trauma in each child's life and so are not a complete measure of the severity of trauma. However, it is apparent that these children were at much higher risk than a typical population of children in the U.S. today. Additionally, the experience of multi and complex trauma can come with its own set of unique constellation of symptoms. Complex trauma can be defined as experiencing multiple and chronic developmentally adverse events early in life that are most often interpersonal in type (Margolin & Vickerman, 2011;Van der Kolk, 2005). Domestic violence, which was experienced by 45% of the children, has also been recognized as falling into this category. Children who experience complex trauma will often exhibit symptoms differently. Typical impairments of functioning for complex trauma survivors include differences or deficits in: (a) affect regulation, (b) information processing, (c) self-concept, (d) behavior control, (e) interpersonal relationships, and (f) biological processes such as somatization and sensorimotor development delays (Margolin & Vickerman, 2011; Van der Kolk, 2005).

Applying Bronfenbrenner's Ecological Model to Better Understand the Study's Children

Understanding the children's trauma. We can use Bronfenbrenner's ecological model when looking at Figure 3 in which the percentages of different types of traumas experienced and the percentages for the primary trauma presenting for treatment are shown. Applying the model to this Figure, we can see the largest numbers of traumas were at the microsystem level, within the family, with almost half of the children experiencing traumatic loss, almost half experiencing domestic violence, and one-third having an impaired caregiver. As further evidence of trauma at the microsystem level, a high number of children experienced abuse, including almost one-third experiencing emotional abuse, over one-fourth experiencing physical abuse, and one-fourth experiencing sexual abuse. Additionally, over one-fourth of children suffered from neglect. The children experienced a higher prevalence of family-level traumas than traumas occurring in outer layers of the ecological model such as in the exosystem or the macrosystem. Fewer children experienced traumas in the exosystem, with less than fifteen percent experiencing community violence and a little over ten percent experiencing school violence. A small percentage of children experienced traumas in the macrosystem level, with five percent experiencing natural disaster and less than two percent experiencing war/terrorism or forced displacement.

Understanding the children's functioning. At baseline the children were shown to be in great distress. As can be seen in Figure 5 "Frequency of Functional Problems" and Figure 6 "Frequency of Clinical Problems," they suffered from PTSD, depression, anxiety, attachment, and behavior problems. Specifically, over half of the children were diagnosed with PTSD, almost half were diagnosed with depression, and about one-fifth had general behavior problems. Over one-third of the children were diagnosed with Generalized Anxiety Disorder and over one-third were diagnosed with Attachment Disorder. The children's symptoms affected their functioning in multiple levels of the ecological system. Also

looking at Figure 5 and Figure 6, at the ontogenic level, almost one-third of the children experienced attention problems. At the microsystem level, almost two-thirds of the children had behavior problems at home. At the exosystem level, almost half experienced behavior problems at school.

The children's difficulties were also demonstrated on the validated measures. From one-fourth to half of the children were in the clinical ranges on the measures of externalizing, internalizing, and PTSD as seen in Table 5. The large percentages of children in clinical ranges underscores the fact that the children in this study were experiencing high amounts of distress in multiple domains.

Factors Affecting Presenting Scores on Clinical Scales, Functional problems, Clinical problems and Clinical Categorization at Baseline

In hypothesis one we predicted scores on clinical scales, functional problems, clinical problems, and clinical categorization at baseline would differ by children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, used English as the primary language spoken at home, and were refugee/immigrants.

Our model confirmed the past literature's findings of age, gender, and number of trauma types as contributors to most of the outcome scores (Dyregrov & Yule, 2006; Huemer et al., 2009; Ostrov & Keating, 2004;Littleton et al. 2012). It also provided us some indication of racial, ethnic, and cultural factors playing a small role in outcome. However, though the predictors were statistically significant, they were most often so small as to be clinically non-significant.

Age. The children's age was associated with internalizing, anxiety, functional problems, and clinical problems. We found older age associated with more symptoms

overall, which is consistent with past studies (Dyregrov & Yule, 2006; Green et al., 1991; Scheeringa, Zeanah, Myers, & Putnam, 2003). We also found younger age associated with more anxiety, which is also consistent with past findings that demonstrate higher occurrence of fears and anxiety in younger children (Dyregrov & Yule, 2006). We were surprised that we found no age association for PTSD symptoms or classification. This finding is different than the literature base, which overall suggests older age is associated with more PTSD (Breslau et al., 2001; Eksi et al., 2007; Khamis, 2005; Nooner et al., 2012).

Gender. In our study, children's gender was a significant predictor for externalizing, PTSD, dissociation, functional problems, and clinical classification for externalizing, internalizing, and PTSD. Boys had higher externalizing scores, more functional problems, and more clinical problems, and girls had higher PTSD scores. These findings are consistent with the literature. Boys have been found to externalize their problems more (Ostrov & Keating, 2004) and girls have been found to have higher rates of PTSD (Green et al., 1991, Nooner, 2012). In contrast to the literature that suggests girls tend to have more internalizing symptoms and depression (Kilpatrick et al., 2003; Macdonald et al., 2010; Nooner, 2012), we did not find any of these differences in our study. Interestingly, in our study boys were also found to have more functional problems and clinical problems. This may be an accurate reflection of the impact of trauma on boys vs. girls. Alternately, this may simply be a function of the lists of problems and disorders being more heavily weighted towards externalizing symptoms that are typical of boys rather than the more subtle problems that girls might have.

Number of trauma types. Our study found the number of trauma types children experienced to be a significant predictor of all of our outcome scores. This included externalizing, internalizing, PTSD symptoms, anger, depression, anxiety, dissociation,

functional problems and clinical problems. For predicting clinical classification of externalizing, internalizing, and PTSD, our study found that the more trauma types children experienced, the greater likelihood they were in the clinical range. These findings are important because they identify that tallying the total types of traumas a child has been exposed to is an important predictor in a variety of behavioral outcomes. Past literature has recognized the importance of number of traumas and the cumulative nature of trauma and its relation to more symptoms but has yet to date looked at a tally of trauma *types* as a predictor (Littleton et al. 2012). The literature has many studies that have established that with more trauma, the higher the risk is for externalizing symptoms (Ford et al., 2012; Ruchkin, Henrich, Jones, Vermeiren, & Schwab-Stone, 2007; Finkelhor, Turner, & Ormrod, 2006), internalizing symptoms (Fritch, Mishkind, Reger, & Gahm, 2010; Krupnick et al., 2004; Suliman et al., 2009) and for PTSD (Fritch et al., 2010; Nishith, Mechanic, & Resick, 2000) but fewer studies that examine the cumulative effect of numerous trauma types (Nilsson, Gustafsson, Svedin, & Goran, 2012). Our study extends these findings beyond trauma number to trauma type and suggests that clinicians should look closely at the total types of trauma experienced when evaluating and treating children.

Racial factors. Overall, we found a very limited amount of evidence that trauma symptoms and recovery differ when comparing racial groups on baseline symptoms. We found that Black/African American children had lower internalizing scores than White/Caucasian children and were 20% less likely to be in the clinical range for internalizing. Additionally, Black/African American children were found to have lower internalizing scores than our unknown racial group. There is limited literature that examines racial differences in response to trauma. A recent study examined trauma-exposed urban adults seeking treatment, with special attention to the association between race and severity

of symptoms of depression, generalized anxiety disorder and PTSD (Ghafoori, Barragan, Tohidian, & Palinkas, 2012). Consistent with our findings, Black/African American adults were found to have lower depression symptom severity when compared to White/Caucasian adults (Ghafoori et al., 2012).

The majority of epidemiological studies have also found Black/African Americans to have lower levels of mood disorders then White/Caucasians (Kessler et al., 1995, 2005;Pole et al., 2008;Woodward, 2012). While some literature has found higher levels of anxiety (such as phobias, etc.) in Black/African Americans, the majority of the literature has found greater levels of PTSD (also classified as anxiety disorder) in Black/African Americans (Asnaani, et al., 2010; Pole et al., 2008).

The overall small effect of race is surprising given the literature that indicates an increased risk of PTSD and symptoms in racial minority persons overall (Pole et. al., 2008). In a review of the literature on PTSD among ethno-racial minorities, Pole et al. (2008) found evidence of higher rates and more severe incidents of PTSD in African Americans, Latino Americans, Pacific Islander Americans, and American Indians. In our study, however, we found no differences on the UCLA PTSD RI scale or on the Briere scale of Post Traumatic Stress. Overall, our results indicate that racial differences play less of a role than we anticipated. Instead, the pivotal factors of number of trauma types, age, and gender carried the usual weight in determining children's symptoms.

Ethnicity. Children's ethnicity was found related to externalizing and internalizing behaviors. Being of Latino ethnicity was found associated with lower externalizing scores and a 24% less likelihood than non Latinos to fall into the clinical range. Latino ethnicity was also associated with higher internalizing, although there was no difference in chance of falling into the clinical range. These findings are consistent with the literature suggesting

Latinos have more internalizing symptoms in response to trauma. For example, in a study examining ethnic differences in response following domestic violence and sexual abuse, it was found that Latinos experienced higher levels of depression (Edelson, Hokoda, & Ramos-Lira, 2007). This effect has also been seen in the non-trauma literature, specifically, that Latinos tend to internalize their symptoms and have higher rates overall of internalizing disorders (Anderson & Mayes, 2010; McLaughlin, Hilt, Nolen-Hoeksema, 2007; Kennard, Stewart, Hughes, Patel, & Emslie, 2006). Latino adolescents were found to have overall higher rates of depression then non Latinos in a longitudinal school-based epidemiological study examining rates of depression (Kennard et al., 2006), and other studies examining Latinos confirm these findings (Anderson & Mayes, 2010; McLaughlin et al., 2007).

We did not find ethnic differences in PTSD symptoms despite the literature suggesting such exists. In a review article examining conditional risk (prevalence, onset, persistence, and severity after trauma) for PTSD, authors found evidence of Latinos having elevated rates of PTSD onset and severity but mixed results for prevalence rate differences and persistence (Alcantara, Casement, Lewis-Fernandez, 2012). Also,
in a study of adult physical injury survivors comparing Latino and non Latino PTSD symptoms, Marshall, Grant, Schell, and Miles (2009) found that Latinos tended to report greater PTSD severity but also higher specific symptoms relating to cognition and sensory experience (e.g., hypervigilence and flashbacks) and fewer symptoms relating to functional difficulties (e.g., concentration and sleep problems).

Cultural factors. When examining our cultural factors we found few significant differences when using our standardized measures. Even where findings were statistically significant, the effect size was small, and so we continue to be reminded that these difference

might not be apparent, or important, to families or clinicians. Still, we want to examine and discuss the very interesting findings that emerged.

We found that speaking English as the primary language at home was associated with lower internalizing scores. In fact, children who spoke English as the primary language at home were 27% less likely to fall into the clinical range for internalizing at baseline than their other-language at home speaking counterparts. To some extent, the other-language children were the Latino children (although we did not have data on what foreign language a child used at home). The correlation between ethnicity-Latino and English speaking was -.576. This demonstrates that there is shared variance between the two variables, but that they are also different enough to look at further (Tabachnick & Fidell, 2013). The finding suggests that children who speak a non-English language at home have a greater tendency to internalize symptoms from trauma. The literature has been mixed in relation to this finding. There is some support for it in the non trauma related literature (Bridges, de Arellano, Rheingold, Danielson, & Silcott, 2010). In a study of 2,942 US Hispanic students (6-10th grades) it was found the children who spoke Spanish in the home were more likely to experience negative internalizing symptoms than children who spoke English at home (Yu, Huang, Schwalberg, Overpeck, & Kogan, 2003). This trend was also found for 1st generation immigrants in Switzerland, specifically that the 1st generation youth scored higher on anxiety symptoms (Vazsoni, Trejos-Castillo, & Huang, 2006). However, there also have been studies that have found the opposite result. For example, in a recent study from a nationally representative Canadian sample, language proficiency predicted an increase of depressive symptoms over time (Nguyen, Rawana, & Flora, 2011). Despite the mixed results in the greater literature, it still would be helpful for clinicians when treating such children to understand this potential trend and specifically to assess other-language speaking children for

internalizing disorders. These are particularly hard to detect overall, and may be even harder in a child who speaks a foreign language notwithstanding that in our study we were able to identify them. Being aware of an increased odds could alert clinicians to be more tuned in to these types of symptoms and thereby look deeper for the existence of internalizing symptoms.

We found further differences with our cultural factors when examining the unstandardized measures of functional problems and clinical problems. Interestingly, these differences favored the "culturally different" groups. The categories of being born outside the United States and of speaking something other than English as the primary language at home were associated with children having *fewer* functional problems.

Our list of functional problems are mainly externalizing behaviors, and thus our findings are consistent with the literature that suggests non U.S born children are at a decreased risk for externalizing problems (Hussey et al., 2007). Our findings suggesting that our "culturally different groups" are doing better can also be more fully understand by examining the immigrant literature. While it is true we are unsure of the exact immigrant status of our non U.S. born and other language speaking children, there is likely to be much overlap.

Our findings are consistent with the studies that have suggested that, despite increased risk factors, immigrants do better in a variety of domains (Georgiades et al., 2007). This has been referred to as the "immigrant paradox" in which children in immigrant families tend to demonstrate positive adjustment (doing better academically and having lower levels of delinquency) despite the increased challenges that their immigration status has afforded them (Nyugen, Rawana, & Flora, 2011). For example in one study comparing immigrant children to Canadian born children, the immigrant children were found to have fewer

emotional and behavioral problems despite being twice as likely to live in poverty (Beiser, Hou, & Hyman, 2002). Of note is that the positive outcomes tend to deteriorate over the generations (Georgiades et al., 2007).

We suggest that these findings may indicate additional resiliencies in the non-English speaking and non-US born children who exhibited fewer functional problems. It is possible that the children who had experienced differences of being from another culture, speaking another language, or being born in a different country were able to build upon those challenging experiences to make them more able to handle trauma when it occurred (Crosnoe & Turley, 2011). It is also possible that these children were better able to exhibit posttraumatic growth following the trauma due to the resiliencies they had built previously (Linley & Joseph, 2004). Particularly for children who speak dual languages this ability may also provide them greater access to community resources and more persons whom they can rely on for support (Golash-Boza, 2005).

Questions raised about cultural issues. Overall, this study raises some interesting questions. In order to fully substantiate these findings we would need to be able to confirm that no pre-trauma differences exist between groups on these measures and that other confounding variables such as similar number and severity of traumas are accounted for which is something perhaps a future study could accomplish. Qualitative studies of the children, their families, and their communities could inform us of their own perspectives of how they have handled challenges and trauma.

While it may seem that overall the non-English speaking and non-US born children are functioning better as suggested by having fewer functional problems, they may be struggling in different ways. Some literature has found immigration status

associated with an increase of psychiatric illness (Gonzales, Favbrett & Knight, 2009), lower self esteem (Perez, 2011), and poor social relations (Huang, Calzada, Cheng, Brotman, 2012). However, other studies dispute such differences (Hansson, Tuck, Lurie, &McKenzie, 2012). The lack of clear consensus represents an area that continues to invite more research. Our findings reflect the dual nature of how the literature stands thus far, but we can use this literature to better understand how being a non-English speaker is associated with having fewer functional problems but more clinical problems. It is certainly possible—and perhaps likely—that the higher total clinical problem scores reflect the fact that these children have experienced more negative and life altering experiences in their lives. These children know they are different in many ways from their peers at school. Further, they carry all of the background which led their families to be in the United States (Davies, 2000). The higher number of diagnosed clinical problems also may reflect clinicians' lack of knowledge about the children's culture or language barriers (Lu et al., 2004) Perhaps clinicians are ascribing clinical problems inappropriately to these children because the language or cultural barriers interfere with a proper assessment (Guttfreund, 1990).

If these children do indeed have more clinical problems, then the post traumatic growth model can be used to understand why they have fewer functional problems. Perhaps they have learned to cope, even with their clinical problems, and are better able to function in their environments, exhibiting fewer functional problems though still having the clinical problems. Additionally, perhaps there is greater parental involvement and higher functioning parents who help. The data available do not allow us to test these intriguing possibilities.

Despite our findings concerning the cultural factors of English speaking at home and US birth, we found no differences when examining refugee/immigrant status. The lack of significant findings concerning the refugee/immigrant group was particularly surprising

given the literature base surrounding the refugee/immigrant experience and the extensive complex trauma this group tends to have experienced (Giaconia et al., 1995; Masinda & Muhesi, 2004; Nader et al., 1993).

We caution against using our lack of findings to conclude that no group differences exist, but instead place these findings in the context of the data available here. First, there were few children classified as refugee/immigrant, just 306 out of the total sample 10,115. We wonder if perhaps the definition of refugee/immigrant in this dataset was too broad. The term “Refugee/Immigrant” may bring to mind families crowded into a small boat, trying to cross the sea. In our study, refugee/immigrant status very likely included a broad range of persons: some who were truly new to the country, some who were second generation immigrants, some who were asylum seekers, and some whose parents had come as college students or professionals and managed to stay. These groups are very different and perhaps far less traumatized than children who had recently experienced displacement as a refugee from their country of origin. Nader et al. (1993) showed us that the highest levels of PTSD have been found in those who fled from a country, followed by those persons living in refugee camps, with lesser levels occurring for those who have been relocated into a new country. Our sample of children were now all in the latter group, relocated into the U.S., though we do not know for how long or how settled they and their families are. Having more information about how recently the family moved and in what capacity (refugee, asylum seeker, immigrant) they were present in the United States would help us better understand whether immigrant children experience trauma in a unique way.

Conclusion hypothesis one. While our models were statistically significant overall, they did not reach a level of clinical significance, and thus, the results of the total models did not strongly support the hypothesis. We were in fact surprised that our predictors accounted for so little in our outcomes, with variance percentages ranging from a little over one percent to five percent for the validated measures. The literature is replete with examples of how at least some of these predictors are related to children's trauma symptoms (such as number of trauma types, age, and gender), yet in this sample, very little of the variance was explained.

We found more support for our hypothesis when looking at our predictors with the non-validated outcome scores of functional problems and clinical problems. Our predictors accounted for thirteen percent of the variance in these other outcomes. The children's symptoms may be most scientifically identified by the validated measures, but these results suggest that another way to describe how children are operating can be seen by looking at their functioning within the various environments in which they participate, e.g., at home, at school, and the community. The simple compilation of number of functional problems and number of clinical problems provide a beginning look into the ecology of the children's lives. These lists look at ontogenic factors of the children themselves (e.g., academic problems, medical problems). They tap into the children's microsystems (e.g., attachment to caregivers, running away) and even look at the exosystem when examining how the children are functioning in their schools (e.g., behavior problems at school, skipping school) and communities (e.g., behavior problems in community, criminal activity).

Factors Affecting Change Scores on Clinical Scales, Functional problems and Clinical Categorization At Three Month (or First Recorded) Follow Up.

In Hypothesis 2 it was predicted that change in scores on clinical scales and functional problems and the clinical categorization at three month (or first recorded) follow up would differ by children's age at treatment, gender, number of trauma types, race, ethnicity, and cultural factors, including whether or not they were born in the United States, had English as the primary language spoken at home, and were refugee/immigrants. This hypothesis was minimally supported. Of our models, prediction of change scores in internalizing, depression, anxiety, and functional problems were significant. The effect sizes were small.

The results from our *t*-tests at three month (or first recorded) follow up indicated there was significant improvement on all the outcome variables from when they first arrived at the clinic for treatment. This was encouraging, as it shows that the children were doing better after receiving even this small amount of treatment. This one set of findings was substantial enough to declare the hoped-for clinical significance.

Age. Children's age was a significant predictor of change in internalizing, anxiety, and functional problems at three month (or first recorded) follow up. The younger the child was, the more improvement in internalizing symptoms and anxiety. The older the child was, the more improvement in total problem scores.

Number of trauma types. The number of trauma types children experienced was a significant predictor of improvement in functional problems. Children with more trauma types had a 16% higher likelihood of falling into the clinical range for externalizing and a 16% higher likelihood of falling into the clinical range for internalizing at three month (or first recorded) follow up.

English as primary language. English as primary language spoken at home was a significant predictor of change in depression scores at three month (or first recorded) follow

up, with those who spoke English at home showing less improvement in their depression scores. This again was an unexpected finding.

Conclusion hypothesis two. The results relating to the follow-up data are particularly important because they demonstrated that the children improved over time. Not only did they improve over time, but they improved quickly, at three month (or first recorded) follow up (i.e., ideally, after three months of treatment). This occurred for all dependent variables tested. Such findings are very encouraging and could mean many things. First and most importantly, it means that these children are functioning better. The symptoms of trauma are dissipating and the problems they are experiencing are lessening. The next step, beyond rejoicing in the improvement, is trying to understand why. The optimistic possibility is that the treatments being used are working. A great many treatments and treatment modalities were used across the 56 centers engaged in the study. To fully understand the changes found here, a next step would be to examine the efficacy of the individual treatments and to determine if indeed all led to improvement, and if so, whether some worked better than others. This could then be focused on treatment efficacy for children of various races, ethnicities, and cultural groups. These massive goals were beyond the scope of the present study. Of course, another possibility for the overall improvement is that children with these symptoms, even untreated, get better over time ((Kronenberg, Hansel, Brennan, Osofsky, Osofsky, & Lawrason, 2010; Smith et al., 2007). Without a treatment versus non-treatment comparison group, there is no way of knowing if the improvements are due to the treatment or if they are just a function of time passing.

Limitations

Limitations of this study include that the data used were collected as part of a quality improvement project and thus were not nationally representative of traumatized children. Instead, the data were representative of a clinical sample that came to a clinic and was treated by the National Center for Traumatic Stress Network Centers across the US.

Another limitation of this study is the operationalization of culture and diversity. Choosing to explore these constructs as part of secondary data analyses placed constraints on the variables of interest. For this reason, the variables of U.S. Born and English as Primary Language Spoken at Home did not fully tap into a cultural construct and may have restricted the ability of our analyses to explore this topic. Furthermore, the variable of refugee status may have been overly broad by including not only refugees but asylum seekers and immigrants. Here, the specific question asked if the child/and or family was a "refugee, asylum seeker, or immigrant with a history or exposure to community violence." While the asylum seeker and the immigrant with a history or exposure to community violence may be similar to a refugee experience, it is important to recognize the possibility of the differences as well.

Notably, this study did not fully examine the severity of trauma. From the available data, we built a straightforward estimate, a count of how many trauma types the child experienced. A more complete picture of the impact of trauma would require examination of each type of trauma in particular, including measures of the frequency, the perceived severity, the age-span, the chronicity, and so on. This was beyond the scope of the present study.

The study was further limited by the lack of having a baseline non traumatized control group. This makes us less able to attribute the children's problems to trauma, as there was no group available that was free of trauma. Finally because the study involved treatment-

seeking participants, the findings may reflect differential access or willingness to seek psychological treatment in the study population as compared to children and families in the general public.

Conclusions and Future Steps

This study's results serve three important functions: (1) Providing further support for the importance of trauma severity, children's age, and their gender in trauma symptoms and treatment; (2) Starting to explore how racial, ethnic, and cultural variables may impact trauma and treatment; and (3) Highlighting the need for an ecological framework when evaluating children's functioning from trauma, and utilizing measures in multiple domains that are consistent with the model.

Support for the importance of trauma severity, child's age, and gender. The results add to the large body of literature that recognizes these three variables as key in trauma symptom presentation and treatment. The findings serve to further highlight that trauma severity—here, measured by the number of types of trauma a child experienced—plays a pivotal role in determining how children will react to traumatic situations, and that it in fact may be the most important factor when projecting trajectory.

Exploration of how racial, ethnic, and cultural variables may impact trauma symptoms and treatment. This study demonstrates that race, ethnicity, and cultural variables play a small but important role in trauma symptoms in children. For example, Black/African American race was associated with lower internalizing scores when compared to White/Caucasian children. These results are a first step in showing that race matters in how children demonstrate their distress. Interestingly, the other racial groups did not differ in their levels of internalizing. These symptoms may be more "universal" than anticipated.

Ethnicity was shown to be related to both externalizing and internalizing scores. Being of Latino ethnicity was associated with lower externalizing scores and higher internalizing scores. However, this difference did not continue at three month (or first recorded) follow up.

Cultural variables were involved in children's trauma symptoms. This study was able to examine only a few cultural variables in a very limited way. We can surmise there are extensive cultural differences for children who were born outside the United States and/or who speak another language at home; these are important, though limited, indicators of culture. Speaking English at home was associated with lower internalizing scores. In fact, children who spoke English as the primary language at home were 27% less likely to fall into the clinical range for internalizing at baseline than their other-language at home speaking counterparts. On the other hand, speaking English at home and being born in the United States were also found to be associated with more functional problems. This suggests that the majority of children (i.e. English speaking, U.S. born children) were faring worse on functional problems than their foreign born or non- English speaking at home counterparts. However, results also demonstrated that being non-English speaking at home was associated with higher clinical problems.

We have no clear explanation for this curious mix of findings—better on this, worse on that. Such a result serves to start the process of exploring how children of different cultures may experience trauma differently, respond to trauma differently, and perhaps respond to treatment differently. Some of these processes may be different than our initial predictions. For example, there may be a protective factor in not being born in this country and in speaking a different language. Perhaps these families have more consistent parenting practices and provide tighter monitoring over their children. It is possible that these families

are more resilient simply because they needed to be resilient in order to be able to emigrate to the United States and, once arrived, to navigate the culture successfully. What this result means and if it can be replicated should be further explored.

Highlighting the need for an ecological framework when evaluating children's functioning from trauma, and utilizing measures in multiple domains that are consistent with the model. Finally, this study underscores the usefulness of using an ecological framework when examining a child's functioning. In this study the validated measures spoke to only one part of the puzzle and showed a less severe example of how these children were doing. However, when we broadened our net (i.e. added outcomes beyond the validated measure scores) to include looking at how children were faring with a tally of functional and clinical problems, a broader understanding of functioning was gained. This included functioning in outer levels of the ecological model such as the school and community, the exosystem, in which problems existed but perhaps were not picked up by the validated measures.

This study adds to the larger literature that is beginning to recognize that issues of culture and diversity are important in trauma diagnosis and treatment. More studies need to be conducted with diverse populations to expand our picture of how such issues affect children who experience trauma. Further, we need to consider how the adults, and the children, in various cultures think about the trauma that children experience, giving a careful consideration of their views of what is trauma and what it means. Clinicians and researchers need to work together in first recognizing and then exploring that diversity and culture matter. Only once this topic is fully embraced can traumatized children from all backgrounds be truly understood and treated.

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From childbearing to childrearing: Parental mental health and infant development

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From childbearing to childrearing: Parental mental health and infant development

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Editorial: From childbearing to childrearing: Parental mental health and infant development

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Editorial on the Research Topic
From childbearing to childrearing: Parental mental health and infant development

Every day, around 385,000 babies are born worldwide. Childbirth is culturally perceived as positive, yet it may be a challenging experience for mothers and fathers. It is estimated that up to one-third of parents have psychological difficulties during pregnancy and postpartum. These difficulties then often affect the relationships between the mother, co-parent, and infant. As the relationships and interactions with both parents are crucial for infant development, parental mental health difficulties may have adverse effects on the family dynamics and the infant. Furthermore, infant characteristics can also affect the relationships and interactions with their parents, making these interactions complex and important to investigate.

This Research Topic "From Childbearing to Childrearing: Parental Mental Health and Infant Development" presents 15 papers - 14 original quantitative studies and one narrative review - examining the associations between parental mental health and different parenting and infant outcomes. Of the original studies, two used experimental designs, six studies had longitudinal and six cross-sectional designs. All studies included mothers, and one study included both mothers and fathers. Regarding the geographical distribution of the papers, 10 papers were from Europe, one from North America and four were international collaborations between researchers from Europe, North America, and Asia. These are summarized below.

Maternal mental health in relation to infant behavior

Maternal mental health is intertwined with infant behavior problems. It was shown that mothers who report infant behavior problems also report more depression and anxiety symptoms and more mother-infant bonding problems in the first 6 months (Frankel et al.; Power et al.). However, this was established in cross-sectional studies, so the causality cannot be confirmed. Nevertheless, in a longitudinal study with mothers of preterm infants, maternal perception of the low infant self-regulation at 3 months predicted maternal depression symptoms at 6 months (Kmita et al.). Therefore, a bi-directional association between maternal mental health issues and infant behavioral or temperamental problems is probable.

Furthermore, it was reported that postpartum depression was related to the infant feeding method. However, no specific type of infant feeding method was a risk factor for postpartum depression *per se*. Other maternal experiences and infant-feeding cues played an important role for breast- and formula-feeding mothers (Kossakowska and Bielawska-Batorowicz). Mental health was intertwined with sleep, where poor sleep quality was both an antecedent and a consequence of impaired mental health. Mothers can be especially at risk because Sánchez-García et al. showed that mothers with children younger than 2 years had more disrupted sleep compared to the control group (women with children older than 6 years or no children). Mothers of infants were more likely to wake up more often during the night, report lower sleep quality, and sleep fewer hours, although different aspects of maternal sleep improved with infant's age.

Parent-infant bonding as an aspect of parenting

Several papers looked into different predictive mechanisms for parent-infant bonding. First, Kalfon Hakhmigari et al. found a possible intergenerational mechanism where maternal recollection of her own parents' parenting was associated with maternal insecure anxious adult attachment style, which was in turn associated with poorer mother-infant bonding two months after childbirth. Other studies focused on parental mental health as a predictor of parent-infant bonding. It was found that fear of childbirth during pregnancy was predictive of a negative birth experience assessed two months postpartum, which was, in turn, predictive of poorer mother-infant bonding at 14 months (Seefeld et al.). The next two studies were consistent with this, showing that both postpartum depression and anxiety were associated with worse bonding. In this association, parental responsiveness had a mediating role in mothers and fathers (Nakić Radoš), while self-criticism was especially detrimental to mother-infant bonding in women with a history of depression or anxiety (Beato et al.). Therefore, it seems that some personality traits have a modifying role in these multi-layered associations.

Parental mental health and infant outcomes

Maternal adverse experiences during her own childhood predicted more toddler emotional problems through their effect on maternal posttraumatic stress disorder (PTSD) symptoms (Ribaudo et al.). Also, maternal PTSD before or during pregnancy was associated with impaired peripartum mental health. Moreover, if mental health problems were comorbid with postpartum depression, mothers reported more feeding and sleeping problems in infants (Martini et al.). Maternal trait anxiety during pregnancy was associated with some infant development outcomes at 12 months (Jeličić et al.). An experimental study showed that exposure to acute maternal stress, measured with the experimental Caretaker Acute Stress Paradigm (CASP), affected infant autonomic nervous system regulation and behavior (Mueller et al.). Another experimental study with a longitudinal design showed that micro-temporal dyadic interaction patterns during the Still-Face paradigm in mid-infancy and maternal anxiety diagnosis predicted the development of insecure attachment in children aged 12–24 months. Moreover, an insecure attachment was associated with hormonal regulation in children at preschool age, showing a higher cortisol level during the stress paradigm compared to the children with secure attachment (Müller et al.).

Interventions for parents and children

The final two papers dealt with early interventions for parents with infants and toddlers. Infant mental health treatment provided at home, on a weekly basis, to parents who reported depression symptoms, parenting stress, or a child's behavioral problems resulted in more positive socioemotional wellbeing of the child (Ribaudo et al.). Stolper et al. provided a narrative review of reviews and meta-analyses of interventions for parents with psychopathology aiming at disrupting the intergenerational transmission of psychopathology. The review first categorized risk and protective factors during the peripartum period into parental, family, child, and environmental domains. The review concluded that no universal intervention for prevention would work for all different families and settings. Instead, effective interventions should be individually tailored, focused on resources, addressing changeable risk factors by using different ways of delivery (individual, dyadic or group).

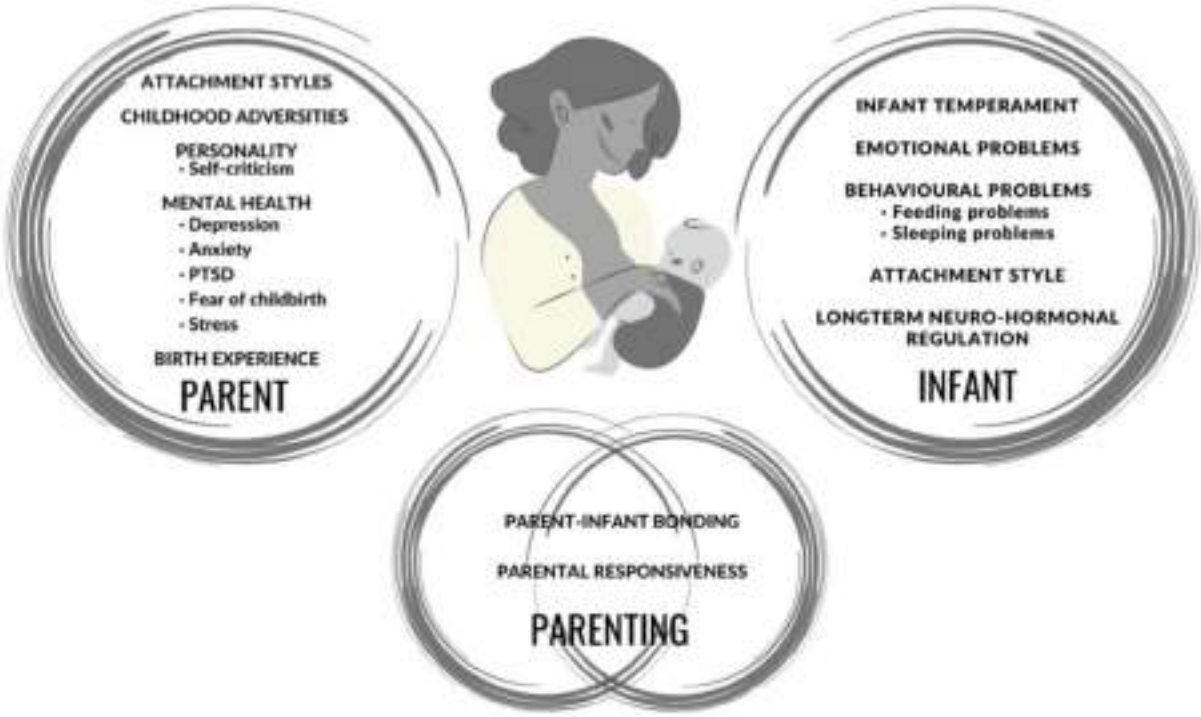

FIGURE 1
Schematic overview of the constructs examined within the Research Topic. (Figure created in Canva).

Gaps in the knowledge and directions for future research

The papers in this Research Topic and overview of the different variables measured in these studies in Figure 1 illustrate the need for greater consideration and understanding of the complexity of relationships between maternal, infant and parent-infant factors. These include pre-birth factors, such as maternal childhood adversity and health; epi-genetic factors, such as the intergenerational transmission of trauma; birth factors, such as complications and trauma; early environment; and ongoing parent-infant and parent-child interactions.

Theories are important to underpin and guide this research, particularly when trying to understand complex relationships such as those between parental mental health and infant outcomes, as well as inter-dependent outcomes, such as attachment style and infant emotional or behavioral problems. Relevant theories that have been applied to this area include the biopsychosocial approach (Blount et al., 2021), which encourages consideration of biological, psychological and social factors in maternal and infant outcomes. The importance of taking a biopsychosocial approach is evidenced by research showing the brain basis of early parent-infant interactions (Swain et al., 2007); intergenerational transmission of trauma (Bowers and Yehuda, 2016), and influence of stress during pregnancy on neonatal behavior (Rieger et al., 2004). An updated dynamic biopsychosocial model needs to be extended to consider the dynamic nature of systems that influence our health. The updated dynamic model proposes that health outcomes are due to reciprocal influences of biological, psychological, interpersonal and macrosystem contextual dynamics (Lehman et al., 2017). It also considers how these influences may vary for different individuals over time. This seems particularly relevant to understanding the complexity of parent and infant interactions and outcomes over the course of infant and child development.

Methodologically, a biopsychosocial or multi-system approach requires multi-method, whole family, longitudinal studies that recognize the importance of the father/partner and couple's relationship (whether co-habiting or separate) in infant outcomes and development (Bergunde et al., 2022). It would also be useful to widen this to include co-habiting family members such as step-parents or grandparents, which was highlighted by a review of risk factors for child maltreatment (Ayers et al., 2019). More large longitudinal cohort studies are therefore needed in this area, such as the Dresden

study on parenting, work, and mental health (Kress et al., 2019) and planned UK Early Life Cohort Study (Early Life Cohort, 2020), which provide multi-method, whole-family, longitudinal birth cohort studies. Such studies have the potential to generate a wealth of knowledge and understanding of biopsychosocial factors associated with infant outcomes and child development.

Also, common with research in other areas, the majority of research in perinatal mental health and infant outcomes is from high-income Western countries where samples are skewed toward White women, well educated, and higher income families, even when the population is more diverse. Thus, it is important to address gaps in knowledge in relation to minority groups and diversity.

In conclusion, this Research Topic presents a range of papers covering different aspects of the relationship between parental mental health and infant development, as shown in Figure 1. It highlights the complex dynamic systems and context, which are likely to influence infant development, and has identified ways in which future research can examine this to increase our knowledge and understanding.

Author contributions

SNR initiated the Research Topic. SNR, SA, and AH were topic editors and wrote the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
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The Relationship Between a Baby's Age and Sleepiness in a Sample of Mothers

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One question of great practical importance for the parents, and especially the mother, after the birth of a baby, refers to how long the time during which they have to go with less and more fragmented sleep actually lasts. Most of the studies only explore this issue up to 6 months of the newborn's life, and less is known about the sleep problems the mothers may have after this initial period. The objective of this study is to examine the relationship between the sleep disruption and daytime sleepiness of mothers with infants until 2 years old compared to a group of women currently not at care of babies. To this end, a sample of 113 women, 67 currently bringing up a baby of under 2 years old, and the remainder without a baby at their care under 6 years old, reported sleep duration, sleep interruptions, sleep quality, and responded to questionnaires of sleep quality and daytime sleepiness. The relationship between the age of the children and the comparison between the groups was used to highlight the sleep problems of the mothers taking care of the infant. The results showed that there was a positive relationship between the age of the infant and the duration of the sleep of the mothers and that the duration of sleep for them was similar to those of the women in the control group about 6 months after the infant was born. However, fragmentation of sleep, daytime sleepiness, and sleep problems were still higher than in the control group for mothers with children between 6 and 12 months old.

Keywords: motherhood, fatigue, sleepiness, baby, age, developmental psychology

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1. INTRODUCTION

The birth of a child marks the beginning of a new phase in the lives of both parents, particularly for the mother. Throughout the first months in the life of a baby, the mothers undergo numerous changes, psychological, physiological and behavioral, and although these are partly understood, there are aspects to them that deserve to be studied in depth.

One question of great practical importance refers to how long the time during which mothers and fathers have to go with less and more fragmented sleep actually lasts. "Will this go on for 1 month, two, or even longer?" is something they often ask themselves. The reason for this is that, if an answer was available, parents could make crucial decisions, such as whether to call in extra help, return to work, carry on studying etc. What is more, when any positive expectations regarding maternity (among which is usually found the hope that the children "will sleep well" from an early age) are left unfulfilled, this leads to feelings of frustration. Nevertheless, given that this information usually comes from informal sources, such as friends, family or other parents of newborn children,

it may often be positively distorted and give rise to expectations that are not realistic. This is why it may be of great value to determine the length of this time objectively so as to be able to offer help to those who are going through this very situation enabling them to face up to it as best they can.

One estimation of the time that it may take the parents to return to their previous sleep patterns has usually been based on the postpartum, the duration of which is usually established as lasting for the first 6 months of a baby's life. It starts with the birth and the expulsion of the placenta-responsible for the secretion of many hormones that may alter the normal rhythms-and continues during lactation and until the child's sleep follows some predictable sleep-wake cycle patterns (Lee, 1998). Research into maternal sleep deprivation is usually centered around this time. For example, in an exhaustive review, Hunter et al. (2009) only mention studies in which the newborns are under 3 or 6 months old (Quillin, 1997; Matsumoto et al., 2003; Signal et al., 2007), and most of the recent studies published on this topic still focus on this period (Creti et al., 2013, 2017; Tran et al., 2015; Kenny et al., 2020; Cattarius and Schlarb, 2021; Da Costa et al., 2021). However, two recent studies have broken this trend and have provided evidence regarding parent's sleepiness when the newborns are over 6 months. So, Sivertsen et al. (2015) interviewed women 2 years after postpartum and found that "a large proportion still fulfilled the diagnostic criteria for DSM-IV insomnia," and Richter et al. (2019) examined changes in mothers' and fathers' sleep before pregnancy and the postpartum period of up to 6 years after birth and observed that, for the first childbirth, they had not yet fully recovered sleep satisfaction and hours of sleep at the end of the study. However, these studies use interviews set at specific points so that they do not provide fine-grained information about how the sleep indicators change in relation to the age of infants.

Although it is true that the internal factors determining the sleep-wake cycle in children do develop between 3 and 6 months of age and that mothers tend to sleep more as the child develops, focusing on this period of postpartum overlooks the fact that there other external factors that affect the mothers well-being: the style of child-rearing, for instance, whether the parents and child co-sleep, the type of lactation, the general organization of the household, the work outside the home, etc., all of these factors may continue to alter a mother's normal sleep rhythms. Moreover, it should not be forgotten that even after the children have managed to achieve an acceptable sleep rhythm, the mothers may still find it difficult to get enough sleep due to psychological problems that may arise associated with the pregnancy and the perinatal period (Fallon et al., 2016). That said, since there is evidence that sleeping habits —including the time people normally go to bed, the time they get up, and the time that passes between these moments— vary according to country and gender (Walch et al., 2016), it is of interest to evaluate whether the abovementioned results are reproduced in Spanish samples.

There are several milestones in the development of children after the 6 months of birth that may contribute to reducing the burden of the parents associated with caring for them. At 10-month postpartum the child's language begins to develop; at 14 months postpartum, the child is able to walk, to explore the environment, and attachment behavior is at its peak (Prenoveau et al., 2017). At 24 months old the children are more independent, have sufficient language skills to communicate with others which helps to manage their negative emotions, and can focus their attention away from stressful stimuli in order to manage their distress as well as to soothe themselves (Spinrad et al., 2004; Dennis, 2006). Thus, it seems of interest to extend the research of the sleep disturbances of mothers until at least the children are up to 24 months old.

There are several types of sleep disturbances that can affect the mothers such as sleep reduction, fragmentation of sleep, daytime sleepiness, etc. One well-identified problem is that of sleep deprivation, which is something common to mothers throughout the first months in the life of their baby (Hunter et al., 2009) and which is associated with the infant's nutrition, care, and sleep rhythm: since the sleep rhythms of the newborn are still not well-established and their need for nourishment, affection, cleanliness, and activity is not yet synchronized with the rhythm of the parents, both the mother and father are often sleep-deprived, in terms of both quantity and quality. This, in turn, may lead to there being many adverse effects on, among other things, their psychological and physical health, and their social relations (Moline et al., 2003; Sharma and Mazmanian, 2003). For example, Okun et al. (2018) found that symptoms of depression and anxiety in a group of 116 women were related to having poor sleep quality. Tham et al. (2016) found that poor subjective sleep quality during pregnancy was associated with borderline high postnatal depressive symptoms highlighting that the origin of the problem might be caused by disturbances that happen before birth delivery. Understanding and mitigating the impact of this sleep disruption is important for the health of the mother, as a large amount of wake after sleep onset and low sleep efficiency are predictive of postpartum fatigue severity and mood in general (Posmontier, 2008; Bei et al., 2010). New mothers usually do not expect the sleep disruption that they experience (Kennedy et al., 2007).

Disruption of sleep at night may cause daytime sleepiness, which may affect the daily activities of the mothers or turn into low productivity on the job and on accident rates, both occupational and non-occupational (Lee, 1998). At the beginning of the postpartum, mothers have less nighttime sleep and they spend a greater time awake following sleep onset (Gay et al., 2004), but it is sleep disruption rather than total sleep obtained that is more influential in daytime sleepiness (Insana and Montgomery-Downs, 2010). For instance, although Montgomery-Downs et al. (2010b) found that the quantity of sleep obtained by new mothers from postpartum weeks 2–16 was relatively consistent (7.2 h), the sleep quality improved over the same period due mainly to a reduction in sleep fragmentation and increase in sleep efficiency. However, this reduction in sleep fragmentation did not happen in the study of Filtness et al. (2014), as they did not observe significant differences in frequency of awakenings during nocturnal sleep between the weeks 6, 12, and 18, with averages of 1.9, 1.65, and 1.7, although they found differences in other indicators.

The objective of this study is to ascertain whether the quantity and quality of sleep in a sample of mothers of newborns in Spain

during the first 2 years of the baby's life differ from that of women of similar characteristics, but who are not raising a child, and to analyze whether any difference is limited to the first semester or carries on beyond this period.

2. MATERIALS AND METHODS

The design of this study corresponds to the description in Shadish et al. (2002) of a quasi-experimental post-test only study. Two groups (one treatment group and one control group) took part in the study, which was retrospective and questionnaire-based. The study consisted of obtaining answers from two groups of women to the questionnaires described in the measures section. Prior to the procedure, written consent was obtained from all of the participants for the aggregate use of the results for research purposes. This study was conducted following the guidelines set out by our institution.

To this end, a convenience sample of 113 women, 67 currently bringing up a baby of under 2 years old, and the remainder without a baby under 6 years old in their care, were interviewed as to a series of relevant variables related to the quantity and quality of sleep they usually enjoyed. The answers were assessed in order to evaluate the hypothesis that both the quality and quantity of sleep enjoyed by women with a baby in their care were reduced when compared to women who did not have a baby in their care during not only the first semester of the newborn's life but also the subsequent ones.

The participants were not furnished with any additional information on the study's objectives before their answers were registered. Once they had finished, the objective of the study was succinctly explained to them and they were compensated for the effort they had made in participating (30 €).

2.1. Participants

Women with babies in their care and willing to participate in a study into sleepiness were contacted while in the waiting room of a pediatrician, one of the co-authors of this article, located in a hospital in the city of Valencia. They were required to be between 25 and 50 years of age and to have no serious health problems. Additionally, their children had to be between 1 and 24 months old.

The women who had no babies in their care were firstly contacted in the pediatrician's waiting room but also through friends, relatives and workmates of the women who had already taken part in the study. The requirements for these women were the same as for the first group, except that they should not have children or that their children had to be at least 6 years old.

The total number of participants in the study was 113, of whom 67 met the requirements necessary to be classified as having children in their care. From now on, this sample will be referred to as "With infants" (for the women with babies in their care). The remaining 46 met the requirements needed to be classified as having no babies in their care and we shall refer to them as "Control" (for the women not currently with babies in their care).

2.2. Measures

Two types of variables were measured in this study: standardized questionnaires related to sleepiness and direct questions concerning night sleep. In addition, the demographic and behavioral variables of the participants were evaluated through *ad-hoc* questions.

2.2.1. Sleepiness Scales

Three scales were used to evaluate the mothers' sleepiness.

- General Sleep Disturbance Scale (GSDS): This scale (Lee, 1992; Shahid et al., 2012) was designed to evaluate the incidence and nature of sleep alterations in working women. The GSDS is a self-report, paper- and-pencil measure requiring 5–10 min for completion. The GSDS queries respondents regarding the frequency with which they've experienced certain sleep difficulties within the previous week. Respondents use an eight-point, Likert-type scale ranging from 0 (meaning "never") to 7 ("every day") to respond to each item. The GSDS is a 21-item scale initially designed to evaluate the incidence and nature of sleep disturbances in employed women. Questions pertain to a variety of general sleep issues, including problems initiating sleep, waking up during sleep, waking too early from sleep, quality of sleep, quantity of sleep, fatigue and alertness at work, and the use of substances to induce sleep. Researchers have suggested that individuals with an average score of three (averaged by number of items) on the GSDS should be considered at risk for sleep disturbance (following guidelines set in the Diagnostic and Statistical Manual of Mental Disorders). A psychometric evaluation of the scale carried out by Lee (1992) found an internal consistency of 0.88 for the whole scale. This scale was used in Sánchez-García (2017).
- Epworth Sleepiness Scale (ESS): This scale (Johns and others, 1991) was designed to evaluate daytime sleepiness by asking the respondents to evaluate the probability of falling asleep in eight different situations. It uses a 0–3 scale. Scores range from 0 to 24, with higher scores indicating a higher propensity for sleepiness and a score of >10 indicating excessive daytime sleepiness (Johns and Hocking, 1997). Each situation represents a moment of relative inactivity, from sitting down reading to sitting in a stationary car at a traffic light. The scale was validated using an adult population of between 18 and 78 years old. As far as its reliability and validity are concerned, it exhibits high internal consistency and good test-retest reliability Test-Retest Reliability of the Epworth Sleepiness Scale in a Sleep Clinic Population (Lee et al., 2018); it also correlates positively with the probability of falling asleep at the wheel (Maycock, 1997). The ESS is significantly correlated with sleep latency as measured by objective measures such as the multiple sleep latency test (MSLT) and overnight polysomnography (PSG), and it can detect changes following continuous positive airway pressure (CPAP) treatment (Johns and others, 1991). It remains one of the most widely used measures of habitual daytime sleepiness (Kaplan and Gasperetti, 2020).

- Karolinska Sleepiness Scale (KSS): The Karolinska Sleepiness Scale(KSS) is a single-item self-report measure of situational "state" sleepiness (Åkerstedt and Gillberg, 1990). This scale measures the subjective level of sleepiness state in the last 10 min. The KSS measures situational sleepiness and, therefore, is sensitive to momentary fluctuations that occur in short time periods. Individuals rate their current level of alertness on a 9-point ordinal scale (1 = "extremely alert," 5 = "neither alert nor sleepy," 9 = "extremely sleepy—fighting sleep"). The KSS is strongly correlated with time of day, and scores increase as the period of wakefulness extends (Kecklund and Akerstedt, 1993). The KSS is significantly correlated with electroencephalographic (EEG) and the psychomotor vigilance task (PVT), indicating that it is a valid measure of sleepiness (Kaida et al., 2006). This scale was used in studies into shift-workers and drivers and is useful to evaluate any changes in the response to environmental influences, circadian rhythm and the effects of drugs. In a validation study, Kaida et al. (2006) found a close correlation between electroencephalographic measurements and behavioral variables. KSS is indicated as a measure of momentary sleepiness (Kaplan and Gasperetti, 2020).

There are many scales for measuring sleepiness (over a 100 according to Shahid et al., 2012) and, as a consequence, choosing one over the others can be difficult—for a recent review of the pros and cons of 24 of these measures see Kaplan and Gasperetti (2020)—. The three scales mentioned before were chosen because they measured different aspects of sleep disruption. The GSDS asks mainly for nighttime sleep problems in the past week such as awakenings, use of alcohol or other substances for sleeping, and sleep satisfaction (Lee et al., 1991). The ESS instead is indicated for measuring habitual daytime sleepiness or average sleep propensity (Johns, 2008). Finally, the KSS asks for momentary sleepiness at the time of responding (Kaplan and Gasperetti, 2020). As the participants filled the questionnaires during the mornings, approximately between 10 a.m. and 1 p.m. the scores in the KSS can be taken as an indicator of sleepiness in the first part of the day.

2.2.2. Evaluation of Night Sleep

We mentioned in the introduction that disruption of sleep in mothers may happen in different ways: reduction of time and fragmentation of sleep being the most common. Fragmentation is the result of awakenings in response to noises made by the baby, that may involve getting off the bed in some cases. Also, mothers can be too alert during the night for deep sleep and experience a low quality in their sleep as a consequence. Nighttime number of hours of sleep is also important but it is common among mothers to recover some of the sleep lost with naps taken in the daytime. Researchers that have explored these aspects of maternal sleep have often used diaries in which mothers recorded the events related to sleep (Insana and Montgomery-Downs, 2010; Filtness et al., 2014). However, as our study was based on an interview we simply asked questions directly to the participants. The questions in our case were:

- How many times do you wake up during the night?
- How many times do you get up during the night?
- How would you rate the quality of your sleep? (Ratings from 1 = very bad, 2 = bad, 3 = normal, 4 = good, 5 very good)
- In total, how many hours do you sleep a night?
- The number of hours you sleep during the day (naps).
- The total number of hours of sleep: Unlike the previous questions, this was not asked directly but was obtained by adding up the answers to the previous two questions.

2.3. Data Analysis

For data analysis purposes, the scores from the scales were added up after inverting the negative items. The data were analyzed graphically (scatter and box plots), *t*-tests, and analysis of variance, using the correction for non-homogeneity of variance (Welch or Games-Howell). Post hoc comparisons were adjusted using the Holm's procedure. Significance was always evaluated at $p < 0.5$. All of the calculations were done and the graphs plotted using R (Team, 2020). There was a very small number of missing values, but given that the analyses were exclusively univariate, the impact was very limited.

The relationship between the age of the baby and the indicators of sleepiness is displayed graphically in **Figure 1**. This figure has a couple of plots per indicator, with a total of eight indicators corresponding to the three sleepiness scales plus the answers to the questions evaluating night sleep. The first plot of each couple is a scatterplot in which the age of the baby is set in the horizontal axis and the indicator is set in the vertical axis. As the relationship between the age of the baby and the indicators was found to be non-linear in many cases, we overimposed a non-parametric loess curve in all the plots to better visualize the relationship between the variables (Cleveland and Devlin, 1988). The second plot of the couple is a boxplot for comparing the two groups of women in our study: the control group (mothers without infants under 24 months old at the time of the study) and mothers with infants. Each boxplot shows overimposed the result of a *t*-test comparing the means of the groups in each indicator. As the scatterplots and the boxplots share the same vertical axis, it is possible to assess when the values of the scatterplot are over or under the median values of the indicators for the two groups of mothers.

Additionally, the mothers were grouped according to if their babies were <6 months old, between 6 and 12, 12 and 18, and 18 and 24 months old. ANOVA tests for each indicator among these four groups plus the women in the group control are shown in **Figure 2**. This figure has a plot per indicator, with five boxplots in each of the plots. Means are displayed with a black dot overimposed on the boxplot. Results of ANOVA tests are shown on the top of each plot. *Post-hoc* comparisons are shown overimposed on the plots with lines indicating pairs of groups whose mean were significantly different between them.

3. RESULTS

There are four parts in this section: Sample description in terms of demographic variables, description of sleepiness variables, comparison between groups of women and relationship with the

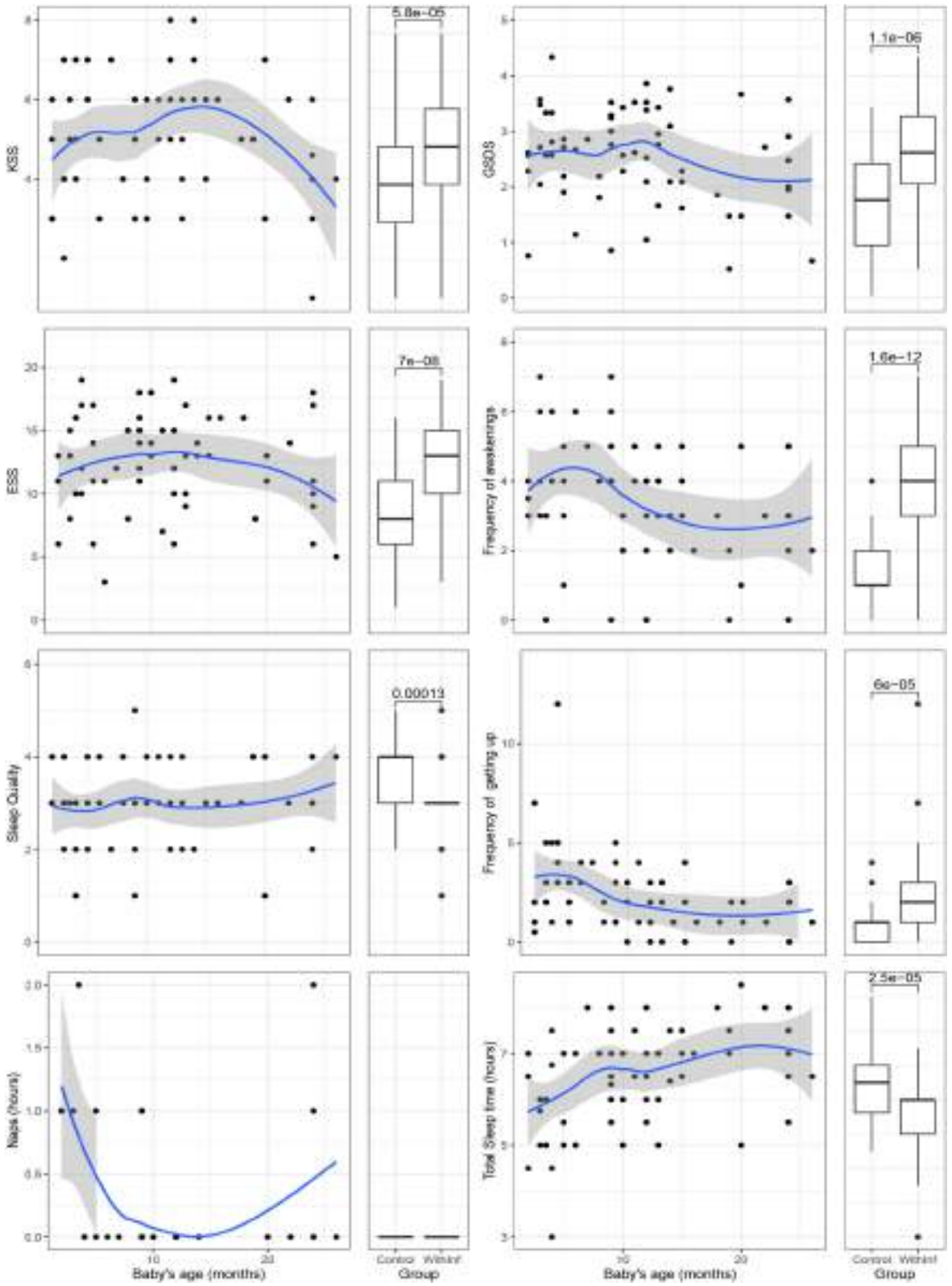

FIGURE 1 | Scatter plots showing relationship between sleepiness variables in mothers with babies of under 24 months old and the normal values of women without babies and box plots showing the same comparison.

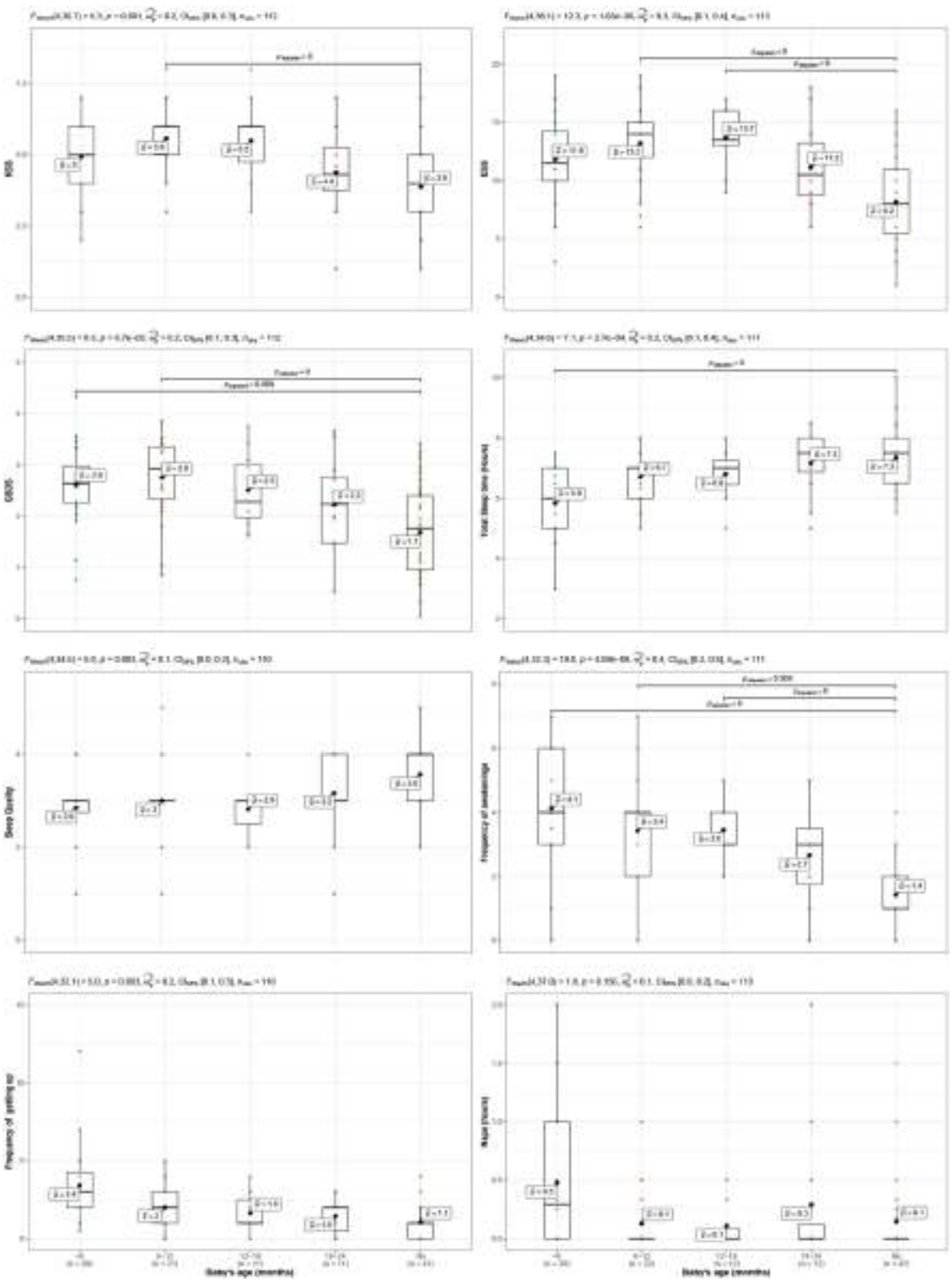

FIGURE 2 | Comparison of sleepiness variables in two cases: that of mothers of newborn babies, whose ages are split into four groups (groups <6 months old, 6–12 months old, 12–18 months old, 18–24 months old) and that of women who have not been mothers recently (No group). Each variable is shown in a panel and each of the panels includes information on the result of an ANOVA test, eta squared, its confidence interval, the sample size, and inter-group comparisons -only shown if significant- assuming unequal variances (Games-Howell) and adjusting for the number of comparisons using the Holm's method.

TABLE 1 | Description of the samples of women taking part in the study who did not have a baby of under 24 months old in their care when the study was carried out (Control) and of those who did (With Infants).

Descriptive variables	Total N		Control	With infant	Total	Stat	*p*
Age	111	Mean (SD)	36.9 (7.9)	34.6 (5.1)	35.5 (6.5)	1.8	0.061
Age of first child	87	Mean (SD)	12.4 (7.7)	12.6 (10.0)	12.6 (9.5)	−0.1	0.909
Married or equivalent relationship	111	Not	10 (22.2)	4 (6.1)	14 (12.6)		0.026
		Yes	35 (77.8)	62 (93.9)	97 (87.4)		
Unemployed?	113	Yes	9 (19.6)	17 (25.4)	26 (23.0)		0.622
		Not	37 (80.4)	50 (74.6)	87 (77.0)		
Currently employed or maternity leave	88	Full time	19 (51.4)	17 (33.3)	36 (40.9)	13.2	0.001
		Part time	18 (48.6)	19 (37.3)	37 (42.0)		
		Maternity leave	0 (0.0)	15 (29.4)	15 (17.0)		
Health problems	112	Yes	0 (0.0)	1 (1.5)	1 (0.9)		1.000
		Not	45 (100.0)	66 (98.5)	111 (99.1)		
Total N (%)			46 (40.7)	67 (59.3)	113		

p value corresponds to a mean difference t-test or a chi-squared test.

TABLE 2 | Descriptive statistics for the sleepiness variables.

Variable	Mean	*SD*	Min	Q1	Med	Q3	Max	Asimmetry	valid n	valid pct
Scales										
GSDS: Do you experience these problems when getting to sleep?	2.2	0.9	0	1.5	2.3	2.9	4.3	–0.2	112	99.1
ESS: What is the likelihood of you falling asleep in situation x?	10.7	4.2	1	8.0	11.0	14.0	19.0	–0.1	113	100.0
KSS: Level that reflects your state in the last 10 min.	4.6	1.6	1	3.0	5.0	6.0	8.0	–0.1	112	99.1
Questions about nigh sleep										
How would you rate the quality of your sleep?	3.2	0.8	1	3.0	3.0	4.0	5.0	–0.5	110	97.3
How many times do you wake up during the night?	2.6	1.8	0	1.0	2.0	4.0	7.0	0.4	111	98.2
How many times do you get up during the night?	1.8	1.7	0	1.0	1.0	3.0	12.0	2.3	110	97.3
In total, how many hours do you sleep a night?	6.7	1.1	3	6.0	7.0	7.5	9.0	–0.8	111	98.2
How long are your naps during the day (in minutes).	12.8	25.3	0	0.0	0.0	20.0	120.0	2.3	113	100.0
Total hours of sleep	6.9	1.1	3	6.3	7.0	7.5	10.0	–0.5	111	98.2

age of the baby, and comparison of women according the baby's ages groups.

3.1. Sample Description

Table 1 shows a comparison between the samples of the two groups of women participating in the study. As can be seen, the age of the two sample groups was similar. In the group without babies, the percentage of women who were married or in an equivalent relationship was slightly lower than in the group with babies, which is what could be expected given that women with infants are more often in a relationship than women without infants. It would be interesting to check the sleepiness of mothers without significant others supporting them but we only had 4 in our study so this was not possible in our case. The percentage of unemployed women (and, therefore, the opposite case, of women who were in a job when the study was carried out) was similar. Lastly, both samples of women were generally free from health problems except for one case, but after an in-depth analysis of this case we included her as the problem did not affect her day-to-day activity.

As this was a pilot study and the sample size was not large, we could not test the relationship between some of the demographic variables and the sleepiness of the mothers with infants.

3.2. Description of Sleepiness Variables

Table 2 shows the descriptives for the sample used in this study.

- GSDS: The mean is 2.2, below the threshold of three that is considered as at risk of sleep disturbance. The standard deviation is 0.9. The minimum value was one and the maximum is 4.3, and 50% of the scores lying between 1.5 and 2.9. This variable was very close to normal as its asymmetry is close to 0 (–0.2).
- ESS: The mean is 10.7, which is slightly over the threshold of excessive sleepiness (10). The standard deviation is 4.2. The minimum value is 1 and the maximum 19, and 50% of the scores lying between 8 and 14. This variable is very close to normal as its asymmetry is close to 0 (*Skew* =–0.1).
- KSS: The mean is 4.6 which is between the "Rather alert" and "Neither alert nor sleepy" categories of this scale. The

minimum value is one and the maximum is eight. This variable is very close to normal as its asymmetry is close to 0 (*Skew* =–0.1).

- Quality of sleep: The mean is 3.2 which is near the "Normal" category. The minimum is one and the maximum is five. This variable was is close to normal as its asymmetry is close to 0 (*Skew* =–0.5).
- Frequency of awakenings: The average frequency of awakenings was 2.6, with a minimum of zero and a maximum of 7. This variable is very close to normal as its asymmetry is close to 0 (*Skew* = 0.4).
- Frequency of getting up during the night: The mean was 1.8, with a minimum of zero and a maximum of 12. This variable shows positive asymmetry (*Skew* = 2.3) due to the outlier.
- Total hours of sleep by night: The mean was 6.7 h, with a minimum of 3 and a maximum of 9. This variable is moderately asymmetric (*Skew* = –0.8).
- Minutes of naps per day: The mean is 12, with a minimum of 0 and a maximum of 120 min. This variable shows positive asymmetry (*Skew* = 2.3).
- Total hours of sleep: This variable was computed summing the two previous variables. The mean is 6.9. The minimum is 6.3 and the maximum is 10. This variable is very close to normal as its asymmetry is close to 0 (*Skew* = –0.5).

As a whole, the data did not show special characteristics apart from one outliers in number of awakenings (7) and other in times getting up (12). Interestingly, some women got up from bed more times than they woke up by night, which can be interpreted as that despite of lying in bed they remained alert without actually falling slept.

3.3. Comparison Between Groups of Women and Relationship With the Age of the Baby

Figure 1 shows the comparison of the women in the group control with the mothers with infant babies (under 24 months old). We will comment on the figures from left to right, top to bottom:

- KSS: The mothers with infant babies with ages under 6 months old had scores near 5. Mothers with babies between 6 and 12 months old had higher scores than those with younger babies and older babies. Mothers with babies older than 12 months old had scores close to the group of mothers with infant babies under 6 months old and the relationship decreases for mothers with babies over 18 months old. The scores for the mothers in the KSS are over the median of the women in the control group except for mothers with children over 18 months old. The global differences between the two groups of women were significant [$\Delta M = -1.26$, 95% CI [$-1.85, -0.67$], $t_{(90.92)} = -4.22$, $p < 0.001$] with women in the control group having lower scores than mothers attending infant babies.
- GSDS: The scatterplot for the GSDS measure shows values between 2 and 3 for mothers with babies under 1 year old, which is below the score of 3, regarded as the threshold for problems of sleep, although the 95% interval of confidence band overimposed on the loess line includes this value during the first year. Then, there is a decrease in scores for mothers with babies over 12 months old but in average they are still higher than the scores of women without infants. The global differences between the two group of women were significant [$\Delta M = -0.84$, 95% CI [$-1.16, -0.52$], $t_{(97.37)} = -5.21$, $p < 0.001$] with women in the control group having lower scores than mothers attending infant babies.
- ESS: The scatterplot for the Epsworth questionnaire measure shows that the mothers with children have scores generally higher than the threshold of 10, which is regarded as the cut-off for sleep problems. The loess curve bends down for mothers with babies over 18 months old, remaining stable for children under this age. The global differences between the two group of women were significant [$\Delta M = -4.13$, 95% CI [$-5.53, -2.73$], $t_{(96.02)} = -5.84$, $p < 0.001$] with women in the control group having lower scores than mothers attending infant babies.
- Frequency of awakenings: Mothers with infant children under 10 months old reported waking up about four times per night, but those with children older than 10 months had only approximately three awakenings per night. The frequency of awakenings for mothers with 24 months old babies was higher than for women without infants. The global differences between the two group of women were significant [$\Delta M = -2.07$, 95% CI [$-2.58, -1.56$], $t_{(103.46)} = -8.03$, $p < 0.001$] with women in the control group having 1.41 awakenings in average vs. 3.48 awakenings of mothers.
- Sleep quality: The relationship between the sleep quality of the mothers and the age of their infants is close to zero as the loess line in the plot is almost horizontal. The global differences between the two group of women were significant [$\Delta M = 0.59$, 95% CI [$0.29, 0.88$], $t_{(104.95)} = 3.98$, $p < 0.001$].
- Frequency of getting up: Mothers get up by night more times when their infants are under 5 months old. One case stands out because one mother reported getting up 12 times per night. Mothers with children over 5 months old children drop the frequency in which they get up. The global differences between the two group of women were significant [$\Delta M = -1.21$, 95% CI [$-1.78, -0.64$], $t_{(100.64)} = -4.19$), $p < 0.001$], with women in the control group having an average frequency of 1.07 in the control group vs. a frequency of 2.27 in the group of mothers with infants.
- Naps: The naps that mothers took varied considerably among them. Two of them reported 2 h of nap and five reported 1 h but the majority indicated zero o close to zero nap time. No discernible relationship between the age of the infant and the nap duration was observed. Also, the differences between the women with and without infants were not significant [$\Delta M = -6.53$, 95% CI [$-15.54, 2.47$], $t_{(110.72)} = -1.44$, $p = 0.153$].
- The total sleep time: The total sleep time was calculated by summing the hours slept by night plus the naps. The relationship between the age of the babies and the total slept time of their mothers is positive and only bends down slightly once the children are 20 months old or over. However, at this point, the mothers slept about the same as the women in the

control group. The differences between the two groups were significant [$\Delta M = 0.79$, 95% CI [0.42, 1.16], $t_{(107.25)} = 4.25$, $p < 0.001$] with women in the control group having an average frequency of 7.34 in the control group vs. a frequency of 6.55 in the group of mothers with infants.

3.4. Comparison Between Babies' Age Groups

The results until here suggest that the mothers may experience sleepiness-related problems that last beyond 6 months, which is what is considered to be the moment when the babies should have regularized their sleeping habits, and consequently their mothers could return to previous sleep habits. In order to verify this hypothesis more accurately, the mothers with infants were split into four groups according to the age of their babies: from 0 to 6, 6 to 12, 12 to 18, and 18 to 24 months. The group of mothers without babies (Control group) was added to these four groups and comparisons were carried out between these five groups through ANOVAs and a posteriori comparison tests (assuming unequal variances and adjusting for the number of comparisons using the Holms method). The results are summarized in the eight panels of **Figure 2**, in which the upper part of each panel shows the result of the analysis of variance, the size of the effect, its confidence interval, and the number of cases used each time.

- KSS: The results of the ANOVA were significant [($F_{(4, 36.73)} = 6.34$), $p = 0.001$] with eta-squared equal to 0.2. The group of mothers with infants between 6 and 12 months old was different from the control group but any other group showed differences.
- ESS: The results of the ANOVA were significant [$F_{(4, 38.10)} = 12.28$, $p < 0.001$] with eta-squared equal to 0.3. The group of mothers with infants between 6 and 12 months old, and between 12 and 18 months old showed differences with the control group.
- GSDS: The results of the ANOVA were significant [$F_{(4, 35.46)} = 8.46$), $p < 0.001$] with eta-squared equal to 0.2. The group of mothers with infants between under 6 months old, and between 6 and 12 months old showed differences with the control group.
- Total sleep time: The results of the ANOVA were significant [$F_{(4, 34.62)} = 7.12$, $p < 0.001$] with eta-squared equal to 0.2. The *post hoc* comparison showed differences between the group of mothers with infants under 6 months old and the control group.
- Sleep quality: The results of the ANOVA were significant [$F_{(4, 34.49)} = 5.01$, $p = 0.003$] with eta-squared equal to 0.1 but its interval of confidence included 0 $CI = [0, 0.2]$. Also, the *post hoc* comparison did not show differences between any of the groups.
- Frequency of awakenings: The results of the ANOVA were significant [$F_{(4, 32.33)} = 18.97$, $p < 0.001$] and the eta-squared was equal to 0.4. All the groups of mothers showed significant differences from the control group except the one with babies between 18 and 24 months old.
- Frequency of getting up: The results of the ANOVA were significant [$F_{(4, 32.15)} = 4.99$, $p = 0.003$] with eta-squared equal to 0.2. However, the *post hoc* comparison did not show differences between any of the groups.
- Naps: The results of the ANOVA were not significant [$F_{(4, 37.01)} = 1.77$, $p = 0.156$].

4. DISCUSSION

The results have shown that mothers with infants have their sleep disrupted in comparison with a group of normal women. So, the mothers had higher scores with respect to nighttime sleepiness problems (GSDS), daytime sleepiness (Epworth), and current sleepiness (KSS). Also, they woke up more times per night, rated their sleep quality lower than the control group, got up more times, and slept fewer hours. Only the time employed in naps did not differ between the mothers and the control group.

The relationship between the sleepiness variables and the age of the infant was non-linear for many of the indicators. So, the nighttime sleep problems (GSDS), the daytime sleepiness (ESS), and the instant sleepiness (KSS) were at their highest point when the infants were about 10 months old. The frequency of awakenings was at its highest point when the children were <6 months, although it remained significantly different from the control group for mothers with children between 6 and 18 months old. The sleep quality ratings however did not show any relationship with the age of the infant, while the total hours of sleep increased almost linearly.

The results are consistent with previous research in several aspects. So, the reduction in sleep during the first months after birth is well established (Gay et al., 2004) and we have found it also in this study. Reduction of sleep after the first 6 months is less studied but (Sivertsen et al., 2015) found that the sleep duration and the time in bed of the mothers at 2 years postpartum were higher than at 8 weeks. Richter et al. (2019) also found that the reduction of sleep was significant after 1 year of birth respect to 1 year before pregnancy and only recovered partially, but not at levels before birth, after the second year. This result is not consistent with ours, as in our case the sleep duration of the mothers with 1 years old children was similar to the women not taking care of infant children but the different methodology (longitudinal study vs. cross-sectional) might lead mothers to provide the information in a different way. A sound methodological design would involve following two groups of women (with and without babies) during the same period of time so that comparisons within and between groups could be carried out.

We did not find a relationship between the rating of the quality of sleep and the age of the infant. Sivertsen et al. (2015) also did not find differences between the week 8 and the year 2 postpartum in two similar indicators (non-restorative sleep, and sleep dissatisfaction), but they found differences with pre-pregnancy levels. Richter et al. (2019) found that the first year was characterized by low levels of sleep satisfaction in comparison with years 2–6 but differences were not significant between 1 and year 2. So, in summary, it looks like the mothers' perception of an improvement in quality of sleep in mothers does not come probably until after the second year postpartum. This finding

should be confirmed with more studies that followed mothers for more than the 2 years limit used in this study.

That the subjective perception of quality of the sleep of mothers does not improve as quickly as the duration of the sleep has been connected with sleep fragmentation (Insana and Montgomery-Downs, 2010; Montgomery-Downs et al., 2010a). In our case, mothers with infant children had more awakenings than women without children with an average of 4 vs. 1. The peak of this problem occurred during the first 6 months of the postpartum period, decreasing afterwards. However, the average of awakenings was still well above of the women without infant children for all the groups of mothers with children under 18 months old. There were also significant differences in the frequency that the mothers got up during the night but no specific age of the children was identified as the cause of this difference.

One important consequence of sleep disruptions is the daytime sleepiness that mothers may experience. This sleepiness may reduce their performance in many tasks and may constitute a safety hazard in the job (Lee, 1992). Our results point out that the KSS, which is an indicator of the instant sleepiness, had its highest value when their children were between 6 and 12 months old. The Epworth daytime sleepiness was also significantly different for the mothers with children between 6 and 12 months and 12–18.

All in all, our study puts into question the assumption that any sleepiness-related problems a mother may have will be resolved by the end of the first semester of a baby's life. So, our results signal that the mothers with children of 12 months old are the ones with more sleep problems, interruptions, and daytime sleepiness despite that their sleep time is not at its worst.

There are several limitations to this study that we shall now comment on. Firstly, both the size of the sample and the method of gathering data mean that generalization to a the reference population cannot be ensured; so, this study should be considered as a pilot study which would mainly be of interest to lay the foundations for a wider-ranging study to evaluate the problems related with sleep-deprivation suffered by mothers of newborns in Spain. Secondly, the variables analyzed herein essentially refer to sleepiness and, although it is known that this is closely related to fatigue, either of which may occasionally be cause or consequence of the other, they should not be mixed up as there is at least one very important difference: fatigue may become chronic and not even rest may help a person to recover from it whereas sleepiness can be alleviated more quickly (Shen et al., 2006). Another limitation is related to the use of subjective measures, which could be substituted for more objective measures using actigraphy that recorded the sleep cycles.

Lastly, this study does not include a bigger number of variables which would help to understand why problems of sleepiness persist beyond the postpartum even though the initial reason, the baby's lack of maturity, should no longer represent a problem. Our recommendation, therefore, is that future research into sleepiness-related problems in mothers should enlarge the size of the sample, improve the sampling method and cover a broader spectrum of variables. Ideally, this research should be longitudinal, include a control group, and follow the evolution of the mothers both before and during the birth and throughout the child-rearing phase for as long as possible.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Anxious Attachment Mediates the Associations Between Early Recollections of Mother's Own Parental Bonding and Mother–Infant Bonding: A 2-Month Path Analysis Model

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Parental bonding (recollection of own parents' parenting), adult attachment, and mother–infant bonding are all closely related yet distinct concepts of the parent–child relationship, sometimes used interchangeably in the literature. This study aimed to examine the associations between these concepts in a longitudinal path analysis design. A total of 262 postpartum women who gave birth at the maternity ward of a large tertiary health center in Israel completed a demographic questionnaire, the Experiences in Close Relationships Scale (ECR), the Parental Bonding Instrument (PBI) at 1–4 days postpartum, and the Postpartum Bonding Questionnaire (PBQ) at 2 months postpartum. Parental care factor (PBI) was found to be associated with mother–infant bonding (PBQ), directly and indirectly through insecure anxious attachment (ECR). Denial of autonomy factor (PBI) was found to be associated with mother–infant bonding (PBQ) only through insecure anxious attachment (ECR). Encouragement of behavioral freedom factor (PBI) was found to be associated with mother–infant bonding (PBQ) in a simple correlation but not in the complete model. The results highlight the intergenerational aspects of parenting and suggest that early childhood interventions with parents may have a long-term impact on child-rearing though generations, and by that on children's development.

Keywords: mother–infant bonding, parental bonding, adult attachment, postpartum, childbirth

INTRODUCTION

Parental bonding, adult attachment, and mother–infant bonding are central concepts of the parent–child relationship (across generations) and are all related to children's development, growth, and wellbeing. These similar yet distinct concepts are sometimes used interchangeably in the literature while not clearly and consistently treated as different concepts (1–4).

In the present study, we aim to expand the understanding of the associations between these concepts by examining how parental bonding and adult attachment are associated with mother–infant bonding. Using a longitudinal path analysis design, we examine whether women's adult attachment orientations measured shortly after birth possibly mediate the associations between parental bonding (the new mother's recollection of the way she was mothered) and mother–infant bonding (her cognitions and feelings toward her infant) at 2 months postpartum. To our knowledge, this study is the first to describe the paths between these close yet different concepts using a longitudinal design.

Mother–infant bonding refers to the emotions and the feelings a mother has toward her infant and herself as a parent. Bonding is believed to emerge during pregnancy or immediately after birth (1). The quality of mother–infant bonding is considered central to infant wellbeing and the child's cognitive and emotional development (5, 6) and was found as an important factor in mothers' later relationships with their children (7–9). Postpartum bonding was found to be associated with a host of factors such as abuse in childhood, family psychiatric history, mother's psychopathology, as well as personality variables [e.g., (6, 10, 11)]. In this study, we focused on the possible associations of mother–infant bonding with the mother's caring model as evolving from her experiences with her own mother, experiences that may have shaped her internal working models of relationships—attachment orientations.

Although similar in name and conceptually closely related to mother–infant bonding, parental bonding refers to the way adults retrospectively report the quality of their parents' parenting, i.e., their childhood relationships and experiences with their parents (12). It was found that mothers' parenting history was associated with the quality of parenting they provide to their infants (13), as mothers who remembered being accepted by their mothers as children were more sensitive and less intrusive with their infants (14). On the other hand, lower recalled care in childhood by the own mother predicted higher dissatisfaction with overall own motherhood (15), while maternal experiences of emotional neglect in childhood were associated with more mother–infant bonding impairments (16).

The Parental Bonding Instrument (PBI) is a scale designed for assessing parenting style retrospectively. Despite its widespread use, there is no consensus regarding its factor structure (17). It was initially conceptualized and assessed as compromised from two factors, care and overprotection (12). However, recent studies reported a different factor structure [e.g., (17)]. In this study, we intend to verify the often reported three-factor structure of PBI: care (reflecting perceptions of the mother as warm and understanding), denial of autonomy (reflecting perceptions of the mother as controlling and overprotective), and encouragement of behavioral freedom (reflecting perceptions of the mother as granting autonomy) (11, 17–19). With regard to parental bonding and mother–infant bonding associations, mothers' perceptions of their child-rearing history (both care and overprotectiveness) were found to be associated with mother–infant bonding (20). However, a later study found that only higher overprotection measured during pregnancy was associated with bonding failure in the postpartum period (21). These findings underscore how the retrospective perception of parenting from own childhood may be relevant to the postpartum mother–infant relationship.

According to the Attachment Theory, early experiences with significant others are internalized and formulate working models that shape individuals' behaviors (22, 23). Those early relations create prototypes for later relationships with close others (24). Attachment with mother/primary caregiver, who can be sensitive and responsive to one's need or not be reliably available and supportive, contributes to the development of internal working models (25). These can mediate the relationship between mothers' early experiences to various aspects of current motherhood (3, 26).

Attachment and maternal–infant bonding refer to different aspects of the parent–child relationship, as bonding emphasizes the mother's tie to her infant, and attachment in general refers to the child's tie to his mother and other caregivers (1, 9). Several studies examined the association between those concepts with inconclusive results pattern. On the one hand, during the transition to motherhood, insecure attachment (anxious and avoidant) was associated directly with bonding difficulties among parents (27) and indirectly mediated by postpartum depression among mothers (28) or mediated by parenting stress (29). On the other hand, Van Bussel et al. (9) reported a weak correlation between mother–infant bonding and attachment style while maternal romantic attachment style predicted attachment with the fetus in the antenatal, but not with the baby in the postpartum period (30) and only women with a dual/disorganized attachment style reported lower bonding than with women with secure and insecure attachment styles (31). This inconclusive results pattern may be explained by the different measures used for attachment and bonding.

In this study, we refer to adult attachment orientations (32)—the internal working models of the mother herself. In order to examine these internal working models in adulthood, researchers focused on a *person's attachment orientation*, which is compromised from two dimensions: *attachment-related avoidance*, which reflects the extent to which a person mistrusts others' intention and therefore defensively strives to maintain behavioral and emotional independence, and *attachment-related anxiety*, which reflects the extent to which a person worries that others will not be available in times of need and anxiously seeks love and care (33).

Past research that examined the relationship between adult attachment and parental bonding during the transition to motherhood revealed that mothers' recollections of their own mothers as supportive and non-intrusive differentiated between securely and insecurely romantic attached participants (3). A recent study reported correlations between recalled care and overprotection in childhood (in opposite directions) and both anxious and avoidant attachment in a sample of pregnant women (15). These findings adhere to the results of several other studies that examined the relationship between parental bonding and adult attachment in diverse populations (2, 34–36). It should be noted that we were interested in the association of recollections of parental bonding and adult attachment orientation, rather than

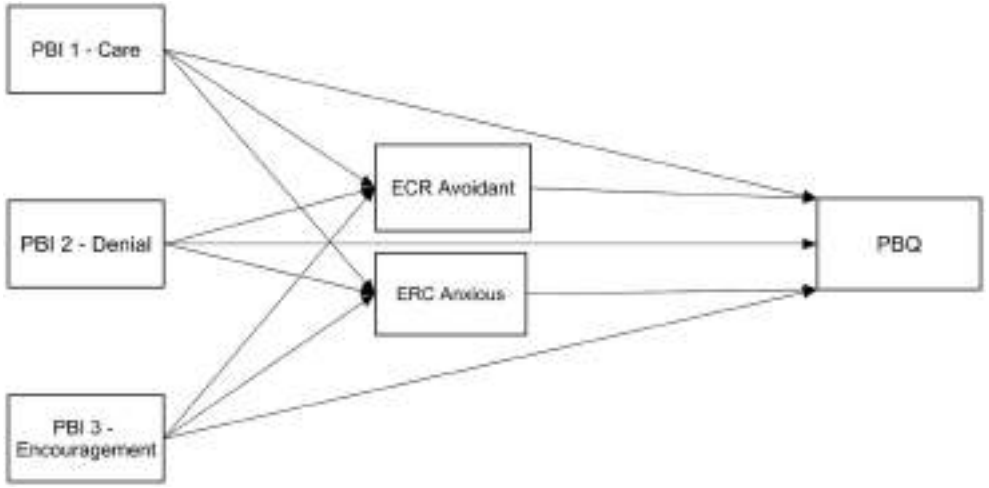

FIGURE 1 | Hypothesized mediation model; Insecure attachment orientations (ECR) will mediate the association between parental bonding (PBI) and mother-infant bonding (PBQ).

the association of parental bonding and attachment to the fetus or attachment behaviors that are often studied (28, 37).

This study aimed to examine the associations between parental bonding, adult attachment orientations, and maternal–infant bonding of postpartum mothers. Despite the review presented here, to the best of our knowledge, although close by describing parent–child relationships (inter-generationally), these are distinct concepts. Parental bonding refers to the way the mother (in our sample) recalls the relationship with her mother in childhood (12). Her adult attachment orientation refers to the way these recollections, among other factors, have shaped the working models she has for relationships with others in adulthood (33). Finally, mother–infant bonding refers to the emotions and the feelings a mother has toward her infant and herself as a parent (1).

We propose a model in which the mother's childhood recollections of her mother parenting her influence her bonding with her infant, and this association is mediated by her adult attachment orientation. While we study parental bonding and adult attachment orientations shortly after birth (along with other demographic and obstetric control variables), we measure their influence on mother–infant bonding at 2 months postpartum. Hence, we hypothesize that insecure attachment orientations (both anxious and avoidant) will mediate the association between recalled parenting by the mother and mother–infant bonding, as higher levels of parental bonding (PBI) will be associated with lower levels of anxiety or avoidance attachment orientation, which will be associated with better mother–infant bonding at 2 months postpartum (see **Figure 1**).

MATERIALS AND METHODS

Sample

The final sample included 262 postpartum women who gave birth in the maternity wards of the Rabin Medical Center (RMC), a large tertiary health center in Israel. Eligibility criteria included delivering at least at 37 weeks' gestation, a singleton pregnancy, and Hebrew speaking. Information about recruitment, data collection, and dropout rates can be seen in **Figure 2**. Comparing dropouts (women who completed only the first time point) to women who completed the second time point with sufficient data showed that completers were less avoidant (ECR) [$M = 2.5$, $SD = 0.9$ vs. $M = 2.8$, $SD = 1.0$, $F_{(1, 481)} = 8.6$, $p = 0.003$], lower in PBI denial factor [$M = 0.7$, $SD = 0.1$ vs. $M = 0.9$, $SD = 0.9$, $_{F(1, 540)} = 12.0$, $p = 0.001$], and older [$M = 32.0$, $SD = 4.7$ vs. $M = 31.0$, $SD = 5.4$, $F_{(1,587)} = 4.5$, $p = 0.035$]. In addition, primiparous women were less likely to complete the second time point (41 vs. 50%, $p < 0.001$), as were women with less than university educational level (38 vs. 53%, $p < 0.001$) and with below average income (43 vs. 56%, $p = 0.002$).

The average age of the participants was 31.7 (±4.8), most (94%) were married, 84% were born in Israel, and 92% were Jewish. Most women (76%) had vaginal births, 9% had elective cesarean section, 10% had emergency cesarean sections, and 6% had an assisted vaginal birth. Just over half of all women (53% of the whole sample, 61% if excluding women who had elective CS) were administered an epidural, and 43% (49% if excluding women who had elective CS) had oxytocin for labor augmentation. For participants' demographic data, see **Table 1**.

Procedure

The study is part of a larger longitudinal study aimed at understanding associations between factors associated with birth and postpartum mental health during the first 6 months postpartum conducted between July 2018 and July 2019. Ethical approval for this study was obtained from the RMC and the Academic College of Tel-Aviv Yaffo institutional review boards. Research assistants, graduate students with appropriate training in research ethics, approached all women at the maternity ward

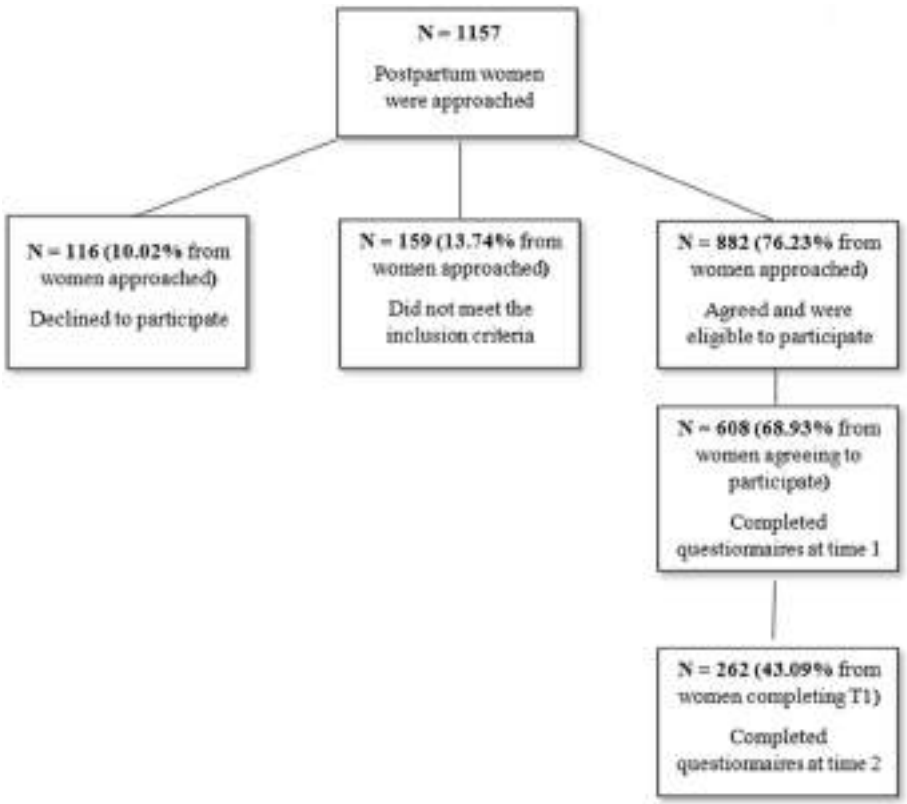

FIGURE 2 | Recruitment and data collection.

on a random day of the week, and after giving informed consent, the participants answered questionnaires at two time points:

T1 (1–4 days postpartum) in person at the maternity ward—obstetric data were taken from the medical files and women completed demographic questions, the Experiences in Close Relationships Scale (ECR) and the PBI.

T2 (2 months postpartum)—using online questionnaires, the participants completed the Postpartum Bonding Questionnaire (PBQ).

Participants who did not respond to the email invitation were reminded once with a phone call. Questionnaires and data output were generated using Qualtrics© 2015 (Qualtrics, Provo, UT, USA; http://www.qualtrics.com).

Measures

Sociodemographic Questionnaire

Sociodemographic questionnaire included questions about age, education level, marital/co-habiting relationship, income level (as compared to the national average per household at the time of the study), religious affiliation, country of origin, and the history or current existence of psychiatric disorders.

Obstetric Data

Obstetric data were extracted from medical records, recording number of previous births, infertility treatments, pregnancy risks, past abortions or miscarriages, and current birth data: type of birth as well as epidural and oxytocin administration. We treated "birth type" as a dichotomous variable for statistical reasons and according to relevant literature that claims that the importance of the birth type variable is whether it was expected or not (38–40). Thus, vaginal birth and elective cesarean sections are considered "Expected birth," while emergency cesarean section and vaginal assisted birth are considered "Unexpected birth." Being primiparous, having higher education, having above average income, being married, having a psychiatric diagnosis, and having an unplanned birth type were dummy-coded as "1" while other values were coded as "0."

Parental Bonding

Parental bonding was assessed with the PBI (12), a 25-item scale designed to measure retrospective recollections and perceptions of early parental attitudes and behaviors that has been widely used for assessing recollections of parent–child relations (41). We used the Hebrew version (42) and inquired only about recollections of mother's parenting. Participants were asked to rate the degree to which each item describes their mother's early behavior and attitudes, on a four-point scale, ranging from 0 (not at all) to 3 (very much). In order to verify the three-factor solution of the scale, we performed parallel analysis, a more accurate method for determining the number of factors in a set of items than the commonly used criterion of eigenvalue >1,

TABLE 1 | Sample demographic characteristics and correlations with PBQ score.

	N (%)	*M* (*SD*), Range	Correlation with PBQ
Age		31.7 (4.8), 20-43	0.03
Primiparous			0.22**
Yes	67 (26)		
No	195 (74)		
Higher education			0.14*
Yes	187 (71)		
No	75 (29)		
Income level			−0.05
Average or below	145 (55)		
Above average	112 (43)		
Unknown	5 (2)		
Marital status			−0.09
Married	246 (94)		
Not married	16 (6)		
Psychiatric diagnosis			0.26**
Yes	10 (4)		
No	252 (96)		
Unplanned birth type			0.18**
Yes	42 (16)		
No	220 (84)		

*$p < 0.05$, **$p < 0.01$.

TABLE 2 | Factor loadings for principal components analysis of PBI with Varimax rotation.

	Care	Denial	Encouragement
FACTOR 1			
Item 6 Was affectionate to me	**0.77**	0.07	−0.29
Item 11 Enjoyed talking things over with me	**0.74**	0.05	−0.22
Item 18 Did not talk with me very much	**0.73**	−0.19	−0.01
Item 12 Frequently smiled at me	**0.70**	0.03	−0.17
Item 1 Spoke to me in a warm and friendly voice	**0.69**	−0.06	−0.28
Item 17 Could make me feel better when I was upset	**0.69**	−0.05	−0.30
Item 5 Appeared to understand my problems and worries	**0.69**	0.04	−0.33
Item 4 Seemed emotionally cold to me	**0.64**	−0.19	−0.01
Item 24 Did not praise me	**0.62**	−0.31	0.00
Item 2 Did not help me as much as I needed	**0.58**	−0.13	0.16
Item 16 Made me feel I wasn't wanted	**0.55**	−0.32	−0.04
Item 14 Did not seem to understand what I needed or wanted	**0.52**	−0.47	−0.24
FACTOR 2			
Item 19 Tried to make me feel dependent on her	−0.14	**0.74**	0.07
Item 13 Tended to baby me	−0.09	**0.70**	0.06
Item 20 Felt I could not look after myself unless she was around	−0.17	**0.69**	0.04
Item 9 Tried to control everything I did	−0.24	**0.64**	0.28
Item 8 Did not want me to grow up	0.00	**0.59**	0.01
Item 10 Invaded my privacy	−0.20	**0.57**	0.36
Item 23 Was overprotective of me	0.16	**0.54**	0.19
FACTOR 3			
Item 22 Let me go out as often as I wanted	−0.09	0.06	**0.83**
Item 21 Gave me as much freedom as I wanted	−0.09	0.14	**0.82**
Item 15 Let me decide things for myself	−0.22	0.27	**0.72**
Item 25 Let me dress in any way I pleased	−0.08	0.08	**0.69**
Item 7 Liked me to make my own decisions	−0.11	0.25	**0.66**
Item 3 Let me do those things I liked doing	−0.36	0.04	**0.54**
Cumulative Explained Variance	**23%**	**52%**	**38%**

Item loadings in bold indicate the subscale in which the item was included.

which tends to extract too many factors (43). Parallel analysis indicated three underlying factors. Exploratory factor analysis using principal components analysis with varimax rotation provided a corresponding solution, almost identical to the factors found in a recent large population-based psychometric validation of the scale as well as other studies [see (17)] apart from item 3 that loaded in our study on the encouragement factor and in the mentioned research loaded on both encouragement and care and item 8 that loaded on the denial of autonomy scale in our study and on the encouragement factor in the mentioned study. These three factors were also found in our previous study of different sample (11). The three factors together explained 52% of the variance in the responses (see **Table 2**): (1) *PBI-Care*, reflecting perceptions of the mother as warm and understanding (12 items; $\alpha = 0.90$); (2) *PBI-Denial of autonomy*, reflecting perceptions of the mother as controlling and overprotective (7 items; $\alpha = 0.79$); and (3) *PBI-Encouragement of behavioral freedom*, reflecting perceptions of the mother as granting autonomy (6 items; $\alpha = 0.85$). Scores were computed by calculating an average for each subscale with higher scores reflecting stronger perceptions. The intercorrelations between the three factors were significant yet moderate (0.23–0.38), supporting their use as three separate factors (see **Table 2**).

Adult Attachment

Adult attachment was assessed by the ECR (44), which assesses the dimensions of anxious and avoidant adult attachment. For the purpose of the study, we used an abbreviated, validated Hebrew version that consists of 24 items divided into two dimensions: anxious (12 items, e.g., "I worry about being abandoned") and avoidant (12 items, e.g., "I feel discomfort when others get close to me") (45). Participants rated the extent to which an item described themselves on a seven-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). A high score indicates higher anxious or avoidant attachment. This scale has been used in previous studies with postpartum women [e.g., (46, 47)]. In the current study, the internal reliability was good ($\alpha = 0.84$ for anxiety and $\alpha = 0.83$ for avoidance).

Mother–Infant Bonding

Mother–infant bonding was assessed by the Hebrew version of the PBQ (48, 49). This 25-item scale assessed the mother's feelings

or attitudes toward her baby (e.g., "I feel close to my baby"). Statements are presented on a six-point scale, ranging from 0 (always) to 5 (never), with reverse coding of positive items. Responses are summed so that higher scores denote **greater** bonding difficulties (poorer bonding). Two items relating to the risk of abuse were not included due to ethical considerations (50). Internal reliability of the total scale was good ($\alpha = 0.89$).

Statistical Analysis

Data were described as *M*(*SD*) and range or as counts and percentages. Correlations between the study variables were assessed using the Pearson correlation coefficient. Exploratory factor analysis for determining the factor structure of the PBI questionnaire used principal components analysis with varimax rotation. Items were assigned to factors on which their loading was 0.5 or higher. Path analysis with 1,000 bootstrap samples was used to test the mediation model. Data were analyzed using SPSS v.25 and AMOS v.25. Using the 15 observations per measured variable rule, we concluded that a sample of about 200 observations should be sufficient for testing our hypothesized model including possible covariates.

RESULTS

Table 1 shows the sample demographics as well as correlations between the demographic characteristics and the outcome variable. The correlations between the study variables, as well as their means and standard deviations, are shown in **Table 3**. All study variables significantly correlated with each other.

Given the correlations shown in **Table 1**, the hypothesized model was tested with being primiparous, education, psychiatric diagnosis, and birth type as covariates, linked to the study variables with which they had significant correlations. The results showed that birth type and the PBI Encouragement factor had no significant effects on any of the other model variables, and so were excluded from the model. The resulting model is shown in **Figure 3**. Results show that the model had good fit [$\chi^2_{(3)} = 1.95$, $p = 0.58$, NFI = 0.99, TLI = 1.04, CFI = 1.00, RMSEA = 0.00] and accounted for 25% of the PBQ variance. PBI Care factor had both direct [$\beta = -0.16$, $p = 0.02$, 95% CI = (−0.28, −0.02)] and indirect effects on PBQ, going through anxious attachment [$\beta = -0.03$, $p = 0.03$, 95% CI = (−0.08, 0.00)]. We found no direct effect of the PBI Denial factor on PBQ, yet we found an indirect effect through anxious attachment [$\beta = 0.04$, $p = 0.04$, 95% CI = (0.00, 0.10)]. While PBI Encouragement factor was significantly correlated with PBQ as can be seen in **Table 3**, this correlation diminished in the presence of the other factors in the final model. Avoidant attachment did not serve as a mediator despite its correlations with the PBI factors and PBQ (see **Table 3**), as anxious attachment accounted for the mediation effect.

In sum, we learn that anxious attachment mediates the relationships between PBI factors (Care Denial) and PBQ: lower PBI care factor was related to higher ECR attachment anxiety, which in turn was related to higher PBQ score, resulting in a negative indirect effect. In contrast, high PBI denial factor was related to higher ECR attachment anxiety, which was followed by higher PBQ score, hence the positive indirect effect. In addition, in the final mode, PBI Encouragement factor was not associated with PBQ and avoidant attachment was not found to be a mediator between PBI factor and PBQ.

DISCUSSION

The current study aimed to examine the associations between parental bonding (PBI), adult attachment orientations, and mother–infant bonding (PBQ) among mothers, in a longitudinal design from childbirth to 2 months postpartum. Our findings indicate that parental bonding care factor was associated with mother–infant bonding both directly and indirectly through anxious attachment, while parental bonding denial of autonomy factor was associated with mother–infant bonding only indirectly through anxious attachment. The third factor, parental encouragement of behavioral freedom was associated with bonding in a simple correlation but was not associated with mother–infant bonding in the complete model. Additionally, parental care and parental denial of autonomy factors were associated with avoidant attachment, though avoidant attachment was not associated with mother–infant bonding. The study findings contribute to the existing literature in several aspects. First, our findings emphasize that parenting models that new mothers have absorbed from their mothers may have shaped their internal working models and, through those, but also directly, may be associated with the way they perceive their bond with their new infant. In particular, we found that childhood recollections of mothering that lack warmth and understanding or are characterized as controlling and overprotective may be associated with higher levels of anxious attachment orientation, which in turn may increase mother–infant bonding difficulties. Our results are in line with previous findings that emphasize that parents' recollections of the way they were parented are important to their postpartum parenthood mental health and psychological wellbeing (51–53). This intergenerational perspective emphasizes that early childhood caretaking experiences of mothers may continue to compromise the mother's capacity to cope during her own parenthood (20) through her internal working models and the bond she perceives with her new infant (28). This finding is of importance as the quality of the maternal infant relationship postpartum, and in particular mother–infant bonding, is considered central to infant wellbeing, cognitive and emotional development, and adaptation throughout life (54–56).

In addition, the findings contribute to the literature regarding the PBI factor structure by replicating the PBI's three factors structure as reported in recent studies [e.g., (17)]. Our study results put a spotlight on parental care, which was the only factor associated directly and indirectly through anxious attachment with mother–infant bonding. It emphasizes parental care as a possible distinct concept from the other two PBI factors (vis-à-vis bonding) and in line with previous studies that report parental care as a clear, cohesive, and stable factor (18, 41, 57). We suggest that anxious attachment orientation may explain the association between parental care and bonding, but our model

TABLE 3 | Descriptive statistics and Pearson correlations between the study variables.

	2	3	4	5	6	*M* (*SD*)
1. PBQ	−0.24**	0.25**	0.17**	0.24**	0.32**	0.4 (0.4)
2. PBI factor 1: Care		−0.23**	−0.37**	−0.31**	−0.27**	2.6 (0.5)
3. PBI factor 2: Denial			0.35**	0.22**	0.33**	0.9 (0.5)
4. PBI factor 3: Encouragement				0.15*	0.23**	0.7 (0.6)
5. Avoidant attachment					0.51**	2.5 (0.9)
6. Anxious attachment						2.6 (1.1)

*$p < 0.05$, **$p < 0.01$.

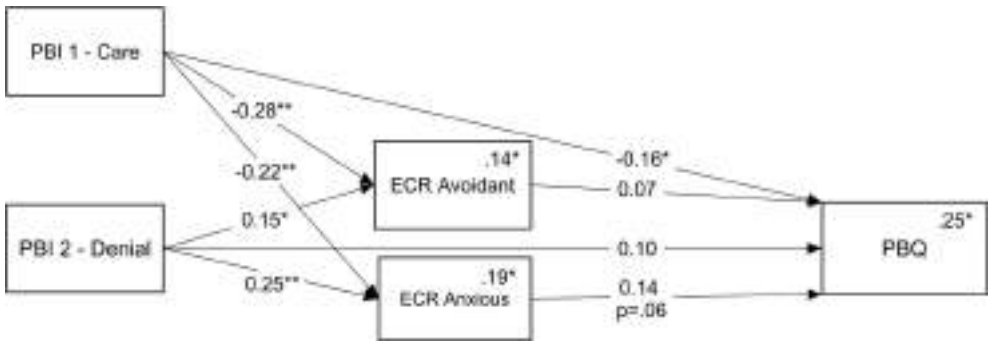

FIGURE 3 | Final mediation model; ECR (anxious attachment orientation) mediating the association between PBI factors (parental bonding care and denial of autonomy) and PBQ. *$p < 0.05$, **$p < 0.01$. While not shown on the graph, this model was analyzed with being primiparous, education, and having a psychiatric diagnosis as covariates. Numbers above the lines are standardized regression weights, and numbers above the endogenous variables and multiple squared correlations.

also alludes to the possible direct association between parental care and mother–infant bonding. It underscores parental care as a significant variable in parenting (15) and as meaningful during the transition to parenthood (11).

In the complete model, the second PBI factor, parental denial of autonomy, was related to mother–infant bonding only through anxious attachment. This finding adds to the literature regarding this factor role, as a previous study found an association between parental denial of autonomy and maternal–fetal attachment (11). The third factor, parental encouragement of behavioral freedom, was not associated with mother–infant bonding in the model. Thus, the third factor, which is relatively new, is yet to be studied with relation to other variables in general and parenting in particular.

Although we hypothesized that both insecure attachment orientations (anxious and avoidant) would mediate the associations between parental bonding and mother–infant bonding, the results indicated differential mediation; only anxious attachment mediated this association in the overall model. It is important to note that we found a simple correlation between anxious as well as avoidant attachment orientations and mother–infant bonding while both parental bonding care and denial factors were associated with both anxious and avoidant attachment orientations. In general, our findings adhere to the literature linking insecure attachment orientations and parenting variables (58) and emphasized that insecure attachment has an important role during the transition to parenthood (59). Our findings demonstrate adult attachment and maternal–infant bonding as different aspects of the intergenerational perspective of parent–child relationship, as adult attachment orientations refer to the internal working models of relationships in adulthood and mother–infant bonding refers to the mother's tie to her infant (1, 9). However, various studies investigating the specific associations of avoidant and anxious attachment orientations and mother–infant bonding report inconsistent findings, similarly to our findings. For example, only avoidance was a significant predictor of mother–infant bonding when controlling for demographic variables and maternal mental health history (29). In another study, there was no direct relationship between attachment and mother–infant bonding; however, anxious attachment was associated with postpartum depression, and depressive symptoms predicted impaired bonding (30). Other studies investigated associations between other attachment orientations (secure attachment and dual/disorganized attachment) with bonding [e.g., (27, 31)]; therefore, more research is clearly needed to elucidate the role of the different insecure attachment orientations vis-à-vis parenting in general and the mediation of the association between parental bonding and mother–infant bonding in particular. Our model suggests that the way mothers report about the mothering they have received in childhood retrospectively may shape their anxious and avoidant orientations, but only anxious orientation was found to have a significant association with bonding to the infant in our model.

Although our study was in a longitudinal design using a relatively large sample, it is not without limitations. First, the study participants were mothers asked to report their childhood recollections of the way their mothers cared for them. Further research is needed both regarding fathers and memories of parenting experiences with fathers. Furthermore, the PBI is a self-report measure of parental bonding reported retrospectively that might be influenced by recall biases, though parental bonding recollections as measured by the PBI exhibited stability over a 20-year period, suggesting that recall biases of parental bonding may be modest (60). Second, in this study we used only self-report measures. Future research could use observational measures of attachment or mother–infant interactions as well as study the participants' mothers and infants to further learn about intergenerational perspectives in more ecological designs. Third, we measured our variables in the first 2 months' time frame, while future research could study parenting perceptions in longer periods after childbirth. Fourth, there was a difference between the first time point assessment that was done in-person and the second time point that was done online, causing a potential confounding. This difference in assessments is a result of following up on a fairly large sample. Recent research of offline vs. online assessment of the PBQ found no difference between assessment modalities in terms of associations with sociodemographic, reproductive, obstetric, and psychological outcomes (61). Lastly, our participants were mostly Jewish, sampled from one health center only, and this may impair our ability to generalize our findings, as parenting practices may be different across cultures.

In conclusion, the present study examined the associations between the close yet distinct concepts of the parent–child relationship: parental bonding, adult attachment orientations, and mother–infant bonding. Our findings demonstrate the associations between those three separate concepts in a longitudinal design, as our model emphasizes that parenting models mothers have received from their mothers may shape their internal working models and those in turn were associated with the way they perceive the bond with the new infant. These findings highlight the intergenerational conceptualization of parenting (62) and emphasize that early childhood interventions with parents might be significant for a long-term impact on the development of future generations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Rabin Medical Center and the Academic College of Tel-Aviv Yaffo institutional review boards. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH, MK, HK, and YP contributed to the conception and design of the study. MM-L and SL organized the database. SL performed the statistical analysis. MK and JH wrote the first draft of the manuscript. JH, MK, and YP wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Parental Sensitivity and Responsiveness as Mediators Between Postpartum Mental Health and Bonding in Mothers and Fathers

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Background: There is a lack of studies that examine the complex relationship between parental mental health, parental sensitivity and responsiveness, and parent-infant bonding. This study aimed to test whether parental sensitivity and responsiveness were mediators between postpartum mental health (depression, anxiety, and stress) and parent-infant bonding in mothers and fathers.

Method: Mothers ($n = 427$) and fathers ($n = 170$) of infants aged up to 1-year-old participated in an online study. The parents completed questionnaires on depression (Edinburgh Postnatal Depression Scale, EPDS), anxiety and stress (Depression, Anxiety, and Stress Scale, DASS-21). Parent-infant bonding was measured by Postpartum Bonding Questionnaire (PBQ) that has three components: Impaired bonding (PBQ1), Anxiety about care and parental distress (PBQ2), and Lack of enjoyment and affection with infant (PB3Q). Parental sensitivity was measured as the number of correct recognitions of infant facial expressions (City Infant Faces Database, CIFD). Responsiveness was measured as a self-report with two subscales of responsiveness and non-responsiveness (Maternal Infant Responsiveness Instrument, MIRI).

Results: The path analysis showed that the model had a good fit to the data. Parental sex was a significant moderator, indicating different paths in mothers and fathers. In mothers, responsiveness and non-responsiveness were significant mediators between depression symptoms and three dimensions of bonding. In fathers, only non-responsiveness was a significant mediator between anxiety and PBQ3. Although recognizing infant facial expressions directly affected PBQ3 in mothers (but not in fathers), it was not a significant mediator between mental health and bonding.

Conclusion: Higher levels of parental mental health problems (depression and anxiety) were associated with lower levels of parental responsiveness, which is, in turn, related to poor parent-infant bonding. Prevention and intervention programs should be offered for both mothers and fathers, focusing on postpartum mental health promotion and enhancing responsiveness in infant care.

Keywords: postnatal depression, anxiety, stress, responsiveness, fathers, mother-infant bonding, maternal sensitivity

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INTRODUCTION

Maternal sensitivity and responsiveness have been identified as crucial for secure infant attachment. Maternal sensitivity seems to be a stable maternal characteristic during infancy (1). It refers to the maternal ability to perceive the infant cues and signals, interpret them correctly, and respond to them timely and adequately (2–4). These iterative processes in mother-infant interactions are essential for infant development as infants learn that their actions affect the environment, especially the secure figure, which gives them a sense of efficacy. Consequently, an infant who feels secure will explore the environment more, which will increase their socio-emotional and cognitive competencies (2).

Shin et al. (5) pointed out that the conception of maternal sensitivity has changed over time. Based on their conceptual analysis, four aspects of maternal sensitivity have been pointed out. These refer to maternal sensitivity as (i) dynamic process, (ii) including reciprocal exchanges between mother and infant, (iii) contingent with infant's previous behavior, and (iv) including appropriate responses based on specific infant cues. Maternal responsiveness is one aspect of sensitivity (5) and refers to maternal prompt and frequent responses to the infant's cues about physical and emotional states (3).

Shin et al. (5) provided a conceptual structure of maternal sensitivity describing its antecedents, affecting factors and consequences. Antecedents are described as maternal identity or identification of self as a mother, and of course, the infant's needs and cues upon which mother will express her sensitivity. One of the consequences of maternal sensitivity is the development of secure mother-infant relationships and higher quality of infant-to-mother attachment. Indeed, there is a bulk of literature showing the association between maternal sensitivity and secure attachment in infancy (1, 6), early childhood (7), and young adulthood (6).

Bonding is sometimes erroneously used as a synonym with attachment (8–10). However, the former can be defined as the maternal feelings and thoughts about the infant (9, 11), while attachment refers to the relationship between the child and the parent and makes the child feel secured (12). Furthermore, the methods of measures differ between the two, with questionnaires to measure bonding (13) and the observational method of Strange Situation Task (14) as a gold standard to measure attachment. As a strong mother-infant relationship, bonding is considered crucial for postpartum development (15). A recent literature review has also shown that maternal sensitivity is sometimes used as a synonym for bonding (16). However, although these are different constructs, there is a lack of studies looking at maternal sensitivity and responsiveness in relation to mother-infant bonding.

As affecting factors on maternal sensitivity, Shin et al. (5) distinguished some positive, such as social support and high self-esteem, and negative factors, such as maternal depression, stress, and anxiety. Maternal mental health in the postpartum period can be seriously challenged, with one in three primiparous women having symptoms of depression, anxiety or stress (17). A recent meta-analysis revealed that around 17% of healthy women report postpartum depression (18) and 8–10% report one or more anxiety disorders (19, 20). Also, comorbidity between postpartum depression and anxiety has been established (21–23).

Poor parental mental health is one of the main risk factors for disrupted parent-infant interactions and may negatively affect bonding and attachment (24). Postpartum depression symptoms diminish the quality of bonding (25–28). However, there are inconsistencies in respect to anxiety and bonding. Namely, some studies showed that anxiety is associated with poor bonding (29), while other studies showed that this relationship is fully mediated by depression. Moreover, once depression was controlled for, anxiety was not associated with poor bonding anymore (28, 30). Nevertheless, one study showed that anxiety was associated with improved mother-infant bonding (31), which the authors attributed to the increased maternal sensitivity. Although, the other study with mothers with social phobia did not show the difference in sensitivity compared to healthy controls (32). A meta-analysis showed that maternal depression symptoms were associated with diminished sensitivity during the first postpartum year (33). However, inconsistencies concerning postpartum depression and responsiveness are evident, as well. It was shown that postpartum depressive symptoms were associated with lower levels of maternal responsiveness (34, 35), or no association was found (36). However, the latter was established in a small sample of mothers with preterm infants.

There is a lack of studies that examines the complex relationship between maternal mental health, maternal sensitivity and responsiveness, and mother-infant bonding. Furthermore, in previous studies, self-report measures of sensitivity and responsiveness or observation during mother-infant interaction have been applied. Although observation is preferred over the self-report measured, the former can also be jeopardized due to personal bias of observer, the difficulty of coding, and change of behavior in the presence of the observer. On the other hand, objective measures of sensitivity, such as facial expression recognition, has been rarely applied. Nevertheless, several new databases of infant facial expression photographs have been developed (37, 38), which could be used as an objective measure of maternal sensitivity. This kind of measures was proven to be sensitive for maternal mental health, as it was shown that, e.g., mothers with postpartum depression tended to rate negative infant faces more negatively (39). Also, previous studies have mainly addressed the quality of bonding as unidimensional, although measured with the Postpartum Bonding Questionnaire (PBQ) (40), which measures different aspects of bonding difficulties. Thus, the role of parental mental health and sensitivity should be examined concerning varying dimensions of bonding.

Finally, previous research on perinatal mental health problems or parental sensitivity has mainly focused on women, thus unjustifiably neglecting fathers (41, 42). Paternal role in the family functioning has substantially changed over the last several decades, with fathers becoming more involved and engaged nowadays (43). Although mothers are rated as more responsive to their preschool children needs than fathers (44), maternal and paternal sensitive parenting have comparable effects on children's cognitive ability (45). Furthermore, it was found that

parental sensitivity was a full mediator between parenting stress and child cognitive abilities and prosocial behavior in both mothers and fathers (46). Also, for parental sensitivity, the vital is the parental ability to mentalize a child's thoughts, emotions, and needs that drive their behavior, the so-called reflective functioning, is essential (47). It was shown that the paternal reflective functioning was associated with their toddler's distress, even after accounting for maternal reflective functioning, and it also buffered the adverse effects of low income (41), thus implying the importance of the father's sensitivity for child development. Furthermore, there is a growing body of literature on paternal mental health in recent years, with a meta-analysis showing that around 8% of fathers have postpartum depression (48). In a recent large study of fathers, several depression profiles emerged with substantial stability from pregnancy to 2 months postpartum, although the depression levels decreased in the perinatal period (49). Another meta-analysis showed similar maternal and paternal depression effects on parenting behavior where depressed parents express less positive and more negative behaviors toward their children (50). Also, postpartum mental health difficulties in fathers extend to anxiety and stress (51), with paternal stress mediating the effect of anxiety on father-infant bonding (51). Parent-infant bonding is similar in mothers and fathers, although fathers report less fear and higher emotional involvement with the newborn in the first days after delivery (52). However, studies that would encompass mental health, sensitivity and responsiveness, and parent-infant bonding in fathers, are still scarce, as well as the studies in mother.

Therefore, this study aimed to examine the mediational role of parental sensitivity and responsiveness in a relationship between parental mental health and parent-infant bonding in both mothers and fathers. Also, we wanted to investigate different aspects of mental health, including depression, anxiety, and stress, as the conceptual analysis (5) pointed out as the affecting factors on maternal sensitivity. Furthermore, we wanted to provide different measures of parental sensitivity, including both objective measures of infant facial expression recognition and a self-report measure of responsiveness concerning various aspects of parent-infant bonding. The hypothesis was that parental sensitivity and responsiveness would mediate the relationship between mental health and parent-infant bonding in mothers and fathers.

MATERIALS AND METHODS

Sample

A sample of mothers ($n = 427$) and fathers ($n = 170$) participated in the study. The inclusion criterium was having an infant of 1–12 months. The sample was predominantly married or cohabiting, highly educated, average to above-average self-reported socioeconomic status and lived in a city (**Table 1**). Approximately 60% of the sample had the first child.

The sample of mothers and fathers did not differ in marital status, education level, socioeconomic status, number of children, and psychiatric heredity (**Table 1**). However, mothers were on average 2.5 years younger than fathers [$M_{\text{mothers}} = 30.80$, $M_{\text{fathers}} = 33.19$, $t_{(595)} = 4.94$, $p = 0.000$] and less mothers than fathers were from the city larger than 100,000 citizens [mothers: 46.4%, fathers 57.6%, $\chi^2_{(2)} = 7.57$, $p = 0.0228$]. Also, more mothers reported psychiatric treatment during lifetime [mothers: 6.1%, fathers 1.8%, $\chi^2_{(1)} = 4.03$, $p = 0.0447$].

TABLE 1 | Sociodemographic data for the sample of mothers ($n = 427$) and fathers ($n = 170$).

	Mothers ($n = 427$)	Fathers ($n = 170$)	Comparison
	M (SD)	***M (SD)***	
Parental age (age)	30.80 (4.56)	33.19 (5.63)	**$t_{(595)} = 4.94$, $p = 0.000$**
Infant age (months)	6.55 (3.23)	6.15 (3.32)	$t_{(595)} = -1.34$, $p = 0.172$
	***n* (%)**	***n* (%)**	
Marital status			
Married or cohabiting	422 (98.8)	170 (100.0)	$\chi^2_{(1)} = 0.85$,
Separated/divorced/single	5 (1.2)	0 (0)	$p = 0.3579$
Education			
Secondary school	107 (25.1)	54 (31.8)	$\chi^2_{(2)} = 3.76$, $p = 0.1529$
College	62 (14.5)	27 (15.9)	
University or higher	258 (60.4)	89 (52.3)	
Socioeconomic status			
Below average	54 (12.7)	21 (12.4)	$\chi^2_{(2)} = 0.60$,
Average	214 (50.1)	80 (47.0)	$p = 0.7420$
Above average	159 (37.2)	69 (40.6)	
Place of living			
Village	74 (17.3)	29 (17.1)	**$\chi^2_{(2)} = 7.57$,**
City (<100,000 citizens)	155 (36.3)	43 (25.3)	**$p = 0.0228$**
City (more than 100,000 citizens)	198 (46.4)	98 (57.6)	
Number of children			
One	252 (59.0)	105 (61.8)	$\chi^2_{(2)} = 1.69$,
Two	119 (27.9)	39 (22.9)	$p = 0.4296$
Three or more	56 (13.1)	26 (15.3)	
Psychiatric heredity[a]	55 (12.9)	13 (7.7)	$\chi^2_{(1)} = 2.80$, $p = 0.0942$
Psychiatric treatment[a]	26 (6.1)	3 (1.8)	**$\chi^2_{(1)} = 4.03$, $p = 0.0447$**

[a]*Answer "yes". Bold font indicates statistical significance.*

Instruments

Edinburgh Postnatal Depression Scale [EPDS; (53)] is a self-report measure of depression symptoms after childbirth. It consists of 10 items with four options different for each item, rated from 0 to 3, out of which seven items are reversely scored. The total possible score ranges from 0 to 30. A higher score indicates a higher level of depression symptoms, and the recent individual patient data meta-analysis established 11 as a cut-off score (54). The EPDS was previously translated and validated in the Croatian perinatal population with a one-factor structure and Cronbach $\alpha = 0.86$ (55). In the current study, McDonald's ω coefficient was 0.86, respectively.

Depression, Anxiety, and Stress Scale [DASS-21; (56)] is a self-report measure with three subscales for depression, anxiety and

stress symptoms presented during the previous week. Each item was rated on a four-point scale (0—*Did not apply to me at all* to 3—*Applied to me very much or most of the time*). The scale was translated to Croatian (57). In the current study, a short version with 21 items (7 per subscale) was used, where the final score for each subscale is multiplied by 2 to be comparable to the full scale with a possible range from 0 to 42 where a higher score indicates a higher level of symptoms (56). The anxiety and stress subscales were used in the current study, with McDonald's ω coefficient of 0.84 and 0.88, respectively.

Maternal Infant Responsiveness Instrument [MIRI; (36, 58)] is a self-report measure of maternal responsiveness to the infant cues and perception of infant's response. The MIRI consists of 22 items rated on a 5-point scale (1—*strongly disagree* to 5—*strongly agree*), where a higher score indicates higher responsiveness. Six items are reversely scored. In the original study, a total score was calculated as a unidimensional construct, and the Cronbach's was α = 0.87–0.89 (36, 58). The MIRI was previously also administered in fathers, with = 0.88 (59). In the current study, to be comparable to both mothers and fathers, we excluded three items referring to the feeding items (e.g., *I believe I know when my baby wants me to feed him/her*). The CFA showed poor fit with the one-factor model [$\chi^2_{(152)} = 1624.12$, $p < 0.001$; $\chi^2/df = 10.69$, RMSEA = 0.127, SRMR = 0.100, CFI = 0.803]. Therefore, exploratory factor analysis was performed where the scree plot indicated two factors: positively framed items loaded onto one factor (Responsiveness) and reversely coded items loaded on the second (Non-responsiveness). The CFA was re-run testing the two model with better fit [$\chi^2_{(151)} = 857.05$, $p < 0.001$; $\chi^2/df = 5.68$, RMSEA = 0.088, SRMR = 0.064, CFI = 0.905] and showed non-significant correlation between the subscales ($r = -0.03$, $p = 0.4850$). The score on the Responsiveness (13 items) and Non-responsiveness subscale (6 items) could range from 13 to 65 and 6 to 30, respectively. Items on the Non-responsiveness scale remained reversely coded. Hence, a higher score on this subscale indicates a higher Non-Responsiveness (exemplary item: *I believe my baby wants me to touch her/him too often*). The McDonald's ω coefficient of internal consistency + was 0.96 for the Responsiveness and 0.77 for the Non-responsiveness.

City Infant Face Database [CIFD; (38)] is a set of 154 black-and-white photographs of infant emotional expressions. Photos were collected from infants varied in sex, age (1–12 months), and cultural background where infants express different emotional states, from positive (smiling and laughing), neutral to negative (sad, angry, scared etc.). In this study, we used a previous selection of 139 photographs validated in the sample of Croatian mothers, fathers, and students (60). In the current study, each participant rated the infant expression on 20 randomly chosen photographs (*negative*, *neutral,* or *positive*). The correct answer was scored with 1 point, so the total possible score ranged from 0 to 20.

Postpartum Bonding Questionnaire [PBQ; (40)] is a self-report measure of difficulties in the maternal-infant relationship and has been validated in the sample of mothers with different forms of maternal-infant disorders. The PBQ has 25 items rated on a 6-point scale (0—*never* to 5—*always*), with several reversely scored items, where a higher score indicates more disturbed bonding. Four subscales measure General Factor (12 items), Rejection and pathological anger (7 items), Anxiety about infant (4 items), and Incipient abuse (2 items) (40, 61). The Cronbach's α of the four factors ranged from 0.35 to 0.75 and was 0.78 for the total scale (40). The PBQ was validated in a large sample of Croatian mothers and fathers, where modified 20-item scale showed the excellent fit of both three-factor and one-factor structure: Impaired bonding (10 items, α = 0.94), Anxiety about care and maternal distress (6 items, α = 0.81), Lack of enjoyment and affection with infant (4 items, α = 0.77) (62). In the current study, the same three-factor structure was followed. McDonald's ω coefficient of internal consistency was 0.93, 0.94, 0.81, and 0.77 for the total scale, Impaired bonding, Anxiety about care, and Lack of enjoyment, respectively.

The sociodemographic questionnaire comprised question on age, marital status, level of education, employment status (before maternity leave for mothers), perceived socioeconomic level, and place of living. Furthermore, psychiatric history was examined. Participants could report a previous episode of depression or changed mood (*no; yes, shorter than 2 weeks; yes, longer than 2 weeks*), receiving psychiatric treatment (*yes, no*), and psychiatric heredity in the family (*yes, no*). A final set of questions referred to the pregnancy and the infant regarding the number of children, having twins from the last pregnancy, the infant age, and sex.

Procedures

The study was conducted following Helsinki 1964 Declaration. The Ethical Committee of the Catholic University of Croatia granted the ethical approval for the research. This cross-sectional study was conducted online via Google Forms with separate links for mothers and fathers. It was advertised on social networks (Facebook groups for parents) and shared through personal communication. The data were collected from May 2018 to May 2019. Each participant read the informed consent and by clicking the "Next" button gave their consent to participate in the study. It took ∼20 min to fill in all the questionnaires.

Statistical Analysis

Samples of mothers and fathers were compared in sociodemographic and psychological variables using the *t*-test and χ^2-test (with Yates' correction when necessary) with SPSS Statistics 21.0 for Windows and GraphPad Prism version 9.0 for χ^2-test. Correlations between the studied variables were examined using the Pearson *r* correlation coefficient. The factor structure of the examined constructs was examined by confirmatory factor analysis (CFA) by MPlus 8.2 software or exploratory factor analysis (Principal Axis Factoring) when necessary.

All variables were normally distributed with skewness and kurtosis index (**Table 2**) within the suggested 3 and 10, respectively (63), except for the parent-infant bonding. Data on Impaired bonding (PBQ1) and Lack of enjoyment and affection with infant (PBQ3) exceeded both skewness index above 3 and kurtosis index above 20, which indicate serious non-normality (63).

TABLE 2 | Descriptive data for psychological variables with comparison between mothers ($n = 427$) and fathers ($n = 170$).

	Possible range	Sample	Observed range	*M*	*SD*	Skewness	Kurtosis	Comparison	Effect size
1. Depression symptoms	0–30	Mothers	0–24	7.04	4.72	0.88	0.87	**$t_{(595)} = -2.99$,**	$r = 0.12$
		Fathers	0–20	5.78	4.52	0.93	0.40	**$p = 0.003$**	
2. Anxiety	0–42	Mothers	0–34	3.47	5.51	2.37	6.49	$t_{(595)} = 0.69$,	$r = 0.03$
		Fathers	0–32	3.51	5.95	2.47	6.92	$p = 0.945$	
3. Stress	0–42	Mothers	0–38	9.18	7.96	0.97	0.79	**$t_{(595)} = -2.12$,**	$r = 0.09$
		Fathers	0–36	7.65	7.83	1.18	1.12	**$p = 0.035$**	
4. Responsiveness	13–65	Mothers	27–65	59.83	8.09	−2.06	3.20	**$t_{(595)} = -5.55$,**	$r = 0.22$
		Fathers	25–65	55.69	8.53	−1.36	1.46	**$p = 0.000$**	
5. Non-responsiveness	6–30	Mothers	6–26	11.04	4.37	0.86	0.07	**$t_{(595)} = 2.91$,**	$r = 0.12$
		Fathers	6–26	12.18	4.14	0.71	0.28	**$p = 0.004$**	
6. Facial expression recognition	0–20	Mothers	5–20	16.52	2.52	−1.59	3.42	$t_{(595)} = 0.45$,	$r = 0.02$
		Fathers	6–20	16.62	2.45	−1.72	3.99	$p = 0.655$	
7. PBQ 1	0–50	Mothers	0–50	2.78	6.12	5.25	32.15	$t_{(595)} = -0.63$,	$r = 0.03$
		Fathers	0–50	2.41	6.98	5.46	31.54	$p = 0.527$	
8. PBQ 2	0–30	Mothers	0–28	4.81	4.14	1.96	6.55	$t_{(595)} = 0.34$,	$r = 0.01$
		Fathers	0–30	4.94	4.69	2.56	9.91	$p = 0.737$	
9. PBQ 3	0–20	Mothers	0–20	0.77	1.85	5.35	40.59	**$t_{(595)} = 2.91$,**	$r = 0.12$
		Fathers	0–16	1.35	2.32	3.31	15.14	**$p = 0.004$**	
10. PBQ total scale	0–100	Mothers	0–95	8.35	10.58	4.19	24.05	$t_{(595)} = 0.35$,	$r = 0.01$
		Fathers	0–88	8.70	12.20	4.33	22.81	$p = 0.730$	

PBQ—Postpartum Bonding Questionnaire: PBQ1—Impaired bonding; PBQ2—Anxiety about care and parental distress; PBQ3—Lack of enjoyment and affection with infant. Bold font indicates statistical significance.

Path analysis of the associations between parental mental health (depression and anxiety), parental sensitivity, and bonding (three aspects) was performed in MPlus 8.2. The maximum likelihood estimation with robust standard errors—the MLR estimator—was used as this procedure takes into account non-normality induced bias in the standard errors (64, 65). The goodness of fit was evaluated by several indices χ^2-test, Root Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual (SRMR), and Comparative Fit Index (CFI). Acceptable model fit is indicated when RMSEA and SRMR values are below 0.08, and CFI values are above 0.90 (66), while a very good fit is displayed when the RMSEA is below 0.06, SRMR is below 0.08, and CFI values are above 0.95 (67). Reliability of measures was calculated as the internal consistency via McDonald ω coefficient, as a better alternative to Cronbach α (68) using the OMEGA macro for SPSS (69). Sample size calculation was performed as per the general rule of thumb to have at least 50 participants per variable in the path analysis and to have a medium sample size of 100–200 per group (70). Given that nine variables were examined, at least 450 participants were necessary, which was exceeded with 597 participants, out of which 170 were fathers.

RESULTS

Descriptive Data

Descriptive data for all psychological variables is presented in **Table 2**. A somewhat reduced range was obtained for depression and anxiety in both mothers and fathers. However, 20.8% of mothers and 14.7% of fathers reported depression symptoms above the proposed cut-off of 11 on the EPDS (54). A full range of observed data was obtained for bonding scores, and the almost whole possible range was obtained for responsiveness and facial expression recognition. The scores were compared between mothers and fathers, showing that mothers reported higher depression symptoms, stress, responsiveness, and a lower level of non-responsiveness. On the other hand, fathers expressed more inferior bonding in the Lack of enjoyment and affection with the infant. However, all effects were small (**Table 2**).

Associations Between Examined Variable

Very similar patterns of associations were established for mothers and fathers (**Table 3**). Higher levels of depression symptoms were associated with higher anxiety and stress levels in both samples with modest correlations. Also, in both mothers and fathers, higher parental mental health difficulties (depression, anxiety, and stress) were related to poor bonding but with small correlations. Further, higher levels of mental health difficulties were associated with lower responsiveness and higher non-responsiveness. Facial expression recognition was not related to parental mental health or responsiveness. However, it had a slight negative correlation with non-responsiveness, indicating that poor facial expression recognition was associated with higher non-responsiveness. Also, poor facial expression recognition was related to a Lack of enjoyment and affection with the infant, in mothers only, but with a small correlation.

TABLE 3 | Pearson's correlation coefficients between psychological variables in mothers ($n = 427$, above diagonal) and fathers ($n = 170$, below diagonal).

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Depression symptoms	–	0.57**	0.67**	−0.17**	0.30**	−0.03	0.21**	0.40**	0.14**
2. Anxiety	0.60**	–	0.66**	−0.13**	0.17**	−0.07	0.16**	0.27**	0.09
3. Stress	0.69**	0.70**	–	−0.10	0.21**	0.03	0.21**	0.43**	0.15**
4. Responsiveness	−0.16*	−0.16*	−0.17*	–	0.02	0.07	−0.30**	−0.33**	−0.30**
5. Non-responsiveness	0.37**	0.44**	0.37**	0.00	–	−0.11*	0.09	0.27**	0.02
6. Facial expression recognition	0.08	−0.03	0.11	0.10	0.09	–	0.11*	−0.06	−0.17**
7. PBQ 1	0.30**	0.29**	0.20*	−0.39**	0.18*	−0.08	–	0.70**	0.52**
8. PBQ 2	0.40**	0.31**	0.35**	−0.42**	0.26**	0.05	0.83**	–	0.46**
9. PBQ 3	0.23**	0.29**	0.29**	−0.25**	0.29**	0.06	0.34**	0.35**	–

*$p < 0.05$ and **$p < 0.01$. PBQ—Postpartum Bonding Questionnaire: PBQ1—Impaired bonding; PBQ2—Anxiety about care and parental distress; PBQ3—Lack of enjoyment and affection with infant.*

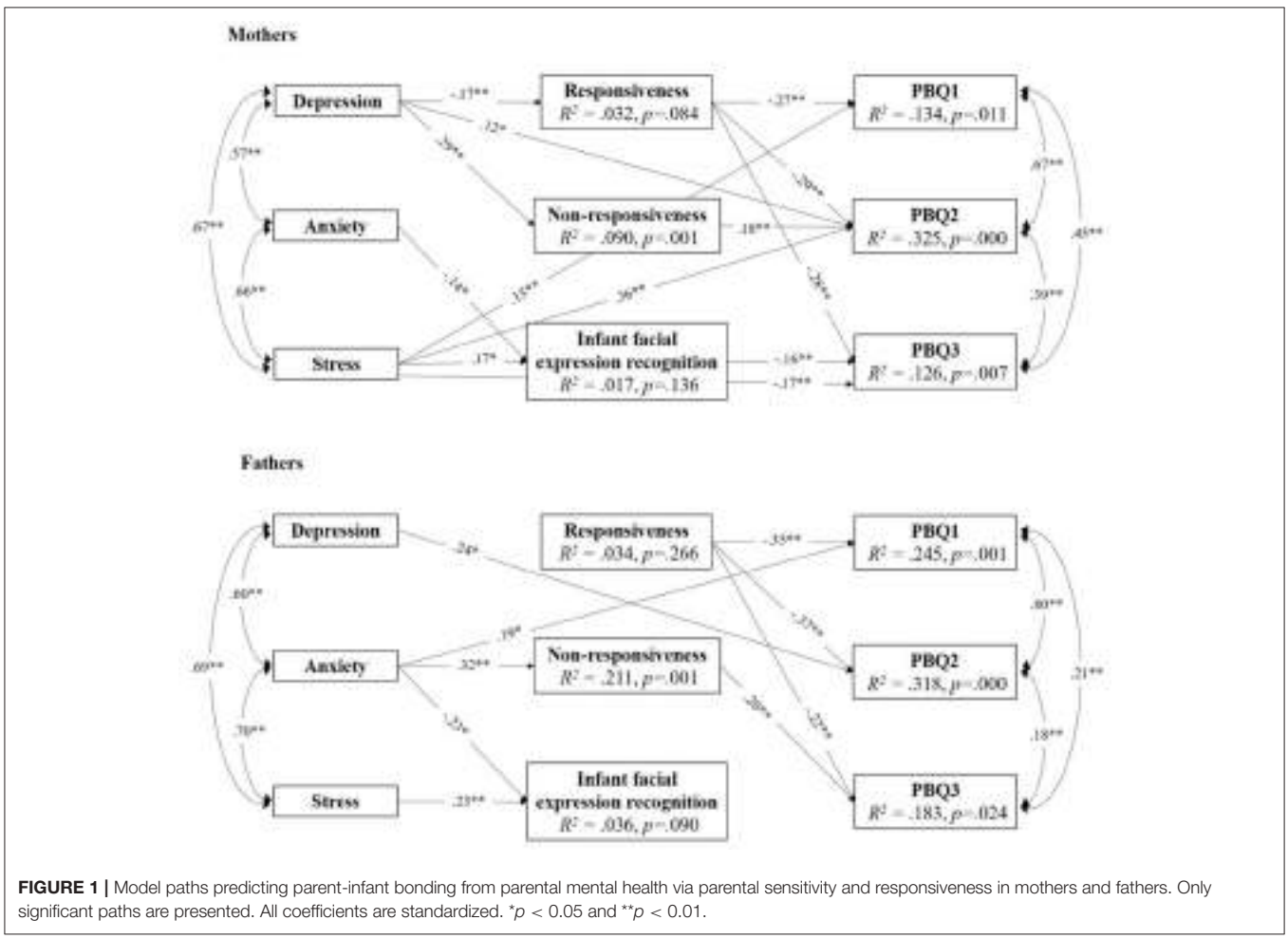

FIGURE 1 | Model paths predicting parent-infant bonding from parental mental health via parental sensitivity and responsiveness in mothers and fathers. Only significant paths are presented. All coefficients are standardized. *$p < 0.05$ and **$p < 0.01$.

Parental Sensitivity and Responsiveness as Mediators

The model of parental sensitivity as a mediator between parental mental health and bonding was tested. Depression symptoms, anxiety, and stress were entered as predictors; responsiveness, non-responsiveness, and facial expression recognition were entered as mediators; and three aspects of bonding were entered as the outcome. All possible direct and indirect effects were defined in the model. The model was saturated with excellent fit to the data [$\chi^2_{(6)} = 14.47$, $p = 0.0248$; $\chi^2/df = 2.41$, RMSEA = 0.069, SRMR = 0.021, CFI = 0.989].

The parental sex was examined as the moderator in the model. This was tested with the nested model with specified parameters set to be equal between mothers and the fathers [$\chi^2_{(48)} = 117.77$,

$p < 0.0001$; $\chi^2/df = 2.45$, RMSEA = 0.070, SRMR = 0.062, CFI = 0.906]. This model was significantly different from the initial model [Satorra-Bentler Scaled χ^2 difference was SBS-$\chi^2_{(42)} = 103.26$, $p < 0.0001$; CD = 1.1766], indicating that the parental sex was a significant moderator. Thus, different paths were established in mothers and fathers (**Figure 1**).

In mothers, responsiveness was a significant mediator between postpartum depression symptoms and all three bonding dimensions (**Table 4**). Namely, higher levels of depression symptoms were associated with lower levels of responsiveness, which was, in turn, associated with Impaired bonding, Anxiety about care and maternal distress, and Lack of enjoyment and affection with the infant. Furthermore, non-responsiveness was a significant mediator between maternal depression and one aspect of bonding. More specifically, higher levels of depression were associated with higher levels of non-responsiveness, which was, in turn, related to poor bonding concerning Anxiety about care and maternal distress.

In fathers, the only significant indirect path was for non-responsiveness. Higher levels of anxiety were associated with higher levels of non-responsiveness, which was, in turn, related to poor father-infant bonding concerning Lack of enjoyment.

Finally, facial expression recognition did not mediate mental health and bonding in mothers or fathers. Nevertheless, it did directly affect bonding in mothers so that mothers who were less accurate at recognition reported higher levels of Lack of enjoyment and affection with baby. Also, even though anxiety and stress did not correlate with infant facial expression recognition in mothers or fathers, in the model, these direct effects were significant, indicating possible suppressor effect (71, 72). Direct effects from parental mental health on all three dimensions of bonding were established (**Figure 1**). However, it is interesting to note that anxiety did not directly affect bonding concerning the Anxiety about care. Also, responsiveness had a direct effect on all dimensions of bonding, both in mothers and fathers.

TABLE 4 | Model estimates of multigroup path analysis: Depression symptoms and anxiety on bonding via responsiveness and facial expression recognition ($N = 603$).

	Mothers			Fathers		
	Path estimates	SE	*p*	Path estimates	SE	*p*
Indirect effects via responsiveness						
Depression → PBQ1	**0.05**	**0.02**	**0.038**	0.02	0.04	0.592
Depression → PBQ2	**0.05**	**0.02**	**0.020**	0.02	0.04	0.592
Depression → PBQ3	**0.05**	**0.02**	**0.043**	0.01	0.03	0.603
Anxiety → PBQ1	0.02	0.02	0.340	0.02	0.04	0.527
Anxiety → PBQ2	0.02	0.02	0.329	0.03	0.04	0.529
Anxiety → PBQ3	0.02	0.02	0.339	0.02	0.03	0.532
Stress → PBQ1	−0.02	0.02	0.377	0.03	0.04	0.528
Stress → PBQ2	−0.02	0.02	0.365	0.03	0.05	0.523
Stress → PBQ3	−0.02	0.02	0.372	0.02	0.03	0.526
Indirect effects via non-responsiveness						
Depression → PBQ1	0.01	0.02	0.386	0.01	0.02	0.541
Depression → PBQ2	**0.05**	**0.02**	**0.004**	0.02	0.02	0.322
Depression → PBQ3	−0.01	0.01	0.664	0.03	0.03	0.211
Anxiety → PBQ1	0.00	0.00	0.908	0.02	0.04	0.489
Anxiety → PBQ2	−0.00	0.01	0.908	0.04	0.03	0.186
Anxiety → PBQ3	0.00	0.00	0.911	**0.07**	**0.03**	**0.034**
Stress → PBQ1	0.00	0.00	0.788	0.00	0.01	0.678
Stress → PBQ2	0.00	0.02	0.775	0.01	0.01	0.666
Stress → PBQ3	0.00	0.00	0.811	0.01	0.02	0.669
Indirect effects via facial expression recognition (CIFD)						
Depression → PBQ1	0.01	0.01	0.468	−0.00	0.01	0.652
Depression → PBQ2	0.00	0.00	0.615	0.00	0.01	0.639
Depression → PBQ3	0.01	0.01	0.387	0.00	0.01	0.666
Anxiety → PBQ1	0.01	0.01	0.313	0.01	0.01	0.494
Anxiety → PBQ2	0.01	0.01	0.564	−0.01	0.02	0.474
Anxiety → PBQ3	0.02	0.01	0.074	−0.01	0.02	0.473
Stress → PBQ1	−0.02	0.01	0.286	−0.01	0.02	0.526
Stress → PBQ2	−0.01	0.01	0.552	0.01	0.02	0.450
Stress → PBQ3	−0.03	0.02	0.077	0.01	0.02	0.448

Standardized coefficients are presented. SE, standard error; PBQ—Postpartum Bonding Questionnaire: PBQ1—Impaired bonding; PBQ2—Anxiety about care and parental distress; PBQ3—Lack of enjoyment and affection with infant. Bold font indicates statistical significance.

DISCUSSION

There was a lack of studies looking into the role of maternal sensitivity for mother-to-infant bonding in the literature, and even more, there was a neglect of fathers. Therefore, this study aimed to examine parental sensitivity as a mediator in the relationship between parental mental health and parent-infant bonding in both mothers and fathers. The model had a good fit to the data, and parental responsiveness was a significant mediator between postpartum mental health and bonding quality. However, different paths were established for mothers and fathers, which will be discussed further.

First, parental sensitivity in the current study was measured by a self-report measure of responsiveness as one aspect of sensitivity (5) and an objective measure of infant facial expression recognition. Also, before going further, it should be noted that the Maternal Infant Responsiveness Instrument was previously used as a unidimensional measure (34–36, 58, 59) without questioning its factor structure. However, the initial psychometric evaluation in the current study showed a poor fit of the unidimensional model to the data. This secondary finding highlights the need for psychometric testing of instruments at each administration. Namely, psychometric properties are not fixed characteristics of the instrument, as they also reflect the sample characteristics and administration circumstances (73). The two-factor structure of the MIRI had a better fit and resulted in subscales of responsiveness and non-responsiveness. These two were mutually uncorrelated, indicating that the non-responsiveness subscale is not a mere negative pole of responsiveness. Moreover, non-responsiveness taps different responsiveness aspects, reflecting fear of taking care of the infant and appraisals of the infant as being too demanding. Furthermore, it was interesting that these two subscales had

a unique role in the relationship between mental health and bonding in mothers and fathers.

In mothers, responsiveness was a significant mediator between depression symptoms and bonding. Higher levels of depression symptoms were associated with lower levels of responsiveness, which was, in turn, related to poor bonding on all three dimensions, i.e., Impaired bonding, Anxiety about the care, and Lack of enjoyment with the infant. In fathers, responsiveness was not a significant mediator between mental health and bonding. However, non-responsiveness was a significant mediator both for mothers and fathers. Despite specific differences in the patterns of mediational pathways, we can summarize that both for mothers and fathers, (non)responsiveness has an important role in the shape of parent-infant bonding.

These findings are somewhat difficult to relate to previous research on bonding, as these constructs have not been examined all together in a mediational model, especially not in fathers. However, previous studies demonstrated an adverse effect of maternal depression symptoms on maternal sensitivity (33) and maternal responsiveness (34). On the other hand, it is not easy to compare findings on parental sensitivity and parent-infant bonding, as previous studies have mainly investigated maternal sensitivity observationally with infant-mother attachment (1, 6, 7). The same goes for examining the relationship between responsiveness and mother-infant bonding. However, Tester-Jones et al. (35) did investigate depression symptoms, maternal responsiveness, and bonding, but they did not relate these constructs in the same model but on the bivariate level. They did show that maternal depression was associated with lower levels of responsiveness and bonding, and these relationships were mediated by infant temperament.

On the other hand, another study did not show an association between maternal depressive symptoms and responsiveness but found a more dominant role of stress for responsiveness (36). However, the latter finding comes from a small sample of mothers with preterm babies who have specific childbirth and postpartum experience. It is known that mothers with preterm delivery are at higher risk of posttraumatic stress disorder following birth (74), which is, in turn, associated with impaired bonding in mothers (75).

The ability to recognize infant facial expressions was previously suggested to reflect maternal sensitivity (38). However, the mediational role of infant facial expression recognition was not established in the current study, either for mothers or fathers. It was expected that depression symptoms would be associated with facial expression recognition, but this was not evident. This finding was unexpected as previous studies showed that depressed mothers were less likely to identify happy infant faces (76) and rated negative infant faces more negatively (39). Different attentional processing of positive and negative infant emotions associated with depression symptoms was evident even during pregnancy (77, 78). A similar effect of depression was demonstrated in fathers, as well. A recent study showed that depressed fathers recognized happy faces with more difficulty but negative faces more easily, which, in turn, affected negatively on the father-infant interaction (79). On the other hand, some studies did not show attentional bias toward negative infant faces in mothers with affective disorders (80). So, the infant facial expressions recognition remains to be demonstrated as a measure of maternal sensitivity to infant's cues and its role in predicting parent-infant bonding.

The findings of this study have several implications for clinical practice. First, the study highlights the need for screening for a wide range of mental health difficulties. In addition to depression symptoms that most screening attempts are focused on (81), anxiety and stress also contributed to parental sensitivity and parent-infant bonding. Also, the screening should be applied to both mothers and fathers (82, 83). Because of the contributing effect of the partner depression (84), both parents can get into a vicious circle of depression, where a parent has a higher probability of developing depression symptoms if their partner also shows depression symptoms. Also, fathers should be provided with the same opportunities in the (prenatal) classes as mothers have to learn about newborn care, parenting sensitivity, and parent-infant bonding. Bonding between fathers and infants is a process that develops over the first year of the infant's life, as shown in the meta-synthesis of paternal experiences (43). The process progresses by getting to know the infant and having physical contact and interaction with the infant, which is especially rewarding for fathers. Therefore, courses for paternal engagement and enhancement in bonding should encourage fathers to take care of infants, play with them, or simply hold them. As they may feel the lack of knowledge and skills in infant care, they should be taught about this in (prenatal) classes and supported by their spouses, as fathers found their partners' support very encouraging (43). Particular focus should be on fathers whose infants are breastfed, as they may feel excluded and may need some additional time to catch up with their infant. Also, concerning the parental role in fathers, future studies should shift more from mere involvement, i.e., quantity, to the father-child relationship quality (42). Furthermore, sensitive parenting should be promoted to ensure a safe environment that is supportive and stimulating for the child development. Parents should comfort the child and provide a secure base for their exploration and autonomy (41, 42).

Several limitations of the study should be discussed. First, this sample of mothers and fathers was a non-clinical sample. Therefore, other possible conclusions could be withdrawn if the sample included parents with clinical depression, anxiety, or a bonding disorder. Nevertheless, at least one part of the parents from the sample struggled with depression symptoms, as one in five mothers and one in six fathers reported clinically significant depression symptoms. Furthermore, the sample was recruited online via social network groups for parents, so one can argue that this sample is self-restricted. Indeed, the sample was urban, highly educated; almost all parents were married or cohabiting, with the majority reporting average to above-average socioeconomic status. As they have decided to participate in this study, they were probably interested in content about parenting and more engaged in their parental role. The sample of fathers was smaller than the sample of mothers; therefore, future studies would benefit from including the larger samples of fathers in order to replicate these findings. Also, the cross-sectional design was applied so one can speculate that different directions of

associations could work as well. For instance, Brockington et al. (40) highlighted that depression in mothers could be caused or exaggerated by bonding problems. Although the model has a solid theoretical background, it was not previously tested for bonding, and future studies should confirm the model in longitudinal studies. Maternal interpersonal sensitivity measured during pregnancy was a stronger predictor of the mother-infant interaction quality than perinatal depressiveness (85), so it would be beneficial to measure maternal sensitivity even during pregnancy.

In this study, the role of anxiety for responsiveness and bonding was found only in fathers. However, it should be noted that a general measure of anxiety (DASS-21) was used in this study, which mainly covers somatic symptoms. Recent research has shown that anxiety specific for the postpartum period has a predictive value for bonding over general measures (86). Future studies could benefit from applying specific measures of anxiety that grasp the parental perinatal experience with more focus. Also, it should be noted that bonding was measured up to 12 months of the infant's age (with a mean at 6 months). However, the PBQ was designed for use in the early postpartum period (40, 61), and it has been mostly used and validated within the first 3 months after childbirth (87–90). Nevertheless, some other studies applied the PBQ within the first postpartum year [e.g., (91, 92)]. Still, the factor structure and reliability across the first year postpartum should be examined in future studies. Furthermore, the infant facial recognition task included the recognition of unknown infant faces. As postpartum mothers have specific dopaminergic reward-related brain network activation when viewing their infants compared to unknown infant's faces (93), future studies should preferably include expressions of their infant.

Finally, it should be noted that the examined set of variables explained up to 32% of the parent-infant bonding variance. It means that two-thirds of the variance remains unexplained, and future studies should include other variables into the model. A recent cross-sectional study showed the interrelation of maternal mental health and bonding with perceived infant temperament (94). Infant temperament has been shown to affect the parent-infant bonding in a prospective study in mothers and father (95, 96). It also mediates the relationship between maternal depression and responsiveness (35) and might have a more substantial effect on infant-mother attachment than maternal sensitivity (97).

Also, previous studies have established the association between breastfeeding and maternal sensitivity. Longer breastfeeding was associated with higher maternal sensitive responsiveness levels during infancy (98) and even increased maternal sensitivity in middle childhood (99). Nevertheless, in the current study, different infant feeding methods were not considered as we wanted to test the same model in both mothers and fathers. The study's strength is including both parents, and further studies should focus on fathers in more depth. Also, future studies would benefit from pairing mothers and fathers so the dyadic relationships within the couple can be examined. A dyadic analysis on first-time parents revealed that postpartum depression levels are affected by own anxiety and parenting stress and partners' depression in both mothers and fathers (84). A recent study showed that mother-infant bonding contributes to father-infant bonding (51), and dyadic relationships of parental mental health and bonding should be further examined. Finally, some more stable characteristics, such as life satisfaction and self-esteem, seem to be more important predictors of maternal responsiveness (58), so the range of examined variables could be expanded.

To conclude, the current study showed that responsiveness has an important mediational role in the relationship between parental mental health and parent-infant bonding, both for mothers and fathers. This finding fits into Shin et al.'s (5) conceptual analysis of maternal sensitivity affected by maternal mental health. The model can be extended to apply not only for attachment as an infant-to-mother relationship but also to bonding as a mother-to-infant relationship and for fathers. However, theoretical and empirical work is needed to provide a solid theoretical basis for future studies on parent-infant bonding. It could have a crucial impact on developing interventions for parents and infants to alleviate mental health problems and their reflection on the bonding issues. A promising early intervention for reinforcing maternal sensitivity, especially in women with psychosocial vulnerability, has been tested recently (100). Future studies should continue developing such programs to help parents enjoy this transition to parenthood and provide safe and warm family relations for the growth of the child.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Catholic University of Croatia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SNR devised the main conceptual idea, supervised the project, performed the analysis, and wrote the manuscript.

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BRIEF RESEARCH REPORT
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Maternal Perceptions of Infant Behavior as a Potential Indicator of Parents or Infants in Need of Additional Support and Intervention

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The goal of the present study is to examine the relationship between early infant behaviors, which can be easily reported by parents, with parent-infant bonding and maternal mental health. It has long been established that child characteristics and behaviors have a significant impact on parent well-being and how parents respond to their infants. Examining parent perceptions of challenging infant behaviors may help health professionals identify high risk infants in need of intervention and mothers in need of additional support. Mothers of 73 infants between the ages of 3.5 weeks and 6 months filled out questionnaires. Infant stomach issues were positively correlated with bonding issues, maternal anxiety and maternal depression. Infant crying issues were also positively correlated with bonding issues, maternal anxiety and maternal depression. Potential clinical and research applications of the instrument include early identification of caregivers in need of support and screening for further clinical assessment and care.

Keywords: infant behavior, parenting, infant risk, infant-parent bonding, parent-child bonding

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INTRODUCTION

Mothers are most often the primary caretakers for their young infants, yet little is known about how they perceive common challenging behaviors. It has been established that child characteristics and behaviors have a significant impact on parent well-being and, consequently, on how parents respond to their infants (1–3). Currently, hospital and community-based interventions target parents who are deemed to be at-risk due to specific risk factors such as parental age and rarely rely on parent perception of infant behavior to triage parents for professional help or intervention. Examining parent perceptions of challenging infant behaviors may help health professionals identify high risk infants in need of intervention and parents in need of additional support. Such efforts are needed to decrease the adverse impact of normative stressors on parent-child relationships and so that interventions can be more targeted, cost-effective, efficient and potentially more beneficial to the parent-child relationship, attachment quality and later infant outcomes.

Early infant behavior is important because it relates to infant-parent attachment and is predictive of behavior throughout life (4). Research evidence suggests that infant behaviors are related to maternal risk of postpartum depression. To this point, qualities of the infant, such as prolonged, excessive or inconsolable crying (5, 6) increase a mother's risk of postpartum depression, something

that impacts roughly 14.5 percent of new mothers within the first 14.5 months of giving birth (7) and has adverse effects on the parent-child relationship (8). Maternal mental health can also impact infant behavior. To this point, postpartum depression impacts infant development across a variety of domains including motor development and cognitive development (9).

Difficulties with infant feeding are highly correlated with crying and are often encompassed within the working definition of an infant with "colic" (10). Less frequently studied infant behaviors that are nonetheless encompassed in many parents' working definition of a "difficult" infant include how good of a sleeper and eater the infant is. Infants who have difficulty with these early self-regulatory behaviors (i.e., crying, sleeping and feeding) are at risk for adverse outcomes later in life (11), suggesting the need for further research into these behaviors. To this point, the volume and timing of infant sleep is one of the most important infant behaviors to new parents (12). However, the above outlined behaviors do not occur in isolation, and each may impact multiple areas of functioning. For example, feeding an infant at night has been shown to create sleeping problems (13–15), and sleeping problems have been associated with stomach aches in young children (16). Stomach issues are noted in research as one of the leading reasons that new parents take children to the doctor outside of routine visits (17). Taken together, these early infant behaviors (i.e., crying, eating, sleeping and stomach issues) are areas of both explicit and implicit concern for parents.

Infant crying is a normative behavior that has been found on average to occur for just over 2 hours per day for infants between 1 and 3 months and about 1 hour per day for infants between 4 and 6 months (18). Concern over infant crying emerges when the crying is excessive as it is associated with maternal depression (19) and increased risk of harm to the infant. For example, infant crying has been implicated as a behavior that could provoke infant shaking by parents (20), increasing risk for injuries such as Shaken Baby Syndrome (SBS).

It is important for clinicians to quickly gather information from parents about their areas of concern related to their infant's behavior.

Existing interventions in the newborn period might benefit from more specified targeting within the population level that is similar to the screenings that are currently implemented in the area of postpartum depression—with assessments that quickly gather information and triage parents to more support. The purpose of this study is to demonstrate that parental perceptions of infant behavior are related to parent bonding and parent well-being. Our hypothesis is that parental belief that their child is having trouble in an area such as crying, eating, sleeping and stomach issues will be correlated with worse outcomes such as impaired bonding or heightened parental depression or anxiety.

MATERIALS AND METHODS

Participants

Seventy-three mothers of infants between the age of 3.5 weeks and 6 months (characteristics of the sample outlined in **Table 1**) were included in the study. Parents filled out questionnaires on anxiety, depression, infant bonding and infant behaviors as part of a larger cross-sectional study investigating the impact of participation in infant floating classes on parent mental health, bonding and infant behavior. Infant floating classes involve placing a flotation device around an infant's neck so that the infant can float in a tub of water and kick their feet. There were no significant differences in any measures across whether parents participated in floating classes with their infants; however, whether or not parents participated in floating classes is included in all analyses to control for any effect of group status on results. The sample was originally 74 parents, but only one father participated in the study. Due to the small sample of fathers, the father was dropped from the sample.

TABLE 1 | Demographics of sample ($n = 73$).

Variables	% (SD)
Parent Sex	
Female	73
Parent Age	32.03 (4.51)
Child Sex	
Male	43
Female	31
Child age in months	3.65 (1.55)
Race	
White	54
African American	3
Asian	8
Multi-racial	6
Not reported	2
Hispanic/Non-hispanic	15/58
Relationship Status	
Single, never married	3
Married	65
Separated	1
Relationship, living together	4
Yearly Household Income	
Less than $50,000	14
$50,000–100,000	10
Above $100,000	49
Highest Education	
High school	2
Some college, no degree	15
College degree	31
Advanced degree	25

Procedures

Participants were recruited through a local infant floating facility in Houston, TX as well as through online postings on Facebook©. Participants completed initial questions to confirm eligibility online, including being a parent of an infant between the ages of 3.5 weeks and 6 months old. Participants were prescreened and excluded from the study if they self-reported that infant had any known health issues that might interfere with the child's

TABLE 2 | Original items in BABI infant behavior scale.

Cry Items	
Cry_1_Reversed	How much does your baby cry?
Cry_2_Reversed	How often does your baby cry?
Cry_3_Reversed	How intensely does your baby cry?
Cry_4_Reversed	How easily is your infant comforted by you when he/she cries?
Eat Items	
Eat_1_Reversed	How satisfied are you with the amount your baby eats?
Eat_2_Reversed	How satisfied are you with how often your baby eats?
Eat_3_Reversed	Compared to other babies your infant's age, how much does your baby eat?
Sleep Items	
Sleep_1	How satisfied are you with your infant's sleep?
Sleep_2_Reversed	Compared to other babies your infant's age, how much does your baby sleep?
Sleep_3	Compared to other babies your infant's age, how often does your baby wake up in the middle of the night?
Sleep_4_Reversed	Compared to other babies your infant's age, how much does your baby nap?
Stomach Items	
Stomach_1	Compared to other babies your infant's age, how much reflux does your baby have?
Stomach_2	Compared to other babies your infant's age, how much gas does your baby have?
Stomach_3	Compared to other babies your infant's age, how much stomach pain does your baby have?

The eating subscale was dropped in its entirety due to issues with item normality and low inter-item correlation. Sleep_4_Reversed was removed after EFA and CFA due to low correlation with other items and lack of face validity with other items.

physical abilities. Four participants were excluded based on this prescreening. Participants were informed that they would be entered into a raffle to win three free sessions at the infant aquatic therapy facility as compensation for their participation, and informed consent was obtained through Qualtrics prior to any study activities. This study was approved by the Institutional Review Board at the University of Houston.

Measures

The Baby Actions and Behavior Index

The Baby Actions and Behavior Index (BABI) infant behavior scale measures critical domains of infant behavior: eating issues, stomach issues, crying, and sleep issues. The authors (LF and EP) created 14 questions assessing infant behavior in these domains: eating ("How satisfied are you with the amount your baby eats"), stomach issues (e.g.," Compared to other babies your infant's age, how much gas does your baby have?"), crying (e.g., "How much does your baby cry?"), and sleep issues (e.g., "Compared to other babies your infant's age, how often does your baby wake up in the middle of the night?") (see **Table 2** for full scale).

Mother-Infant Bonding Scale

Mother-Infant Bonding Scale [MIBS; (21)] is an eight-item, self-report scale assessing emotions mothers may have experienced toward their infants. This measure was designed to identify difficulties experienced by new mothers in establishing a relationship with their babies, and was intended for use in the first weeks after the child's birth through 4 months postpartum (22). Participants were asked to identify to what degree they have felt various emotions toward their infant in the past few weeks by responding on a four-point Likert scale from *very much (0)* to *not at all (3)*. Emotion prompts include "loving" [very much (0) to not at all (3)] and "resentful" [reverse scored; very much (3) and not at all (0)]; higher total scale scores indicate worse bonding. This measure has demonstrated high sensitivity in detecting bonding alterations between new mothers and their babies (23) and has evidenced moderate concurrent validity with two other measures: the Postpartum Bonding Questionnaire (24) and the Maternal Postpartum Attachment Scale (25). Reliability analyses have demonstrated a Cronbach's alpha, or internal consistency score of 0.71, evidencing acceptable reliability (21). The Cronbach's alpha for the MIBS was 0.59 in the present study.

Edinburgh Postnatal Depression Scale

Edinburgh Postnatal Depression Scale [EPDS; (26)] is a 10-item, self-report measure developed to help identify new mothers who may be at risk for postpartum depression. Research has demonstrated a potential long-term negative impact of postpartum depression on the child, including behavioral disturbances (27) and later cognitive deficits (28). This scale was created in response to research confirming that the period after childbirth is frequently characterized by some form of psychological distress for new mothers (29), and that at least 10–15% of mothers experience depression during this time (26). Participants respond to prompts about how they have felt in the past seven days on a four-point Likert scale with scores from 0 to 3 (e.g., *yes, all the time* to *no, not at all*; *yes, quite often* to *never*, etc.), and total scores range from 0 to 30. Higher scores on this scale indicate higher symptomology of depression. Item examples include "I have felt happy," "I have felt sad or miserable," and "things have been getting on top of me." Cutoff scores have previously been determined; Cox, Holden and Sagovsky identified a cutoff of 12/13 for moderate depression, which was replicated by Harris (30) (using Diagnostic and Statistical Manual of Mental Disorders-III criteria [DSM-III]) and Murray and Carothers (31) (using Research Diagnostic Criteria [RDC]). Additionally, Cox, Holden and Sagovsky recommended a cutoff score of 10 to include minor depression as well as increased sensitivity of the scale or ability to capture people with a diagnosis of depression (32). This was also confirmed by Harris (30), as well as Murray and Carothers. Previous research using a cutoff of 10 has demonstrated accurate later classification of mothers at 4 weeks later (85.4% accurately classified) and 8 weeks later (82.5% accurately classified) (33). This measure has also demonstrated satisfactory validity, split-half reliability and adequate sensitivity to changes in depression over time (26). Reliability analyses have demonstrated a Cronbach's alpha of 0.87, evidencing good reliability (26); the Cronbach's alpha in the present study was found to be 0.87.

Generalized Anxiety Disorder

Generalized Anxiety Disorder is a seven-item scale (GAD-7; 33) assessing anxiety. This measure asks participants to identify how often they have been bothered by certain problems, and participants respond on a four-point Likert scale (with scores from 0 to 3) from *not at all* to *nearly every day*. Items include "feeling nervous, anxious, or on edge" and "not being able to stop or control worrying." Scores range from 0 to 21 and higher scores on this scale indicate higher symptomology of anxiety. Scale authors suggest a cutoff point of 10 for identifying anxiety. At this cutoff, the scale has yielded a sensitivity of 89% in a primary care sample (34), and in a sample of pregnant and postpartum women, it has yielded a sensitivity of 76.0% (35). Reliability analyses evidenced a Cronbach's alpha of 0.92, demonstrating excellent reliability (34) and a Cronbach's alpha 0.91 in the present study. Additionally, this measure has been found to have found good construct as well as factorial and procedural validity (34).

Data Analysis Plan

Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were conducted to examine the validity of subscales in the BABI scale (36). This was done to ensure that the intended scales functioned as originally conceptualized before proceeding to any other analyses with the subscales. To explore our hypothesis that parental belief that their child is having trouble in an area such as crying, eating, sleeping and stomach issues will be correlated with worse outcomes such as impaired bonding or heightened parental depression or anxiety, correlations were conducted to examine the relationship between the BABI scale and important variables such as Mother-Infant Bonding, postpartum depression and anxiety. Variables were deleted listwise. Because the infants in our sample varied by almost 6 months in age, Cronbach's alphas were examined separately for all measures.

RESULTS

Exploratory and Confirmatory Factor Analyses

Prior to use of the BABI to explore our hypothesis, preliminary construct validity was established with an exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) using the Mplus statistical software [version 7.11, (37)] to ensure that subscales of the BABI measured their intended facets of infant behavior. Before conducting factor analyses, we checked the normal distribution of our items and their correlations. We found that all items were normally distributed, except for one item for eating issues, which slightly violated the normality assumption *EAT_1R*; skewness = 1.40 and Kurtosis = 1.96). In addition, the correlation between the other two items for eating issues (*EAT_2R* and *EAT_3R*) was unexpectedly small, $r = 0.16$. Due to these problems pertaining to items on eating issues, we decided to remove all three items for eating issues. There were three remaining scales: crying, sleeping and stomach issues. We also removed one item on sleeping issues (*SLEEP_4R*) due to its low correlations with other sleep items ($r = 0.13$ with *SLEEP_1* and $r = -0.04$ with *SLEEP_3*), possibly due to the fact that (*SLEEP_4R*) asks about infant napping whereas the other items (*SLEEP_1*, *SLEEP_2R*, and *SLEEP_3*) ask about general sleep behaviors. Low correlations among items led us to have a poor performance of a factor analysis (38). In the final analysis, we included 10 items: four items addressing crying issues (*CRY_1R, CRY_2R, CRY_3R,* and *CRY_4R*), three items addressing sleeping issues (*SLEEP_1, SLEEP_2R*, and *SLEEP_3*), and three items addressing stomach issues (*STOMACH_1, STOMACH_2,* and *STOMACH_3*).

TABLE 3 | Varimax-rotated factor loadings of exploratory factor analysis for the baby actions and behavior index (BABI).

	Factor 1	Factor 2	Factor 3
CRY_1R	0.89	0.07	0.10
CRY_2R	0.92	0.08	0.07
CRY_3R	0.81	0.13	−0.16
CRY_4R	0.66	−0.02	0.12
SLEEP_1	0.03	0.84	0.20
SLEEP_2R	0.18	0.86	−0.05
SLEEP_3	−0.00	0.82	0.05
STOMACH_1	0.11	0.20	0.68
STOMACH_2	−0.12	0.05	0.88
STOMACH_3	0.14	−0.06	0.90

We conducted EFA with the varimax rotation. The scree plot suggests that a three-factor model best captures the items in our scale. Additionally, the eigenvalue of the three-factor model was higher than one, whereas the eigenvalue of the four-factor model was less than one, further indicating the validity of the three-factor model. Factor loadings of the final three-factor model are presented in **Table 3**.

Due to the fact that the items were written as part of a subscale structure when the scale was originally conceptualized, we also conducted a CFA. Our CFA model result is presented in **Figure 1**. We included one correlation between residual variances for *CRY_1R* and *CRY_4R* because the modification index suggested the correlation. Furthermore, we believe that these two items are meaningfully related—infants who are harder to console when they cry will exhibit prolonged crying (i.e., cry more than other babies of the same age). The model fit was very good: $CFI = 0.970$, $RMSEA = 0.068$, and $\chi^2_{(df)} = 41.47_{(31)}$, $p = 0.099$, suggesting that our scale consists of three distinct behavioral issues found in infants. Due to this very good model fit, we did not further conduct a *post-hoc* analysis to improve our model fit.

Partial Correlations

Partial correlations between the BABI stomach issues, crying issues and sleep issues subscales and the Mother-to-Infant Bonding scale, anxiety scale, and postpartum depression scale were conducted in order to further establish construct validity (controlling for whether or not the mothers participated in floating class). Our hypothesis, that maternal belief of their child having trouble in an area such as crying, sleeping and stomach issues (*note: eating removed due to violation of the normality assumption*) will be correlated with worse outcomes such as impaired bonding or heightened parental depression or anxiety,

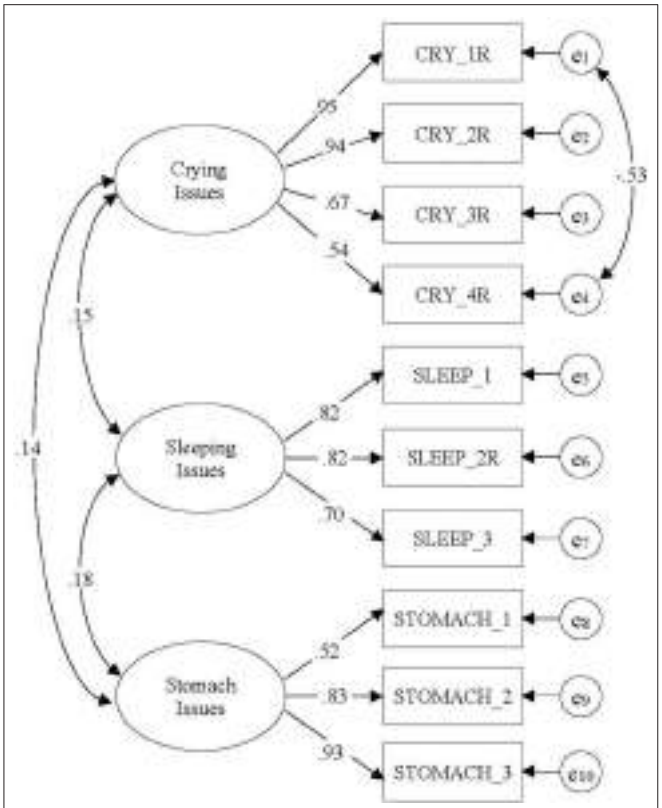

FIGURE 1 | The confirmatory factor analysis model with crying issues, sleeping issues, and stomach issues. Numbers indicate standardized factor loadings and correction coefficient. CFI = 0.970, RMSEA = 0.068, and $\chi^2_{(df)} = 41.47$ (31), $p = 0.099$.

TABLE 4 | Partial correlation coefficients among study variables.

Measure	MIBS	GAD anxiety	EPDS depression
Infant stomach issues	0.31**	0.24*	0.25*
Infant crying issues	0.34**	0.26*	0.25*
Infant sleep issues	0.15	−0.03	−0.04

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level (2-tailed). Controlling for whether the child had ever participated in floating classes. Missing variables deleted listwise. N = 69.*

was partially supported. Significant results were found for the following relationships: infant stomach issues were positively correlated with bonding issues, maternal anxiety and maternal depression; infant crying issues were also positively correlated with all three outcome variables: bonding issues, maternal anxiety and maternal depression (see **Table 4**).

Cronbach's Alphas

Cronbach's alphas for the BABI were as follows: stomach issues was $\alpha = 0.77$, crying issues was $\alpha = 0.86$ and sleep issues was $\alpha = 0.80$.

DISCUSSION

In this study, perceived stomach issues and crying were both related to mother-infant bonding issues, higher maternal anxiety, and higher postpartum depression. Correlation coefficients are a common indicator of effect size. Although the correlations are statistically significant, they have relatively small effect sizes (39).

Assessments of newborns and young infants' behaviors such as crying, sleep and stomach issues are critical for a number of reasons: they help clinicians identify infants in need of care, help researchers identify infants at greater risk, and may help to identify new mothers who require additional support with their infant. Although the latter function of infant assessments is the least frequently used in practice, it represents a valuable addition with public health benefits to current, often observational, behavioral assessments as an implicit measure of infant-centered issues. While a number of infant behavioral assessments are currently used, there are several significant shortcomings to existing measures (e.g., restricted age of infant, requirement for extensive training of administrator, cost of the assessment, absence of established behavioral norms for comparison). Assessments of parental perception of infant behavior such as the BABI can potentially be given to large amounts of parents because they take little time and training to administer and can be used for the first half-year of an infant's life, before issues with parent-child relationships become more pervasive. Allocating resources to parents based on their perceptions of problematic infant behavior has implications for clinical practice as it could potentially help clinicians provide resources more effectively to the mother-infant dyads that need them the most.

The crying issues subscale was the only subscale in the BABI that did not have a comparative assessment where parents compared the amount that their infants cry to other infants. LF and LP were attempting to gather what they believed to be the most important indicators of domain specific infant behavior based on their expertise in infant development, and they did not believe that comparing the amount infants cry to other infants was as important as other factors such as intensity, frequency and ease of comforting. Of note, this subscale has the best internal consistency of all of the subscales ($\alpha = 0.86$).

This study demonstrates the relationship between infant issues and postpartum depression, but further research is needed to tease apart the directionality of these associations. Additionally, a considerable amount of the research on infant behaviors has focused on the impact of infant crying (5, 6, 40); however, there has been very little investigation into the impact of infant stomach issues on parental psychological status and vice versa. Focusing on parent perceptions of infant behaviors could be an important area for future research for individuals interested in Public Health.

Focusing on parental perceptions of infant behavior has the potential to aid professionals such as pediatricians in triaging parent-infant dyads to closer clinical follow-up or interventional supports. Screening for postpartum depression takes place routinely at gynecological offices, primary care practices and pediatrician's offices, which serve as ideal entry points for further assessment and referral. Even though screening for

postpartum depression is common in early postpartum pediatric appointments, controversy exists around whether it is intrusive to screen parents for postpartum depression and other issues at their children's health visits (rather than focusing on their child) since pediatricians are tasked with providing healthcare for the child and not necessarily the child's parents (41). To the point of focusing on the child, infants of mothers with depression and/or anxiety display variations in some behaviors [e.g., (42, 43)]. This study demonstrates the potential to focus on parental perceptions as they are related to maternal mental health and issues in parent-infant bonding.

Many of the at-home intervention programs are best understood as secondary prevention efforts and typically target populations with previously identified risk-factors [e.g., parental age, immaturity level; (44)] rather than parent report about trouble that they are having with their child. Although these programs appear to be a promising intervention for some parents, there are several limitations including parents being reluctant to having unfamiliar visitors in their homes (45), insufficient training of the individuals administering the intervention (46), and high average cost per family ($5,962) for running the programs (47). Targeting home visitations to parents with certain beliefs about their child (e.g., their infant is difficult compared to other infants), and consequently an explicit perceived need, might be more effective than targeting entire groups of parents (e.g., young parents).

A shift of focus to parent perceptions of infant behavior could help clinicians better allocate resources to the parents who need them the most. Interventions such as the Period of PURPLE Crying exist to normalize crying (48) and to prevent SBS as it relates to infant crying. The program is delivered to new parents in the hospital, in community settings such as at prenatal or well-child care visits, and through media (20). Findings are inconclusive regarding the effectiveness of the program in reducing SBS (49, 50). This might have to do with the fact that this intervention is designed to target a large audience (e.g., caregivers, community members, health care professionals) and is not specifically tailored for parents based on child characteristics such as how much they think their infant cries. We are missing critical entry points for intervention and opportunities to meet parents in the following situations: when perceived needs are high, when these concerns interact with known risk factors for maternal mental health, and when adverse outcomes occur for their offspring.

Limitations and Future Directions

Previous studies have found infant sleep issues to be associated with maternal depression; however, the directionality of this relationship is unknown (40). That finding was not replicated in this study. Future research might consider adding sleep questions that probe perceived quality of infant sleep. Furthermore, although this study focused on risk (parent mental health and issues in parent-child bonding), a beneficial future direction will be to identify protective factors in parent-child bonding.

The cross-sectional design prevented us from looking at test-retest reliability of the BABI Scale. It also prevented us from understanding directionality in terms of infant challenging behavior and new mothers' mental health. Therefore, it is possible that maternal mental health is impacting how parents perceive their infant's behavior. Longitudinal testing will be key to determine if parent assessment of infant behavior predicts only concurrent parent psychological status or if parent assessment of infant behavior at one time point is predictive of parent psychological status at a later time point. Infant sleep issues were not related to bonding issues or mothers' reported symptoms of maternal of anxiety or depression, however, larger studies are needed to explore these issues future. Longitudinal studies should probe the directionality to better understand whether mothers of infants who exhibit stomach issues and crying are more at risk for postpartum depression or if mothers with postpartum depression are more likely to perceive their infant's behaviors to be difficult in the first place. The directionality has important implications for points of intervention. It would also be interesting to examine the impact of parent education programs on parent perception of their infant's behavior using longitudinal studies.

Additionally, the sample consists of mostly white, middle-to-upper class, educated mother-child dyads, which may limit the generalizability to other diverse social and cultural groups. Researchers should attempt to replicate study findings with larger more diverse samples, and information about the test-retest reliability of this measure over time needs to be gathered. It is possible that relationships between infant behaviors such as sleep and parent mental health and infant-parent bonding issues will be significant with larger samples. Therefore, researchers should continue to pursue these research questions with larger more diverse samples. Additionally, further analyses can be done to examine if parent perceptions of infant behavior differ across parents from different demographic backgrounds. It would also be interesting to examine trends in parent perceptions of infant behavior across first-time vs. experienced parents.

Assessing parent perceptions of challenging infant behaviors represents a potential way for health professionals to identify infants who are higher risk and in need of intervention and parents in need of additional support. It may be of particular clinical importance for researchers to establish cutoff scores in order to screen for parents who indicate higher risk for problems such as bonding issues with their infant, infant abuse or parental depression and anxiety. However, these scores can only be determined through the application of this scale with large, diverse samples of parents of newborns.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Houston IRB. The patients/participants provided their informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LF is first author and TU is responsible for statistical analysis. All authors contributed to and approve the manuscript.

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REVIEW
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How to Support Parents of Infants and Young Children in Mental Health Care: A Narrative Review

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Objective: The aim of this narrative review is to gain insight into the appropriate intervention targets when parents of infants and young children suffer from psychopathology.

Background: Psychopathology in parents is a risk factor for maladaptive parenting and is strongly related to negative cascade effects on parent-child interactions and relations in the short and long term. Children in their first years of life are especially at risk. However, in adult mental health care, this knowledge is rarely translated into practice, which is a missed opportunity for prevention.

Methods: Electronic databases were searched for reviews and meta-analysis. In addition, sources were obtained via manual search, reference mining, expert opinion, and communications from conferences. In total, 56 papers, whereof 23 reviews and 12 meta-analyses were included.

Results: Findings regarding targets of intervention were identified in different interacting domains, namely the parental, family, child, and environmental domains as well as the developing parent-child relationship. A "one size fits all" intervention is not appropriate. A flexible, tailored, resource-oriented intervention program, multi-faceted in addressing all modifiable risk factors and using different methods (individual, dyadic, group), seems to provide the best results.

Conclusion: To address the risk factors in different domains, adult and child mental health care providers should work together in close collaboration to treat the whole family including mental disorders, relational, and contextual problems. A multi-agency approach that includes social services is needed.

Keywords: parental mental disorder, infants and early childhood, intergenerational transmission of psychopathology, targets of intervention, review

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INTRODUCTION

Children of parents with a mental disorder are at increased risk for developing mental health problems during their lifetime. The degree of transmission of psychopathology from parent to child ranges from 41 to 77% for the whole diagnostic spectrum (Hosman et al., 2009).

The risk for the child appears to be greater during pregnancy and early life, because these phases are crucial for the development of the brain and building a secure attachment relationship that impacts the development of the young child (Agorastos et al., 2019; Aktar et al., 2019). Pregnancy,

childbirth, and parenting are likely to be more challenging for parents with a mental disorder, and as a consequence may aggravate the psychopathology of the parent(s) (Barker et al., 2012; Falkov, 2012; Aktar et al., 2019). The transactional model (Sameroff, 2004) illustrates how the reciprocal nature of the parent-infant relationship over time affects both parent and child. For instance, if the parent is inadequately responsive to the infant due to their psychiatric symptoms, resulting in under-, over- or highly unpredictable stimulation, the infant will experience confusion and feel unsafe during interactions with the parent, which puts them at risk for developmental delays, insecure attachment styles, challenging behavior, and for the parent, less satisfying and more stressful parenthood. Hence, early childhood is an essential time window for the prevention and treatment of unfavorable parent-child interaction cascades. Therefore, in addition to treatment of the mental disorder of the parent, it is important to pay close attention to parenthood and the evolving parent-child relationship and to act as early in the child's life as possible to repair negative parent-infant interaction patterns (Forman et al., 2007). However, it remains unclear what should be the targets and means of both parent and child in mental health care to reduce the risk of psychopathology during infancy and early childhood.

The high degree of intergenerational transmission does not take place via a direct or simple pathway. Reupert et al. (2015) provide an overview of a number of different, mostly overlapping conceptual models that provide insight into the factors and mechanisms of transmission. The integrative model of Goodman and Gotlib (1999) for transmission of risk to children of depressed mothers is based on empirical data and clarifies the interrelated and interacting risk factors. Falkov (2012) developed the family model to promote transformation in mental health services to focus on the family rather than concentrating solely on the individual, with the aim to prevent the intergenerational transmission of psychopathology. Hosman et al. (2009) present a developmental model of intergenerational transmission of psychopathology with risk and protective factors within four different domains (parent, child, family, and environment) many of which are related to parental mental disorders. This model, as presented in **Figure 1**, is comprehensive in providing insight into which factors and mechanisms could be involved in the process of transmission.

However, there is not yet an all-encompassing framework that predicts and clarifies the developmental pathway by which parental mental disorder affects children, for this process is influenced by the presence and accumulation of interacting risk and protective factors (Maybery et al., 2015; Reupert and Maybery, 2016).

The objectives of this paper are, first, to identify important and effective intervention targets when parenting of infants and young children is included in the treatment of parents with psychopathology, in order to break through the cycle of intergenerational transmission of psychopathology, and second, to determine which among all the mentioned targets should have higher priority in order to achieve the goal of reducing the risk of transmission of psychopathology. In line with the purpose of this paper, we take a developmental-transactional perspective (Sameroff, 2004; Sroufe et al., 2009), which means that psychopathology develops through an interaction between person and environment and evolves over time. Although most research focuses on parents with a specific classification according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5; American Psychiatric Association [APA], 2013), in clinical practice there is wide variety in the phenomenology of mental disorders (Allsopp et al., 2019). Therefore, we will not focus on a specific classification to avoid the false impression that one is dealing with a homogeneous group that can be treated in a uniform way. We chose a narrative review because we wanted to include a wide range of data from a diverse body of literature, and many sources do not lend themselves to a quantitative pooling of results. The focus for this review will be on parents with serious psychopathology, predominantly of a chronic and complex type, that would be encountered in mental health care settings.

In this narrative review, we will present findings about intervention targets in mental health care to break the cycle of transmission of mental disorders and adverse outcomes. This covers intervention targets within different interacting domains, namely the parental, family, child, and environmental domains as well as the developing parent-child relationship.

MATERIALS AND METHODS

Electronic databases (PsycINFO and Web of Science) were searched for reviews in the period 2009–2021 using the following search terms: intergenerational transmission of psychopathology, OR parents with a mental illness, OR parental psychiatric disorder, AND/OR risk and protective factors, AND infants, OR infancy, AND interventions, AND reviews, AND Children of Parents with a Mental Illness (COPMI), AND Children of Mentally Ill Parents at Risk Evaluation (COMPARE). Because of the broad topic of this literature review and the variety of scientific fields that are involved (e.g., parental psychiatry, developmental psychopathology, infant mental health, attachment, resilience science, trauma and toxic stress, genetics and epigenetics, neuroscience and neuroendocrinology), we first searched for reviews and 916 hits of research papers and reviews were found. After reading the title of all, 117 were selected as relevant to the topic and after reading the abstract 33 for close reading, whereof six papers were included in the review. The inclusion criteria were: (1) risk and protective factors for child's psychopathology and adverse outcome related to parental mental disorders; (2) the period of infancy or early childhood; (3) young child, and family resilience; (4) interventions; (5) review; (6) meta analytic study; (7) English language; (8) peer reviewed. Exclusion criteria were: (1) child's cognitive development or school achievement related to parental mental disorder; (2) risk factors to specific child mental health disorders, such as ADHD, autism spectrum disorders, not specific related to parental mental disorders; (3) interventions preventing parental mental disorder not related to child outcomes; (4) interventions whereof the period of early

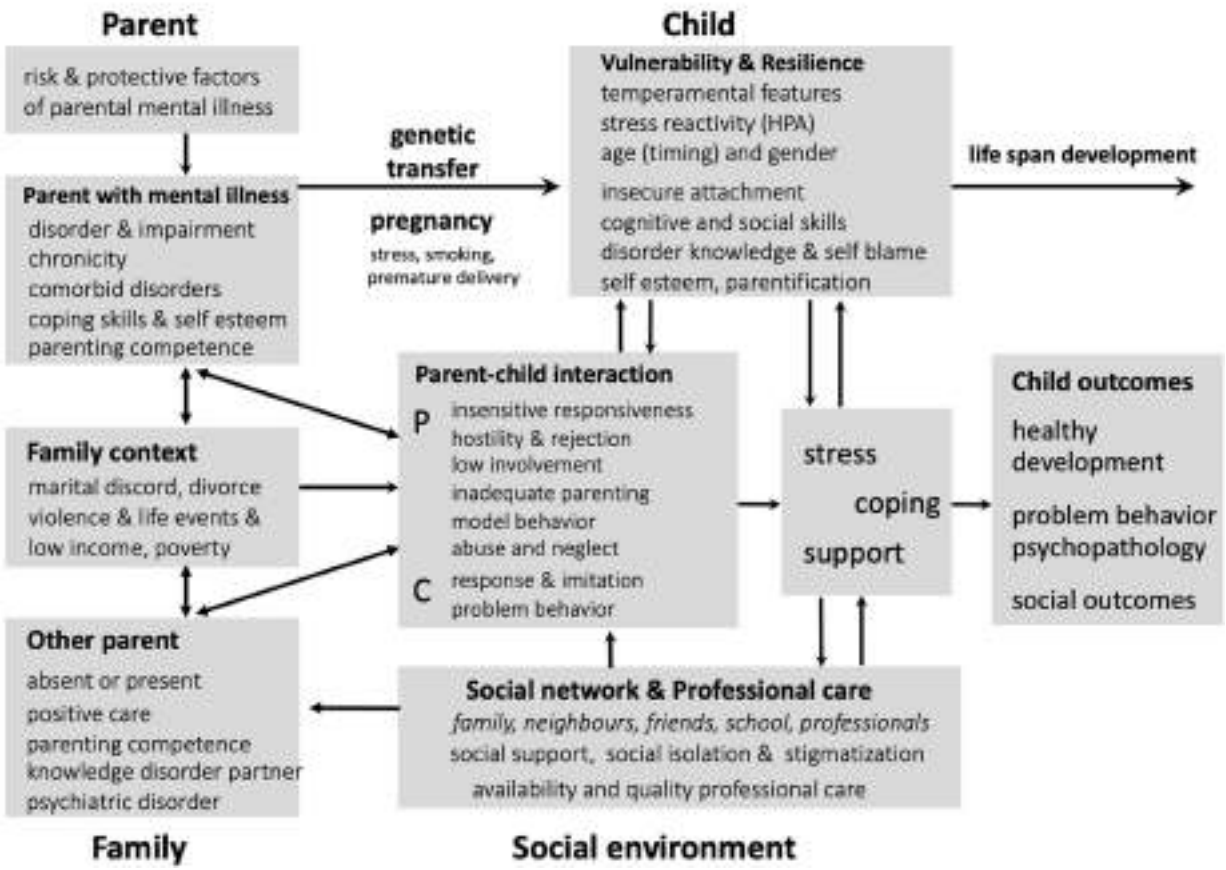

FIGURE 1 | Transmission mechanisms and factors in families with parental mental disorders (Hosman et al., 2009).

childhood was not a substantial part; (5) interventions related to physical health of the young child (medical, nutrition). However, crucial risk and protective factors in relation to intervention targets to prevent the transmission of psychopathology during infancy and early childhood according to the model of Hosman et al. (2009) were missing (e.g., attachment, resilience, adverse child experiences). We conducted additional hand searching and reference mining, alongside obtaining information from other sources such as communications at conferences and correspondence with experts. This resulted in 17 new reviews, so a total of 23 reviews were included. In addition, 12 meta-analytic studies were included. We could not find any reviews or meta-analyses on the particular impact and intervention targets in the presence of cumulative risk factors, poly victimization, and how to promote resilience during infancy and early childhood. On these particular topics we searched for papers in the same manner as described above, using the same inclusion and exclusion criteria and 21 papers about intervention targets have been added. In summary, this review on appropriate intervention targets when parents of young children suffer with psychopathology is based on 56 publications.

RESULTS

Because no reviews have been found about different intervention targets related to risk and protective factors for parents with psychopathology and their young children in mental health care, the focus in this section is to present an overview of the risk and protective factors that are specific to the phase of early childhood. In particular, the modifiable factors for the different domains (parental, parent-child relationship, family, child, and environmental) are subsequently reviewed in relation to intervention targets. We finally end by summarizing risk factors, and the targets of intervention which aim to modify the risk factors into protective factors.

Risk and Protective Factors

Interaction mechanisms among risk and protective factors in the four different domains, as presented in **Figure 1**, highly impact child's development and mental health outcome. Therefore, all risk factors suggest directions in treatment of parents and their young child to prevent the risk of intergenerational transmission of psychopathology (Christiansen et al., 2019). Risk factors related to the parental, family, child, and environmental

TABLE 1 | Risk factors during pregnancy and early childhood in different domains related to parental mental disorder.

Parental domain	Family domain	Child domain	Environmental domain
Genetic transmission[1]	Early parenthood[16,17]	Difficult temperament[4,6,2,3]	Low socio- economic status[16,31,32]
Maternal anxiety and stress in pregnancy[2,3]	Single parenthood[16,17]	Mental health disorders[23]	Poverty[4,18,17,33]
Severity, chronicity or early onset of the disorder[4,5,6]	Child abuse (physical, emotional, sexual)[4,18,19,20]	Genetic vulnerability to environmental influences[24]	Housing problems[18,32]
Comorbidity (e.g., substance abuse)[4,6]	Child neglect (physical, emotional)[18,19,20]	Effects of early life stress and trauma/ACEs[25,26]	Social isolation[18,32]
Unresolved (childhood) trauma[7,8,9]	Unpredictable or lack of daily routines[11,21]	Insecure and disorganized attachment[4,6,10,27,28,29,30]	Belonging to a minority group[34], perceived discrimination[32]
Absence of treatment[6,10]	Mental disorder/addiction other parent/family member[22,6,19]		Low quality of neighborhood[18,32]
Problematic parenting[4,11,12,13,14]	Interparental conflict/violence[4,16,18,19,12,20]		Absence or low quality of emotional and practical support network[16,32]
Frightened, frightening disrupted parental behavior[8]	Absent of both biological parents[19]		Absence or low quality of adult and child professional care[6]
Impaired and distorted parental mentalization[15]	Criminal trouble/imprisoning family member[3,12,18]		No possibilities for alternative care[18]
	Low level of education[16,17]		

[1]Kendler and Prescott, 2007; [2]Korja et al., 2017; [3]Van den Bergh et al., 2017; [4]Beardslee et al., 2011; [5]Carter et al., 2001; [6]Hosman et al., 2009; [7]Christie et al., 2019; [8]Madigan et al., 2006; [9]Suardi et al., 2017; [10]Aktar et al., 2019; [11]Falkov, 2012; [12]Hughes and Cossar, 2016; [13]Hugill et al., 2017; [14]Laulik et al., 2013; [15]Sharp and Fonagy, 2008; [16]Barker et al., 2012; [17]Evans et al., 2013; [18]Brockington et al., 2011; [19]Felitti et al., 1998; [20]Kessler et al., 2010; [21]Stepp et al., 2012; [22]Bijl et al., 2002; [23]Slade, 2009; [24]Bakermans-Kranenburg and van IJzendoorn, 2007; [25]Agorastos et al., 2019; [26]Chu and Lieberman, 2010; [27]Fearon et al., 2010; [28]Granqvist et al., 2017; [29]Sroufe et al., 2009; [30]Van IJzendoorn et al., 1999; [31]Stein et al., 2014; [32]Silva et al., 2016; [33]Lund and Cois, 2018; [34]Cyr et al., 2010.

domains, with references to the literature, are presented in **Table 1**.

Protective factors which can play a protective role in the transfer of psychopathology in the different domains are presented in **Table 2**.

An epidemiologic study by Kessler et al. (2010) showed that childhood adversities often co-occur. Several studies indicate a dose-dependent response relation of childhood adversities to mental health outcomes, which means that the number of traumas and adversities is a significant predictor of mental health disorders (Barker et al., 2012; Evans et al., 2013). A longitudinal study (Barker et al., 2012) investigated the impact of the exposure of infants from birth to 2 years old to several risk factors and the impact of maternal depression on child psychopathology at 7 years. They found evidence that a substantial proportion (37–41%) of the association between risk factors and maternal depression was explained by increased risk factor exposure. Beside exposure to maternal depression, each additional risk factor increases the odds at least 20% for child psychopathology.

Targets of Intervention in Different Domains

The following section will describe intervention targets in the domain of the parent, the family, the child, and the environment, and the early parent-child relationship as a crucial transmission mechanism, all of which are considered to be important in limiting the risk of transmission of psychopathology from parent to child.

Parental Domain

Genetic transmission and epigenetic regulation

The risk of *transmission of specific genes* from parent to child which increases the probability of psychopathology in the child (Kendler and Prescott, 2007), is not a modifiable factor. This significant risk justifies categorization as a high-risk group that needs preventive interventions. Epigenetic changes in transcription of genes have been shown in interaction with the environment, especially in early development and following adverse experiences. *Maternal anxiety and stress during pregnancy* are major risk factors for later negative child difficulties (Van den Bergh et al., 2017). Exposure to early life stress and childhood trauma, possibly arising from parental psychopathology, further enhance the risk of epigenetic programming which over time may lead to stress-related disorders (Agorastos et al., 2019). The quality of the parental environment is an important factor that can be modified and therefore it is a crucial target of intervention.

Parenting in relation to psychopathology

Much is known about how parenting can be affected by a mental disorder. Most studies address concerns related to depression in mothers and its influence on their caregiving such as unresponsiveness, intrusiveness, hostility, or high expressed emotions (Beardslee et al., 2011). There is also evidence of problematic parenting by parents with a personality disorder, for instance switches between hostile control and withdrawn behaviors as well switches between intrusiveness and coldness (Stepp et al., 2012; Laulik et al., 2013). An association has been found between PTSD and impaired parenting and less than optimal parent-child relationships (Christie et al., 2019). A systematic review of the relationship between *maternal*

TABLE 2 | General protective factors in early childhood in different domains, which may have a buffering effect on families where a parent has a mental disorder.

Parental domain	Family domain	Child domain	Environmental domain
Physical health[1]	Presence of a well-functioning other (step-) parent[7,8]	Physical health[1]	Stable and adequate income[1,6,15]
Self- and parental efficacy[1,2,3]	Warm, cohesive family interaction[1]	Easy temperament[1,10,7]	Adequate housing[1]
Good emotion and stress regulation[1,4]	Marital stability, support and satisfaction[1,3,4,6,9]	Insusceptible for environmental influences[11]	Safe neighborhood[1,15,16]
Effective coping skills[1,2,4]	Small family (<4 children)[1]	Secure attachment[1,2,4,12,13,14]	Social support (emotional/practical) [1,6,7,16,17]
Internal locus of control[1]	Moderate or high level of education[1,6]		Involvement in the community[1,6,15]
Positive belief systems[1,2,3]	Supportive and stimulating parent-child interaction[1,2,4]		Access to good quality childcare and school[1,4,6]
Appropriate parental mentalization[5]/secure attachment[6]			Access to good quality (mental) health care[1,6,7,16]

[1]Benzies and Mychasiuk, 2009; [2]Doty et al., 2017; [3]Korja et al., 2017; [4]Masten, 2018; [5]Slade et al., 2005; [6]Tharner et al., 2012; [7]Hosman et al., 2009; [8]Stein et al., 2014; [9]McEwen, 2003; [10]Beardslee et al., 2011; [11]Bakermans-Kranenburg and van IJzendoorn, 2007; [12]Seifer, 2003; [13]McGoron et al., 2012; [14]Schechter and Willheim, 2009; [15]Silva et al., 2016; [16]Brockington et al., 2011; [17]Falkov, 2012.

childhood trauma (emotionally abusive or neglectful experiences) and parenting found tentative support for a range of adverse parenting outcomes, including increased parenting stress and a higher risk of maltreatment, lower empathy, and greater psychological control (Hughes and Cossar, 2016). Hugill et al. (2017) found support for an indirect pathway from childhood sexual abuse of parents through parental depression to parenting stress. Notwithstanding the above mentioned risks, parenting can also be a positive resource for parents with mental disorders, as it may be a source of structure and stability and act as a motivator to manage their symptoms in a better way (Schrank et al., 2015).

Problematic parenting behavior and distorted parental mentalization

Parenting can be a key moderating or mediating factor in transmission of mental disorders from parent to child and therefore should be an important target of intervention (Brockington et al., 2011; Stein et al., 2014). Specific *problematic parental behavior* related to mental health problems includes overinvolvement (intrusiveness and/or overprotection), underinvolvement and neglect (unresponsiveness to physical and emotional needs), negative involvement (hostility and irritability), inconsistent involvement (inconsistency in providing daily structure and predictability), inadequate discipline and control (harsh discipline and criticism), role reversal (parent seeks comfort from child), developmentally inappropriate expectations, and lack of modeling (Falkov, 2012).

Parental mentalization or parental reflective functioning (PRF) refers to the parent's capacity to understand their own as well as their child's internal states. It allows them to regulate and comfort their child in an appropriate way and for that reason plays a vital role in the development of attachment and the child's self-regulation and capacity to mentalize (Slade et al., 2005). *Distorted parental mentalization* is associated with disorganized attachment and development of psychopathology in their children (Sharp and Fonagy, 2008). Low reflective function (RF) has been found among adults with different types of mental disorders (Katznelson, 2014).

The nature of the parental mental disorder

The chance that the child will develop a disorder is not strongly dependent on the specific disorder of the parent (Bijl et al., 2002). *Severity, chronicity, and degree of comorbidity of parental psychopathology* has been shown to contribute more to parental behavior than specific disorders (Carter et al., 2001) and to the likelihood of transmission (Beardslee et al., 2011). In this context, a*bsence of treatment* is an obvious risk (Hosman et al., 2009; Beardslee et al., 2011). *Early onset* (before age 30) of a disorder is an additional risk, because of the higher likelihood of adverse social, educational and work circumstances found in young mothers (Hosman et al., 2009).

Allsopp et al. (2019) demonstrate that most DSM-5 classifications are associated with adversities or trauma in childhood. Acknowledging the possible role of trauma or adversity in the unfolding of psychopathology, interventions should also address past traumatic experiences. This is crucial because the presence of *unresolved childhood trauma* in parents is known to be an important threat to their parenting, for example, in *frightened, frightening, and disrupted behavior,* and the early parent-child relationship (Madigan et al., 2006; Suardi et al., 2017). Indeed, parents' post-traumatic stress symptoms may impair self-regulation and the parent's ability to regulate the young child, who depends greatly on interactive co-regulation with the caregiver (Chu and Lieberman, 2010; Suardi et al., 2017). The child's behavior or distress itself can provoke and revive the post-traumatic stress symptoms caused by unresolved trauma experienced by the parent. In this process, parent and child may be caught in an unintended repeating traumatic interaction circle. Therefore, screening and treatment for unresolved parental childhood trauma will benefit the parent, the child, and their relationship (Chu and Lieberman, 2010; Suardi et al., 2017).

Although treatment of parents' mental disorders and trauma can play a role in the prevention of mental disorders in their children, interventions targeting the parent-infant relationship have been shown to produce larger overall effects in improvement of this dyad than individual interventions targeting mothers only

(Kersten-Alvarez et al., 2011; Tsivos et al., 2015; Thanhäuser et al., 2017; Aktar et al., 2019). Evidence suggests that explicit attention has to be paid to the parent-child relationship in order to improve the emergence of undesirable patterns, such as a lack of parents' responsiveness to the child (Carter et al., 2001; Nylen et al., 2006; Forman et al., 2007; Schechter and Willheim, 2009; Barlow et al., 2010; Barker et al., 2012; Barnes and Theule, 2019).

Summary

Parental mental disorders may be a serious threat to the quality of parenting. Parenting is a key moderating and mediating factor in the process of transmission of mental disorders. The capacity of the parent to understand their child's emotion and behavior and to help their child's regulation in appropriate ways depend on parental mentalization. Parental behavior and parental mentalization as highly influential factors are strongly related and therefore important targets for intervention.

The severity, chronicity, comorbidity, and early onset of parental mental disorder and unresolved parental childhood trauma increase the likelihood of intergenerational transmission of psychopathology. Treatment of the disorder and unresolved childhood trauma of the parent(s) should be accompanied by explicit attention to the developing parent-child relationship in order to prevent the emergence or continuation of undesirable parent-child interaction patterns.

The Early Parent-Child Relationship

The parent-child relationship is generally the most proximal and influential relational system for the child. Preliminary support in clinical samples suggest a link between higher levels of *insecure attachment* in infants and parental behavior related to mental disorders, but further research is needed (Aktar et al., 2019; Barnes and Theule, 2019). Seifer (2003) argued that fostering resilience of very young children of a parent with a mental disorder on the individual level is complicated, as they have not developed the functions and skills needed to develop resilience such as verbal skills and high-level cognitive functioning. Furthermore, they function in limited social contexts and miss independent access to various social communities that are assumed to be a protective factor for older youth. The focus of the resilience process needs to be the parent-child system (e.g., attachment) as an interim outcome because if there are unresolved disturbances in this relationship it will increase the risk of adverse child outcomes (Seifer, 2003). A positive change in that relationship will have positive spillover effects over time on other domains with long-term benefits to the parent (parental efficacy, positive emotions) and child (cognitive, emotional, and social functioning) (Doty et al., 2017).

Enhancing secure attachment as a protective factor

Secure attachment can be seen as an interim outcome and a buffering protective factor against the development of psychopathology (Seifer, 2003; Schechter and Willheim, 2009; McGoron et al., 2012). Parental sensitivity to children's cues is associated with and currently seen as an important—but not the only—predictor of secure attachment (Bakermans-Kranenburg et al., 2003), and for that reason is a key target in many attachment-based interventions. Parental sensitivity refers to the ability to accurately perceive and interpret the infant's signals and communications and respond appropriately. However, a recent meta-analysis (Zeegers et al., 2017) of parental mentalization and sensitivity as predictors of infant-parent attachment highlights a direct effect of parental mentalization on infant-parent attachment independent of parental sensitivity, as well as an indirect impact on attachment via its effect on sensitivity. Therefore, parental mentalization as well as parental sensitivity are important targets for interventions to enhance secure attachment. This implies helping parents to think about behavior as an expression of the intentions and internal mental states of their child. It also necessitates changing the parental representation of the child, with the result that the parent is able to see the child as having an inner life separate from their own (Slade et al., 2005).

Reducing the risk of insecure and disorganized attachment

Insecure and especially disorganized attachment in young children has been associated with later mental health outcomes such as problematic stress management, externalizing and dissociative behavior, and borderline personality disorder (Van IJzendoorn et al., 1999; Sroufe et al., 2009; Fearon et al., 2010). Disorganized attachment is the opposite of organized attachment, and entails the child becoming stuck in an unresolvable conflict between being afraid of the parent and at the same time needing comfort from the parent. This conflict, described as "fright without solution," is observable in a breakdown of attachment strategies in a stressful situation in the presence of the parent. For instance, it may involve contradictory behavior such as seeking proximity to and turning away from the parent, and stereotyped behavior such as extended rocking. On a biobehavioral level there is a measurable increased level of cortisol (Spangler and Grossmann, 1993).

There are different pathways to disorganized attachment, and one is directly related to parental psychopathology. An association has been found between subtly frightened, frightening, and disrupted maternal behavior and disorganized attachment in infancy (Madigan et al., 2006). Due to unresolved parental trauma and loss, parents themselves may become sources of chronic stress for their infants because of an ongoing state of fear, dissociative behavior, limited availability and responsiveness, and restrictive and overprotective behavior (Chu and Lieberman, 2010; Suardi et al., 2017).

Given the association between disorganized attachment and later mental health outcomes, preventive interventions targeting attachment relationships in infancy are needed. A recent meta-analysis (Facompré et al., 2018) demonstrates that interventions targeting disorganized attachment have been generally effective. The interventions in the studies focused on enhancing parental sensitivity to the infant's cues, on modifying the parental representations of the child in relation of the caregiver's own attachment history, and on the effect of practical support and education on child development. The findings show no significant differences among the intervention foci. Another meta-analysis of interventions that aim to decrease or to prevent disorganized attachment in early childhood shows a reduction in

disorganized attachment, with the majority of the interventions focusing on maternal sensitivity (Wright et al., 2017). On the other hand, Benoit et al. (2001) argue that interventions should target disorganizing interactions between caregivers and their children. Instead of blaming parents for their children's disorganized attachment, Granqvist et al. (2017) emphasize that caregivers need help to learn to follow the child's lead, avoid alarming behavior and provide nurturance, make sense of traumatic experiences, break social isolation, and learn strategies to remain with the child in the moment rather than become lost in memories.

Summary

The way parents interact with their infants is essential for building a secure attachment relationship during the first year of life, and is associated with healthy social and emotional development outcomes. Secure attachment can be seen as an intermediate outcome and a buffering protective factor against the development of psychopathology. Given the association between disorganized attachment and later mental health outcomes, preventive and curative interventions targeting attachment relationships in infancy and early childhood is a desirable response. Intervention should target enhancing parental mentalization and sensitivity, reducing disorganizing interactions between caregivers and their children, promoting practical support, and education about child development.

Family Domain

The parent and the parent-infant relationship usually function in the broader context of family life. Family factors, such as the functioning of the other (co-)parent, quality of the partner relationship, and family functioning are strong predictors of mental health outcomes. *Low level of education, early parenthood, and single parenthood* are not modifiable risk factors (Barker et al., 2012; Evans et al., 2013), although attention can be paid to diminish the social consequences for instance by social work interventions.

The other (co-)parent

Children whose *parents both have one or more mental disorders* have an increased risk of developing a disorder themselves (66%) compared to children whose one parent has a mental disorder (51%), and almost twice as high compared to children with parents without a mental disorder (35%) (Bijl et al., 2002). Healthy functioning of the other parent is mentioned as an important protective factor because it might have a buffering effect on the impact of the parent with a mental disorder on the child, and for this reason the (co-)parent should be routinely involved in the assessment phase of treatment (Stein et al., 2014). Improved child outcomes have been found when fathers are involved in family focused interventions (Harold and Sellers, 2018).

Quality of the partner relationship

This is mentioned as an important protective or risk factor because of its direct impact on the parental mental disorder and indirect impact on the child's outcome. Social support through a loving and caring relationship with a partner appears to have an ameliorative effect on psychopathology caused by early life adversity (McEwen, 2003).

Interparental conflicts predict children's problematic functioning even after controlling for other family and ecological characteristics (Cummings and Davies, 2002). A recent study found that the association between fetal exposure to parental mood disorder and children's internalizing problems at 24 months is mediated by poor postnatal quality of the couple's relationship (Hughes et al., 2019). This study recommends clinical interventions to improve couple relations during pregnancy to benefit the child's later outcomes. Korja et al. (2017) mentioned marital support and satisfaction as moderators that may attenuate the negative impact of prenatal exposure to maternal stress, depression, and anxiety.

Given the high prevalence of *interparental violence* against women with perinatal mental disorders (depression, anxiety, and PTSD), mental health services should identify and respond to interparental violence against women they treat (Howard et al., 2013). In the presence of interparental conflicts, interventions that target these conflicts at the level of the interparental relationship may benefit the child's psychopathological outcomes in the long term significantly more than interventions that target the parent-child relationship (Harold and Sellers, 2018). Therefore, the interparental relationship should get priority.

Quality of family functioning

Benzies and Mychasiuk (2009) mentioned warm interaction and family cohesion as one of the most significant protective factors for families with a parent who has a mental disorder. It provides family members a safe haven for development and is known as a buffering factor which protect children from the negative consequences related to low-income. Fostering protective factors in the family is a strength-based intervention which promote family resilience to cope with adverse events.

Unpredictable or lack of daily routines is a risk factor (Falkov, 2012), often associated with the presence of a borderline personality disorder at the parent, which should be prioritized over attachment issues (Stepp et al., 2012). Kessler et al. (2010) analyzed data from 21 countries and found that childhood adversities associated with maladaptive family functioning such as parental mental disorder, *interparental violence*, *criminal behavior*, *neglect*, and *physical and sexual abuse* of the child were the strongest predictors of mental disorders over the course of the child's lifetime. Child maltreatment is associated with disorganized attachment and adverse outcomes (Cyr et al., 2010). The prevalence of child maltreatment is elevated in the presence of a parental mental disorder, even more so when both parents are affected (Chang et al., 2018). In a review regarding the impact of traumatic stress from birth to age 5, Chu and Lieberman (2010) argued that the prevalence of trauma in early childhood is highly underestimated and seldom investigated by researchers. Childhood trauma and stress has been estimated to account for 45% of the variance of psychopathology beginning in childhood and 26–32% in adulthood (Tyrka et al., 2013). Finkelhor et al. (2007) highlight the role of poly-victimization, a phenomenon neglected by researchers and practitioners. If a child was exposed

to one kind of trauma or adverse experience it is more likely that they will have been exposed to additional traumas. For this reason, they argued that professionals need to assess for a broader range of traumas and early interventions. The impact of traumatic stress depends on the quality of the parent-child relationship, because for the infant the attachment relationship is an important resource for regulating emotions and stress (Chu and Lieberman, 2010; Shonkoff et al., 2012). The child's traumatic experiences should be treated in the context of the caregiver-child relationship (Chu and Lieberman, 2010).

A parent with psychopathology is one of the risk factors in the Adverse Child Experiences (ACE) Study (Felitti et al., 1998), a huge epidemiological study in the United States which has been replicated several times. It shows how adverse childhood experiences or traumas from infancy to 18 years of age can lead to medical disease and psychopathology. The effects of ACE start in early childhood and can be long-lasting (Felitti et al., 1998). The 10 empirically selected ACE categories, mostly related to family functioning, are *abuse (emotional, physical, sexual*), *neglect (physical, emotional*), and household dysfunction *(parental violence, household member was addicted, imprisoned, mentally ill or in psychiatric hospital, not raised by both biological parents)* (Liming and Grube, 2018). An individual ACE score is calculated by counting the number of categories experienced in childhood. The ACE Study found that the impact of the different ACE categories is more or less the same, and with an ACE of four or more, the risk of adverse outcomes is significantly increased. Young children age 0–6 with three or more ACEs were significantly more likely to exhibit behavioral problems (e.g., aggression, attention problems), mental health problems (e.g., anxiety), and overall problems compared with children with no ACEs (Liming and Grube, 2018).

Summary

Family factors can act as strong protective or risk factors for intergenerational transmission. Assessment of family factors is necessary and should include the role and mental health of the other parent, the quality of the couple relationship and family functioning, especially the presence of ACEs and trauma. Maladaptive family functioning is a strong risk factor. Interparental violence or marital conflict should get a higher priority for intervention than the parent-child relationship. Warm and supportive interactions between family members is a strong protective factor. To reduce the impact of ACEs and early childhood trauma, treatment should be in the context of the current attachment relationship.

Child Domain

Child vulnerabilities

Infant characteristics may function as a protective as well as a risk factor. Vulnerabilities may be independent of the parent's psychopathology as well as result of exposure to risk factors related to parent's psychopathology or an interaction of both. However, children's vulnerabilities pose a risk for the developing parent-child relationship, for they challenge parenting and the mentalizing capacity of the parent (Sharp and Fonagy, 2008).

Differences in reactivity, activity and self-regulation are seen as features of temperament whereby a difficult temperament refers to negative affect or irritability, withdrawal in response to novelty, high intensity of emotions and irregularity of biological processes such as feeding and sleeping (Korja et al., 2017). An infant or young child with a difficult temperament demands much more effort from the caregiver in the interpersonal regulation compared to a child with an easy temperament. Therefore a *difficult infant temperament* is a frequently identified risk factor (Korja et al., 2017; Van den Bergh et al., 2017), and conversely an easy temperament is a protective factor in the presence of risk (Benzies and Mychasiuk, 2009; Beardslee et al., 2011).

In accordance with the fetal programming model, there is robust evidence that early negative environmental factors, such as maternal anxiety, depression or stress in pregnancy (Korja et al., 2017; Van den Bergh et al., 2017) constitute a major risk factor for negative outcomes for the child later in life due to the plasticity of biological systems of the fetus in adaptation to the environment. Korja et al. (2017) suggest that there is evidence of an association between higher prenatal stress and anxiety and elevated negative reactivity or poorer self-regulation, both features of a child's temperament. Exposure to prenatal stress, possibly resulting in difficult childhood temperament, can increase the risk of later psychopathology, partly due to the impact of non-optimal parenting provoked by the child's difficult temperament. Van den Bergh et al. (2017) found that maternal stress during pregnancy was related to increased risk for behavioral problems and a wide range of mental health problems in the offspring. Prenatal exposure to maternal anxiety or depression is associated with many aspects of brain functioning in offspring such as impulsivity and attention.

To prevent unborn children from suffering the negative effects of maternal stress during pregnancy, Van den Bergh et al. (2017) recommended that pregnant women should be protected from undue hardship and stress and advised to avoid preventable stressors. Korja et al. (2017) suggest maternal caregiving sensitivity, maternal self-efficacy, and marital support and satisfaction (see also Tharner et al., 2012) are moderators that may attenuate the negative impact of fetal programming. Based on these findings, they advise preventive approaches and active treatment to help mothers who are experiencing prenatal stress or anxiety and prevent their offspring from having long-term difficulties in self-regulation. To mitigate the risk of early transmission of psychopathology Aktar et al. (2019) suggest intensive treatment of prenatal and postnatal depression alongside with interventions targeting the mother-infant interactions.

Children with *mental health disorders* themselves according to the Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC:0-5^{TM}) (Zero to Three, 2016), challenge the pleasure of and confidence in parenthood. For example, those on the autistic spectrum, who are born with fundamental problems in understanding social information and developing relationships with others, may be a challenge for their parents due to the

lack of reciprocity. Parents of these children are in need of help connecting with their child (Slade, 2009).

As mentioned before *early life stress and trauma* leave their traces on child's development (Agorastos et al., 2019) and may also contribute to an *insecure and disorganized attachment style,* which need treatment as discussed in the section on the early parent-child relationship (Granqvist et al., 2017).

Susceptibility to environmental influences

Bakermans-Kranenburg and van IJzendoorn (2007) highlight the role of *genetic factors in creating differences in susceptibility* to positive or negative environmental influences. If there is a high susceptibility to environmental influences, risk factors such as maltreatment or neglect will have a highly negative impact on child development, whereas a supportive environment will be of great benefit and contribute to the development of resilience. If there is a low susceptibility to environmental influences, there is less impact of negative child rearing experiences on children's development, but there is also little benefit from treatment. These individual differences underline the importance of an individual assessment, while the presence of risk factors and exposure to traumatic experiences will not automatically lead to a disorder or adverse child outcomes.

Summary

Children's vulnerabilities as a difficult temperament, mental health disorders, the impact of trauma, insecure and disorganized attachment, challenge the mentalizing capacity of the parent, and therefore represents a risk factor for the development of the parent-child relationship. Exposure to prenatal stress, anxiety, or depression, and as a possible consequence the development of a difficult temperament and behavioral problems in the child, can increase the risk of later psychopathology. Preventive approaches, such as stress reduction during pregnancy, psycho-education, and active treatment of the parent-child relationship will help parents when their offspring have long-term difficulties in self-regulation. Parental sensitivity, self-efficacy, and marital support and satisfaction are moderators that may attenuate the negative impact of fetal programming. In the presence of a mental disorder or disorganized attachment style in the child, parents need specific help in learning how to stay connected, during which they also self-regulate in a healthy manner.

Environmental Domain

The parent-child relationship develops within a larger ecological context with complex interactions between proximal factors (e.g., parenting) and distal factors (e.g., poverty) (Little et al., 2004). Research with a focus on social and economic determinants of mental health found evidence for a association between worse mental health and *poverty* (Silva et al., 2016; Lund and Cois, 2018), *low socio-economic status*, *low quality of neighborhood*, *housing problems*, *perceived discrimination*, *social isolation*, and *lack of social support* (Silva et al., 2016).

Barker et al. (2012) have found evidence for additional or independent impact of environmental risk factors (e.g., *low socio-economic status*, *low emotional, and practical support network*) along with parental mental disorders on children's adverse outcomes. A meta-analysis by Cyr et al. (2010), shows an impact on child insecure and disorganized attachment by cumulative socio-economic risks of which low income, and *belonging to a minority group* is mentioned beside other risk factors. To explain this relationship between the accumulation of environmental risk factors and disorganized attachment, it is hypothesized that parents are so occupied with their personal and daily concerns, for example about money, housing, employment, that they withdraw from interacting with their child and are lacking in being predictably and safely available to them. Families with cumulative risk factors are at risk for chaotic living and child-rearing conditions, and neglect (Cyr et al., 2010).

A review of the effects of perinatal mental disorders on the fetus and the child (Stein et al., 2014) shows that children of parents with a mental disorder in low-income families are more affected by a parent's mental disorder than children in more affluent families, and therefore interventions could be most important in such adverse circumstances.

Children of depressed mothers are exposed to significantly more risk factors than children of mothers without depression, with on average 2.3 risk factors for the former versus 1 risk factor for the latter (Barker et al., 2012). These risk factors include beside others, *low socio-economic status*, and *an inadequate emotional and practical support network*. Brockington et al. (2011) mentioned, as an example of the latter, families *without possibilities for alternative care* and Hosman et al. (2009) mentioned the *absence or low quality of adult and child professional care*.

All above mentioned authors argued, that social and economic risk factors should be targeted to improve (parental) mental health and reduce the number of risk factors to which children are exposed, especially risk factors that are responsive to intervention. In addition, the focus should be on enhancing protective factors such as social support, alternative care, and resources (Brockington et al., 2011; Falkov, 2012; Tharner et al., 2012).

Summary

Adverse socio-economic conditions and the presence of a (parental) mental disorder often occur simultaneously and reinforce each other. Children exposed to both are more affected than children exposed only to the latter. Consequently, besides treating the parental mental disorder, socio-economic risk factors should be targeted. Social support, for instance by the extended family, and possibilities for alternative care are important protective factors to take in account.

Summary of Intervention Targets

An overview of above mentioned risk factors, intervention targets, and the intended results which will act as a protective factor in the domain of concern is presented in **Table 3**.

Given the multiple interacting risk and protective factors and the large variety of family contexts, there is no universal approach for prevention and treatment. Little et al. (2004) argued that there are several points at which it is possible to intervene in the causal chain, and make a distinction between the role of proximal and distal processes in developmental deficiency,

TABLE 3 | Risk factors and targets of intervention in different domains to prevent for intergenerational transmission of psychopathology and adverse outcome.

Domains	Parental disorder	Partner relationship and family life	Parent-infant relationship	Child	Environment
Risk factors	Early onset Severity Comorbidity Addiction Unresolved (childhood) trauma Absence of treatment	Early and single parenthood Absence of both parents Conflict or low quality in partner relationship Psychopathology (addiction) of other parent Child abuse or neglect Unpredictable or lack of daily routines Imprisoning/criminal trouble family member Low level of education	Problematic parenting and parent-child relationship Disorganizing interactions between parent and infant	Difficult temperament Mental health disorders Early life stress Trauma/ACEs Significant risk with ≥3 ACEs Insecure and disorganized attachment	Low socio-economic status Poverty/debts Housing problems Social isolation No supportive network Belonging to minority group Low quality of neighborhood Absence or low quality of support network, and professional care No possibilities for alternative care
Targets of Interventions	Treat the mental disorder Treat (childhood) trauma Treat addiction problems	Involve partner Address interparental violence and child abuse or neglect Enhance marital support and satisfaction Treat mental health problems of other parent Promote consistency in daily structure	Involve other parent Diminish problematic and disorganizing parental behavior Enhance parental mentalization and sensitivity Educate parent about child development Enhance parental efficacy	Treat infant problems, trauma and early life stress in the context of the parent-child relationship	Enhance social support (extended family, friendships) and if necessary, make provision for alternative care Reduce the impact of environmental risks (e.g., housing, financial, poverty, criminality, stress)
Results/protective factors	Better mental health	Warm and supportive marital and family life	Secure attachment	Optimal development	Increased capacity to carry out parental tasks Supportive network

whereby the first operates nearby (e.g., poor parenting) and the latter far from the developmental deficiency (e.g., poverty). Children's exposure to cumulative risks almost always has a greater impact on development than exposure to a single risk, and interventions targeting the full range of risks are more likely to be effective (Evans et al., 2013). There is also a suggestion of more benefit for children's development when there is an accumulation of resources in the presence of risks (Evans et al., 2013). Therefore, intervention targets can differ and should be based on assessment of the individual profile of vulnerabilities and strengths to meet the needs of parent(s) and children in their contexts (Stein and Harold, 2015). A flexible, tailored for each individual family, resource-oriented intervention program, multi-faceted in addressing all modifiable risk factors and using different methods (individual, dyadic, group) seems to provide the best results (Nylen et al., 2006; Kersten-Alvarez et al., 2011; Evans et al., 2013; Schrank et al., 2015; Stein and Harold, 2015; Van Santvoort et al., 2015; Masten, 2018).

DISCUSSION

The aim of this article was to identify modifiable targets for intervention in the treatment of parents with serious mental disorders and their young children, and which targets should be prioritized to reduce the risk of transmission of psychopathology. The epidemiology of the intergenerational transmission of mental disorders provides grounds for concern about children of parents with a mental disorder, especially in infancy and early childhood, due to vulnerable periods in brain development and also a period of high sensitivity to stress (Agorastos et al., 2019). On an individual level, the probability is increased by cumulating risk factors and the absence of protective factors.

This paper provides a comprehensive review of intervention targets related to risk and protective factors that can help prevent the transmission of psychopathology from parents with young children in mental health care. An important conclusion of this review is that the literature shows that intervention targets are identified in different interacting domains, namely the parental, family, child, and environmental domains, as well as the developing parent-child relationship. A second conclusion is that given the multiple interacting risk and protective factors and the great variety of phenomenology of mental disorders and family and environmental contexts, there is no general approach for prevention and treatment to prevent parents and their young children from suffering intergenerational transmission of mental disorders (Schrank et al., 2015; Van Santvoort et al., 2015). Therefore, intervention targets can differ and should be determined by and based on individualized assessment of the risk profile to meet the needs of the parent(s), the child, and their relationships in their context (Nylen et al., 2006; Van Santvoort et al., 2015). A flexible, tailored, and resource-oriented program for treatment with different intervention methods (individual, dyadic, group) will promise the best results (Nylen et al., 2006; Schrank et al., 2015; Reupert and Maybery, 2016; Masten, 2018).

Unfortunately, this paper will not provide an answer to the question of which targets should be prioritized in treatment to reduce the risk of transmission of psychopathology. No research

has been conducted that has analyzed which treatment targets have which impact in preventing intergenerational transmission or in reducing the risk factors associated with it (Christiansen et al., 2019). Despite this, some hypothesis can be made regarding urgency and aspects in treatment. In high risk samples where risk factors co-occur cascading models can guide the process of decision-making about which intervention target in which domain will have the greatest effect and therefore deserves priority. Cascading effects occur on processes that strengthen resilience as well as on processes that negatively reinforce each other resulting in a worsened situation.

Doty et al. (2017) present a cascading resilience model in which parenting interventions were postulated as an leverage point in promoting positive spillover effects in the domain of the parent (parenting efficacy, positive emotions, emotion regulation), the child (development, biological stress), the family (relationships, stress regulation), and functioning in the community (sociability, trust, social networks).

Harold and Sellers (2018) present in their review a cascade model in which interparental conflict is a feature of family stress which negatively affect children. They state that the target on interparental relationship is a direct source of influence on the parent-child relationship. Interparental support will have a moderating effect on the parental symptoms (see also McEwen, 2003), a positive effect on the quality of parenting and co-parenting (see also Korja et al., 2017; Hughes et al., 2019), security in the family, and will via this pathway improve child's long-term mental health outcome. Therefore they argued that in the presence of interparental conflict, this should get a higher priority for intervention than interventions targeting the parent-child relationship. Considering the statements above, it will be obvious that the (co-)parent should be routinely involved during the assessment procedure (Stein et al., 2014).

Stepp et al. (2012) argued that mothers with a borderline personality disorder first need psychoeducation about childhood development and expectations, and skill training to promote consistency in warmth and parenting strategies, before they can benefit from attachment-based parent-child treatment.

This underscores the second conclusion that individualized assessment of the risk profile of the family should be made by professionals, before simply intervening on one domain, in order to decide which intervention targets will proceed the best spillover effects on other domains.

An important and often overlooked risk factor in mental health care is parents' unresolved childhood trauma, which could play a significant role in causing their psychiatric symptoms (Allsopp et al., 2019). This is an important threat to parenting, because post-traumatic stress implies problematic self-regulation, which threatens the interpersonal regulation of the infant (Suardi et al., 2017). Hence, screening for unresolved childhood trauma during the assessment procedure and consideration of the impact on parenting and the parent-child relationship should be undertaken.

However, although treatment of the mental disorder and trauma of the parent is important, it will not automatically change undesirable patterns in the parent-infant relationship (Forman et al., 2007; Thanhäuser et al., 2017). Disruption to the parent-child relationship will affect both child and parent, with consequences for the future. In line with the transactional model (Sameroff, 2004), the child is at risk of behavioral and emotional problems, and in that case, parenting is more challenging and less satisfying. This poses a risk of worsening the parent's symptoms, which could in turn further increase the child's problems. Therefore, in mental health care practice, assessment of parenting and the parent-infant relationship should be an essential part of the overall assessment in the interest of both parent and child (Brockington et al., 2011; Falkov, 2012). As a consequence of their own problems, a parent may be biased regarding their own parenting behavior and their child's behavior. Mothers with severe and pervasive mental disorders such as a personality disorder tend to view their struggles and behavior as ego syntonic, and Laulik et al. (2013) recommends for this reason that wherever possible, mental health care of these parents should include assessment of the attachment style of parent and child. Hence, assessment of the parent-infant relationship should be done through observation.

In addition to screening for parental trauma, the same should be done for the young child. It is important to assess the infant for traumatic experiences and exposure to parental stress from conception and treat them in the context of the attachment relationship (Chu and Lieberman, 2010).

Children are more affected by their parent's mental disorder if their family is low in socio-economic status (Stein et al., 2014). Accumulation of environmental risk factors puts children at serious risk of developing a disorganized attachment style (Cyr et al., 2010), which is associated with later psychopathology (Sroufe et al., 2009). These risk factors make it challenging for parents to be consistently available and to regulate infants' distress in a predictable and safe manner. Parents' absorption in managing their daily troubles may result in chaotic living and child rearing conditions, and child neglect. Thus, contextual risk factors are important targets for intervention to diminish parental stress. In addition, it is important to enhance social support and search for possibilities for alternative care.

Limitations

We have restricted our literature search mainly to reviews, which may have limited our identification of significant articles and potentially excluded other findings. Our choice to search for reviews was motivated by the broad field of science involved in our research question, with the possible risk that specific topics have been excluded simply because no review article about them has appeared. We have tried to address this risk by adding papers and meta-analytic studies and longitudinal research on missing issues. Another limitation is that the bulk of research focused on mothers. The influence of the psychopathology of fathers, as well as the possible buffering influence of a healthy father in case of a maternal mental disorder, has been less investigated. Furthermore, research into the transmission of parental psychopathology to offspring has mostly focused on a single mental disorder, and therefore does not offer guidance for practice in which comorbidity is present. The impact and interaction of other risk factors in transmission besides the parental mental disorder has seldom been investigated.

Despite these limitations, this review hopefully puts forward an useful overview of the present state of knowledge, identifying modifiable targets that are most helpful to parents in mental health care, enabling them to improve their parenting and develop a secure relationship with their young child, for the benefit of both. In addition, it will hopefully help professionals in adult and infant mental health care to help parents to break the cycle of intergenerational transmission of psychopathology.

Implications for Clinical Practice

As shown in this review, risk factors in the transmission of psychopathology in different domains are highly interrelated and interactive, with negative cascade effects on both parents and children. Children of parents with a mental disorder are more likely to be exposed to more family and environmental risk factors than children whose parents do not have a mental disorder. Intervention targets and ports of entry for treatment are not simple to determine. A "one size fits all" intervention is not appropriate for parents with serious mental disorders and their young children. Thus, professionals need to carefully consider which intervention targets will be most likely to benefit each individual family. Specifically, which domains, which timing and combination of treatments, whether to focus on proximal or distal processes or on protective factors that moderate the influence of risk factors, the intensity of the intervention, and which professional(s) will be working with the family all need to be considered.

In practice, "no single service can fulfill the needs of both parent and child" (Falkov, 2012, p. 8), neither adult mental health care nor infant mental health care, so it is essential for these mental health care professionals to work together in close collaboration. However, adult mental health care and even child mental health care are both appropriate places to reach and help parents and their young children by assessing and treating the whole family including mental disorders, relational, and contextual problems. To address problems in the broader context of the family and society, a multi-agency approach including social services is needed.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and method, and read and commented on the manuscript text of this review article. HS read all the included manuscripts of the review and put the manuscript into writing. All authors approved the final version of the manuscript.

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Acute Maternal Stress Disrupts Infant Regulation of the Autonomic Nervous System and Behavior: A CASP Study

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Exposure to maternal stress is assumed to influence infant health and development across the lifespan. The autonomic nervous system (ANS) is especially sensitive to the effects of the early caregiving environment and linked to predictors of later mental health. Understanding how exposure to maternal stress adversely affects the developing ANS could inform prevention. However, there is no agreed upon definition of maternal stress making its study difficult. Here we use the Caretaker Acute Stress Paradigm (CASP) to study the effects of maternal stress in an experimentally controlled laboratory setting. The CASP has 5 episodes, a natural play, followed by a caretaker stressor (or control) condition, another play, a classic still face episode, followed by another play. A total of 104 4-months-old infants and their mothers were randomly assigned to either the caretaker-stress or caretaker-control condition. Changes in behavior, heart rate (HR), and respiratory sinus arrhythmia (RSA) before and after the introduction of the stressor (or control condition) were recorded and compared. Infants in the maternal stress condition showed significantly more behavioral distress [$X^2 = (1, N = 104) = 4.662$, $p = 0.031$]. Moreover, infants whose mothers were in the stress condition showed an significant increase in heart rate after the caretaker condition [$F_{(1, 102)} = 9.81, p = 0.002$]. Finally we observed a trend to faster RSA recovery in infants of the control condition [$F_{(1, 75)} = 3.539$, $p = 0.064$]. Results indicate that exposure to acute maternal stress affects infant regulation of the autonomic nervous system and behavior.

Keywords: maternal stress, infant regulation, autonomic nervous system, infant stress reactivity, caretaker acute stress paradigm, still face paradigm

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INTRODUCTION

Early exposure to maternal stress influences health and development across the lifespan (1–6). Research in humans and animals suggests that exposure to maternal stress has long-term consequences on the offspring's stress reactivity (7), with a subsequently increased vulnerability for psychological disorders later in life (8–10). The autonomic nervous system (ANS) is especially sensitive to responding to the effects of the early caregiving environment (11–13) and crucial in the prediction of mental health (14, 15). However, research so far has paid little attention to the underlying mechanisms linking maternal stress to a dysregulation of the child's ANS.

Development of Infant Regulatory Capacity

The early caregiver-infant interaction is a primary developmental context during the first year of life (16–18). While the infant's self-regulation capacity is not yet mature, the caregiver's sensitive and reliable co-regulation is crucial for the infant to cope with everyday stress. The caretaker-infant dyad usually cycles between matching with active co-regulation and dysregulated mismatching states (18, 19). These regulatory mismatches are not inherently harmful. Through reliable and repeated reparations of mismatched interactions, the infant learns that unwanted affective states and unbalanced interactions can be transformed into successful exchanges between both partners, leading to a better adaption to stress and probably future resilience (20, 21). However, if dysregulation becomes chronic and attempts to repair the interaction repeatedly fail, stress can become toxic for the child (22).

Models such as the Mutual Regulation Model (23) assume that maternal stress interferes with maternal caregiving capacity and leads to inconsistencies in the dyadic co-regulation (4, 20, 21, 24–26), which is hypothesized to be a crucial factor in the development of a child's stress response (23). Until self-regulatory capacities become more robust over the first year of life, the caregiver is a critical source of external regulation and has a key role in co-regulating the infant's emotion (16, 27). The maturation of self-regulation extends throughout childhood and the caregiver continues to serve a crucial co-regulatory function through the fourth to fifth year of life (28). Within the interaction, the caregiver's consistent and sensitive response helps the child organize its behavioral and physiological response to stress.

Regular and predictable regulatory scaffolding by the caretaker helps the infant learn how to regulate more effectively. Exposure to stress is hypothesized to lead to a depletion of resources (29, 30), resources that would otherwise be used for growth for the child or in the parent to co-regulate the dyadic interaction. When the exposure to stress becomes chronic, the diminishment of resources may result in long-lasting effects on the quality of the dyadic interaction and infant development (16, 17). Calming Cycle Theory [CCT (22)] further differentiates psychological co-regulation and physiological visceral-autonomic co-regulation. According to CCT, early shaping of visceral-autonomic co-regulation begins before birth through Pavlovian conditioning. The theory moves past attachment theory and connects how the emotional relationship between mother and infant is in part responsible for the development of the quality of the child's autonomic and behavioral regulation (31).

What unifies these theories is that all concur that a child's earliest experiences shape the development of self-regulatory capacities with long-lasting effects, for good or ill, on later mental health (17, 30, 32, 33). To date most research has focused on behavioral-affective regulation of infants in the presence of maternal stress. Recent studies on underlying biological mechanisms look at the infant's hormonal stress response, how sensitive caregiving buffers an increase of stress hormones and protects the developing brain from the potentially toxic, harmful effects (16, 16, 30, 34, 35). Even though the autonomic nervous system plays a critical role in reactivity to and regulation of stress and is sensitive to the infant's early experiences, little research, in particular experimental research has investigated its development in the context of maternal stress (36, 37).

Role of the Autonomic Nervous System

The autonomic nervous system controls central and peripheral biophysiological responses to the environment. It goes through a period of rapid development from the last trimester of pregnancy well-into infancy, making it susceptible to environmental influences (38). The ANS has two systems that are engaged in ongoing regulation of cardiac function; the parasympathetic nervous system (PNS), which controls the body's physiological homeostasis at rest. The sympathetic nervous system (SNS) is more involved in activating the "fight or flight" response during a perceived threat. Activity of neurotransmitters that innervate the vagus nerve, the tenth cranial nerve connecting visceral organs through sensory fibers with the brain, is assumed to play a significant role in creating physiological resting state homeostasis as part of the PNS (39, 40). The PNS is involved in decreasing heartrate after stress exposure and plays a critical role in returning the body to its resting state. Therefore, vagus nerve activity is assumed to indicate PNS's neural regulation by decreasing arousal and returning the body to homeostasis after a confrontation with a stressor. Due to its role in the resting state recovery of the PNS, vagal tone has been linked to self-regulatory processes. However, vagus nerve activity itself is difficult to investigate directly and respiratory sinus arrhythmia (RSA), a measure of changes in HR linked to respiration, has emerged as a proxy (41). Heart rate accelerates with inhaling and decelerates with exhaling (42). RSA is assumed to increase with PNS activation and decrease with PNS withdrawal allowing HR to increase (37). Heart rate is controlled by both PNS and SNS, but can increase without observable changes in RSA, accordingly, RSA is commonly used as a measure of PNS activity (43). Additionally, the SNS has a slower frequency and is therefore hard to measure, especially in moving infants. Thus, the majority of research on infants ANS reactivity in the presence of a stressor focuses on average heart rate (HR), heart rate variability (HRV), and respiratory sinus arrhythmia (RSA).

The Still-Face (SF) paradigm has been widely used to study infant stress reactivity [for reviews, see (44, 45)]. A recent meta-analysis identified 33 peer-reviewed studies that investigate its impact on changes in measures related to the autonomic nervous system (37). While many of the reports differ in exact measurements or calculations, a majority describes very similar results. For instance, infant heart rate is often observed to increase from the natural play episode to the SF episode (46–49). Results are more equivocal for recovery of heart rate after the SF episode; some studies found no change in infant heart rate from SF stressor to the reunion (46, 49, 50), while others report a significant decrease in infant heart rate (47, 51). Gunning et al. (52) divided infants by the characteristic of neonatal irritability. They found that non-irritable infants showed a recovery of heart rate during the reunion after the SF while irritable infants did not.

Several studies also looked at the relation of maternal stress on infant stress reactivity. Enlow et al. (46) found that maternal trauma was linked to a less pronounced recovery of heart rate

after the SF stressor. Stress during the prenatal period was associated with greater changes in infant RSA during the SF episode (38). Two studies investigating the effect of maternal anxiety found a reduced infant RSA during baseline (13, 53), and one study found higher infant RSA after the SF stressor for infants of mothers with elevated anxiety levels (54).

The Current Study

However, most of these studies have two methodological flaws; they stress the infant, not the mother, and they vary widely in their definition of maternal stress. The term maternal stress has been used as an umbrella spanning various forms of adverse life conditions mothers may face, such as poverty, low SES, low social support, as well as mental health problems such as depression or anxiety (55–57). While all of these conditions may cause "stress," there are large variations in how they may affect the caretaker's experience, physiology and everyday life. Moreover, it is difficult to differentiate which of them are closer to real toxic stress or daily challenges that many people face (55). Experimental studies that control for covariates usually stress the infant (e.g., still face experiment or cold pressure stress), studies that evaluate caretaker stress are often retrospective studies using correlational measures, making causal conclusions difficult (16, 58).

Aim of the present study is to evaluate the impact of standardized maternal stress in a controlled laboratory environment on infant behavioral and autonomic regulatory capacity. The Caretaker Acute Stress Paradigm (CASP) (59) allows studying the immediate effects of maternal stress, induced by infant cry vocalizations and distress images of infants on infant self-regulation, a clear and comparable definition of the construct ("maternal stress"). The cries of the caretaker condition were chosen as a stressor as infant cries have relevance to parenting, adding to the ecological validity of the paradigm. Previous research further indicates that infant cries produce a reliable stress response (60–62) and more distressing cries have been shown to recruit regions of the brain associated with arousal and attention (63, 64).

We hypothesized that infants of mothers in the caretaker-stress condition of the CASP would show decreased behavioral regulation and increased reactivity of the autonomic nervous system to the modeled caretaker-stress, compared to the infants of a caretaker-control group. Changes in behavior, heart rate (HR), and respiratory sinus arrhythmia (RSA) were recorded. Infant average HR and RSA before and after introducing a caretaker stressor or non-stressor control condition were compared to investigate how an acute experimental caretaker stressor may affect the infant's ability to self-regulate.

METHODS

Participants

Participants were recruited at the maternity ward of a large Harvard Medical School-affiliated hospital. A hospital employee reviewed maternal and infant medical records for study inclusion and exclusion criteria (e.g., serious medical and/or mental maternal health issues). A recruiter visited the rooms of healthy full-term infants and their mothers to either talk with the mother about the study or to leave written material with contact information if the mother was unavailable. All potential participants were contacted 3 weeks before the infants were 4-months old.

A total of 104 4-months-old infants (+/−1 week) and their mothers participated and were randomly assigned to either the caretaker-stress or caretaker-control condition of the CASP before their arrival to the laboratory. The majority of mothers were white 54.7% (black: 26.4%, did not wish to answer: 9.4%). All infants were delivered full-term (37 weeks or greater) and were clinically healthy at birth as determined by pediatric examination, with no chronic medical conditions or time in the neonatal intensive care unit. Infants also were clinically healthy at the time of testing. Mothers were between 20- and 42 years of age at the time of birth, with no serious chronic health conditions and at least a high school education.

Experimental Procedure

Participants came to the laboratory when the infant was 16-weeks old (+/−1 week). Informed consent was given, all questions were answered, and mothers signed the consent form. To collect cardiac data, seven electrodes (MindWare Technologies Ldt.) were placed on mother and infant. Infants were lying on a changing table in the waiting room, with one research assistant placing the electrodes on the infant. At the same time, a second research assistant placed the electrodes on the mother. Next, mother and infant were brought to the observation room where the infant was seated in a highchair while the mother sat on a chair facing the infant, close enough to touch and interact with the infant. The electrode wires from mother and infant were connected to MindWare, and the research assistant made sure the wires were tucked away so that the infant would not be able to reach them. Two wall-mounted video cameras were used to record mother and infant. Research assistants were able to monitor the study room and physiology from an adjacent control room. Physiology and video were initialized simultaneously through E-Prime® software to ensure exact timing on both measures. The mother was given an earpiece connected to a walky-talky so that a research assistant could provide instructions about the procedure without entering the room.

The Caretaker Acute Stress Paradigm

The Caretaker Acute Stress Paradigm (CASP) was developed to observe the influence of maternal stress on maternal and infant reactivity within an experimental setting (59). The CASP has a standard 30-second physiology baseline and five episodes, each 2-min long. Mothers are seated in a standard chair, infants placed in a highchair facing the mother, close enough that the mother can touch and interact with her child. Following a resting baseline during which the mother sits quietly while the infant watches a video, the dyad engages in a face-to-face natural play (episode E1). The acute caretaker experimental episode (E2) follows in which the caretaker is exposed to an auditory and matching visual and auditory stressor or non-stress control condition. After a brief recorded introductory narrative that the infants were undergoing a medical procedure, caretakers in the experimental

condition hear infant cries over headphones while watching matching images of crying infants on a screen in front of them. In the control condition, mothers hear infant vocalizations (e.g., cooing, gurgling) over the earphones while watching matched images on a screen and a recorded narrative that the infants were playing with an adult.

To ensure mothers focus on the experimental condition, and the infants would not be aware of the mothers' reaction, a screen was set up between her and her infant. All infants stayed in their highchair, were turned away, and a research assistant entertained them with bubbles and finger puppets for the 2-min of the stimulus episode. Thus, infants had the exact same experience regardless of maternal experimental condition.

Next, mother and infant were reunited for another face-to-face play episode (E3), followed by a classic still-face episode (E4) where the mother is asked to stop the interaction, sit back, and maintain a neutral "poker-face" (still-face). The final episode is another face-to-face play (E5; see **Figure 1** for the entire paradigm). The CASP paradigm ended after E5 or was terminated early if an infant showed significant distress (e.g., crying) for more than 30 consecutive seconds. All infants who made it to episode E3 for at least 30 s were included in the study.

MEASURES

Maternal Depressive Symptoms

Maternal stress is often linked to maternal psychopathology, especially maternal depressive symptoms. To assess a possible impact of maternal depressive symptoms on the experimental manipulation, mothers were asked to complete the CESD-R (Center for Epidemiologic Studies Depression Scale-Revised) (65).

Infant Stress Reactivity: Drop Out

The procedure was terminated if an infant showed distress for 30 consecutive seconds either in E3 (play episode after the caretaker stress), E4 (the still-face episode), or E5 (the reunion play episode after the still-face) and were labeled drop-outs. Drop-out episode (E3, E4, or E5) was recorded in the study notes and reviewed for accuracy (30 s distress) on the recorded video. The drop-out episode was then used as a measure of infant stress reactivity, to evaluate whether there was a difference in paradigm termination between the caretaker stress and control condition.

Infant Stress Reactivity: Behavioral Distress

First sign of distress (e.g., the first negative vocalization or cry) was coded by two raters until an agreement was reached to compare if the caretaker-manipulation impacted the infants affect regulation, independent of the duration of that first sign of stress.

Infant Heart Rate

Continuous cardiac data sampled at 1,000 Hz was collected on from mothers and their infants. Software from MindWare Technologies LTD was used for data cleaning and to generate the mean heart rate (HR) for mothers and their infants for each of the 2-min episodes of the CASP paradigm or the matched play-sessions of the control group.

Statistical Analysis

All statistical analyses were carried out with IBM SPSS Statistics for Mac, version 23.

RESULTS

Maternal Depressive Symptoms by Group

The average CESD score was 8.29 ($SD = 5.654$, range: 1–23) for the control group and 10.51 ($SD = 8.895$, range: 0–34) for the experimental group. General linear modeling showed that there was no significant difference in CESD score between groups ($p = 0.141$). In addition, there was no statistical difference in CESD scores between mothers of infants who dropped out of the paradigm due to too much distress compared to mothers of infants who did not drop out ($p = 0.367$).

Infant Dropout After the Caretaker-Manipulation

To evaluate the impact of the caretaker-manipulation on infant stress reactivity, we evaluated the number of infants who showed enough distress to terminate the paradigm. Chi-Square analysis comparing the caretaker-stress group with the control group revealed a significant difference in drop-out rate after the caretaker-manipulation. Significantly more infants in the maternal-stress group dropped out compared to infants in the maternal control group [$X^2 = (1, N = 106) = 4.662$, $p = 0.031$; see **Figure 2A**].

First Sign of Distress During the Paradigm

The episode of first distress was correlated with dropout episode [$r_{(105)} = 0.699$, $p < 0.000$]. A Chi-Square analysis showed that infants of mothers in the stress condition showed their first sign of distress during the (usually positive) play after the caretaker manipulation, while infants of the maternal control group had a higher rate of first distress during the following SF episode [$X^2 = (1, N = 31) = 4.288$, $p = 0.038$; see **Figure 2B**].

Differences in Infant Heart Rate

Univariate general linear modeling showed that there was no difference between infant heart rate during baseline ($p = 0.209$). However, a repeated measure analysis comparing infant heart rate before and after the caretaker stress episode revealed a significant main effect of group by time [$F_{(1, 102)} = 9.81$, $p = 0.002$; **Figure 3**], with a significant increase in infant heart rate from the first play episode (E1) to the second play episode (E3), when mothers were in the stress condition.

Differences in Infant Respiratory Sinus Arrhythmia

Univariate general linear modeling showed there was no significant difference in infant RSA by group at baseline ($p = 0.386$). Infants in the control condition showed a trend for faster RSA recovery [$F_{(1, 75)} = 3.539$, $p = 0.064$, **Figure 4**] during the second play episode (E3) after the caretaker control condition

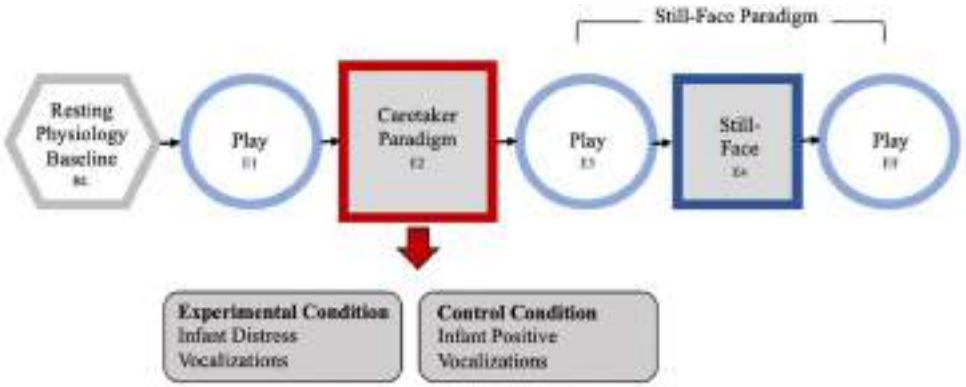

FIGURE 1 | The Caretaker Acute Stress Paradigm, containing a standard 30-s physiology baseline and 5 episodes, each 2 min long. First the dyad engages in a face-to-face natural play (episode E1). The acute caretaker experimental episode (E2) follows: the caretaker is exposed to an auditory and matching visual stressor or control condition. Caretakers in the experimental condition hear infant cries, in the control condition mothers hear infant laughter and giggles over the earphones while watching matched images on a screen. Next, mother and infant were reunited for another face-to-face play episode (E3), followed by a classic still-face episode (E4) where the mother is asked to stop the interaction, sit back, and maintain a neutral "poker-face" (still-face). The final episode is another face-to-face play (E5).

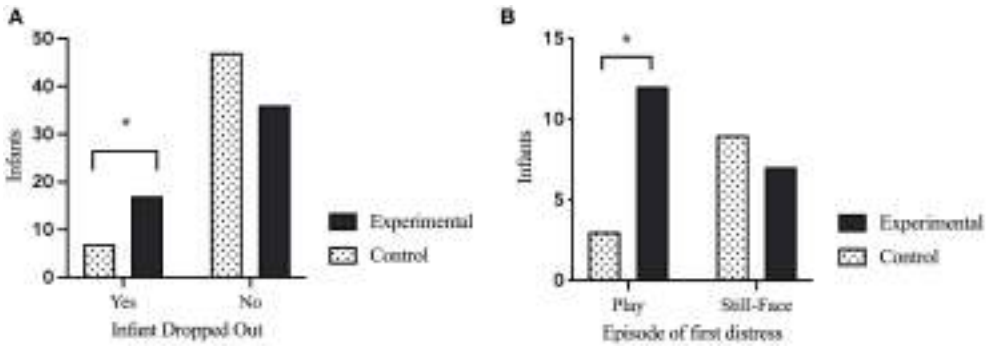

FIGURE 2 | Infant behavioral stress reactivity. **(A)** Infant drop-out of the paradigm due to exhibition of distress crying for 30-consecutive-seconds. Infants in the maternal stress condition had to terminate the procedure significant more often than infants in the control condition [$X^2 = (1, N = 106) = 4.662$, $p = 0.031$]. **(B)** Episode of first distress in the infants during the CASP paradigm. Infants in the maternal stress condition showed first distress significantly more often in the play episode after the caretaker-stress (or control) manipulation compared to infants of the maternal control condition [$X^2 = (1, N = 31) = 4.288$, $p = 0.038$]. $p < 0.05$*.

(E2) compared to infants whose mothers participated in the experimental condition (E2).

Impact of Baseline Heart Rate on Infant Stress Reactivity

A regression analysis was performed to evaluate whether infant baseline heart rate may have contributed to the infants first sign of distress or drop out of the paradigm. Neither maternal nor infant baseline heart rate had a significant association with dropout episode (infant HR_{BL}: $p = 0.893$; maternal HR_{BL}: $p = 0.124$) or first episode to show distress (infant HR_{BL}: $p = 0.459$; maternal HR_{BL}: $p = 0.346$).

DISCUSSION

The present study explored the impact of maternal stress in a laboratory setting on subsequent infant regulation. The newly developed CASP paradigm (59) experimentally manipulates maternal stress in order to observe the immediate effects of maternal stress on the infant and dyad. Our results indicate that exposure to acute caretaker stress affects the infant and the dyad.

On a behavioral level, infants in the maternal stress condition compared to the infants in the control condition showed distress earlier in the paradigm, their distress was more intense, and more of them required early termination of the paradigm. First, infants in the caretaker-stress condition, showed first signs of distress on average more often during the play episode right after the caretaker-intervention, compared to infants whose mothers were in the control condition, who showed more often stress during the typical infant stressor (still face paradigm). The results indicate that maternal stress affects the infant not only during a dyadic challenge, but it has a disruptive effect even on the natural play after the caretaker-stress condition, which is typically expected to be a positive face-to-face play interaction with the mother. Second, infants in the caretaker-stress condition were more likely to require a termination of the experimental procedure as they showed more than 30-s of consecutive distress.

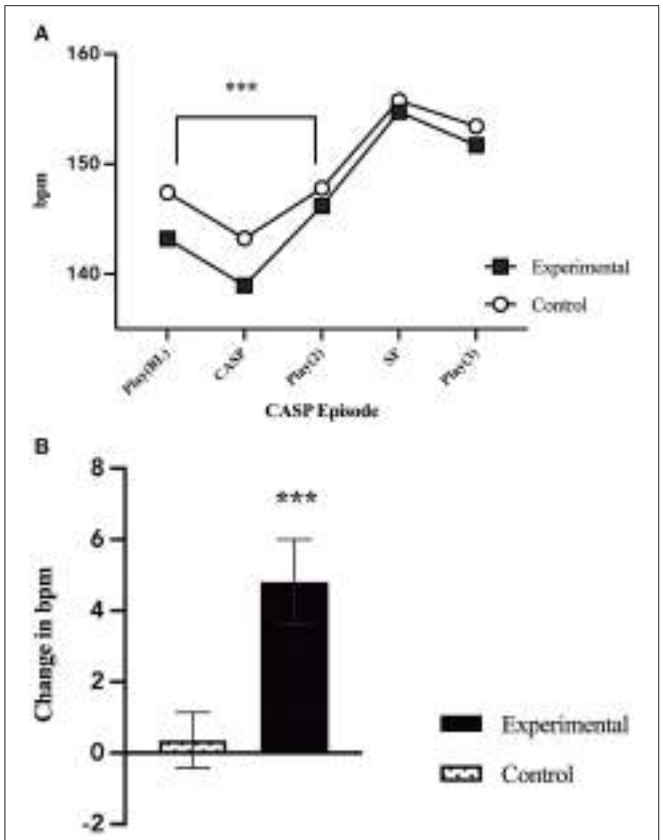

FIGURE 3 | Changes in infant heart rate. **(A)** Infant average heart rate throughout the five CASP episodes by group. There was a significant increase in heart rate from play 1 (E1) to the second play (E3) for infant's who's mothers were in the caretaker-stress condition [$F_{(1,\ 102)} = 9.81$, $p = 0.002$]. **(B)** Comparison of the change in infant average heart rate during play 1 (E1), before caretaker manipulation, and play 2 (E3), after the caretaker manipulation, by group (caretaker-stress or caretaker control condition) [$F_{(1,\ 102)} = 9.81$, $p = 0.002$]. $p < 0.01^{***}$.

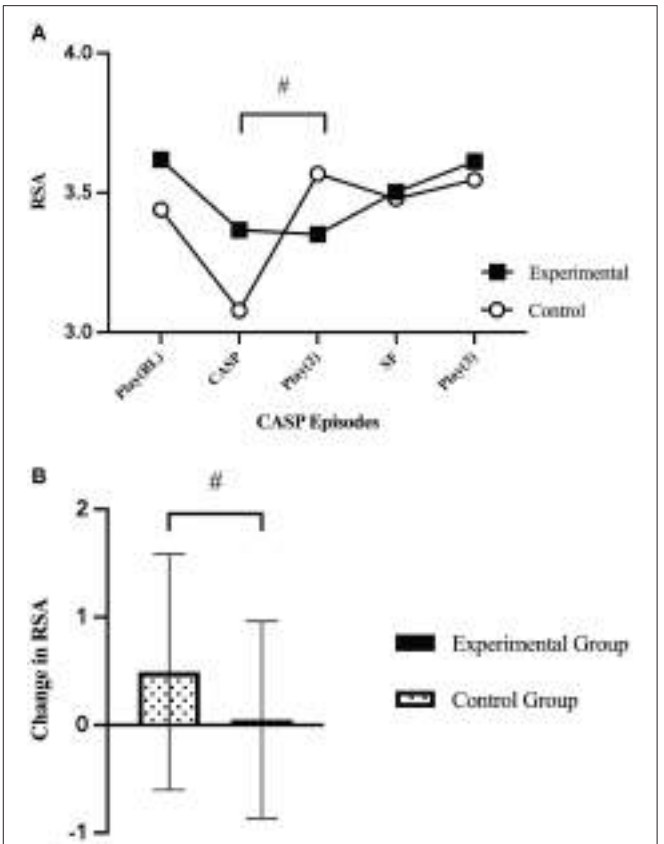

FIGURE 4 | Changes in infant RSA. **(A)** Infant average RSA throughout the five CASP episodes by group [$F_{(1,\ 70)} = 1.26$, $p = 0.294$]. There was a marginal trend between grous in the change in infant RSA from the caretaker manipulation episode (E2) to the second play episode (E3) [$F_{(1,\ 75)} = 3.539$, $p = 0.064$]. **(B)** Change in infant average RSA from the caretaker manipulation (E2) to the second play episode (E3) [$F_{(1,\ 75)} = 3.539$, $p = 0.064$], by group (caretaker-stress or caretaker-control condition). $p < 0.065^{\#}$.

It could be speculated that maternal stress depleted the dyadic resources to co-regulate over the full length of the paradigm. Interesting is also, that less infants of the caretaker-stress condition drop-out during the infant stress paradigm (still face). This could be explained with infants sensible to stress reaching their tolerable limit in the caretaker-stress condition earlier, not making it to the infant-stress episode. These experimental findings support the correlational findings by Pesonen et al. (66) that continued maternal stress over the pre- to postnatal period is associated with higher infant reactivity and by Feldman et al. (67) that infants of mothers with symptoms of depression showed less mature regulatory behaviors and more negative affect.

As regards physiology the infants in the experimental condition showed a significant increase in heart rate after the caretaker stress that was not observed in infants of mothers in the control condition. As the procedure was the same for all infants, the difference indicates that the acute stress in the experimental condition experienced by the caretaker was picked up, reacted to by the infant which may have interfered with the infants' self-regulation, as well as with the dyadic co-regulation. A similar trend was found for infant RSA, a measure of regulation rather than arousal. We observed that the infant RSA in both groups decreased, an indication of dysregulation during the caretaker stress (or control) condition, probably due to the brief separation from the mother. However, infants whose mothers were in the control condition had a faster RSA recovery as soon as the caretaker episode was over when they were reunited with their mothers. The majority of infants from the caretaker stress condition, contrariwise, did not show an RSA recovery after the infants were reunited with their mothers. The RSA recovery finding supports the original hypothesis of this study that caretaker stress leads to a disruption of regulatory resources, which then interferes with the dyad's ability to regulate stress (29, 30). Previous studies on maternal stress, namely maternal psychopathology, have found similar results, indicating a higher mean heart rate and weaker RSA recovery in exposed infants (38, 68).

Overall, the results indicate that even a brief and acute maternal stressor impacts infant physiology and emotional stress regulation. The findings are in line with research observing a lower dyadic ability to regulate after prolonged exposure to

maternal stress (16, 34) and the observation that children exhibit an elevated stress response after exposure to high maternal stress (69, 70). However, most studies related to caregiver stress find that current levels and previous levels of high stress often overlap, making it difficult to distinguish whether previous or current exposure has a greater impact (70). The CASP paradigm allows us to investigate the impact of acute maternal stress on the dyadic interaction as well as the infants stress response. While acute stress may not be comparable to chronic exposure, it still allows for controlled laboratory observations with a control group to develop a better understanding how caregiver stress may affect the infants behavioral and physiological regulatory organization.

Limitations and Future Directions

Limitations of this study include not accounting more detailed for maternal background. Previous studies have shown that maternal prenatal mental health, such as own adverse childhood experiences (ACE) or lifetime traumatic stress can affect infant regulation (69, 71). Future studies with the CASP should control for these measures or actively use them to create groups to learn more about the effect of maternal ACE or traumatic experiences on dyadic regulation of acute caretaker stress. The present study included current maternal depressive symptoms (CESD), while there was no statistical difference in maternal depressive symptoms between groups, there was a numerical difference in the highest CESD score in the caretaker-stress condition compared to the caretaker-control condition (34 vs. 23). However, we also tested if there was a difference in our main behavioral variable (infant drop-out of the paradigm) and found no statistical difference in maternal depressive symptoms of infants in the caretaker-stress and caretaker-control condition who had to terminate the procedure due to the 30-s consecutive distress limit.

Similarly, the majority of participating dyads were white. Previous research shows that maternal stress and factors that cause maternal stress, such as racism or lower socioeconomic status, are still more present in populations that belong to the global majority (back, indigenous, and people of color), which could have affected the results.

While the CASP is an attempt to measure maternal stress in a controlled laboratory setting, it measures acute, not chronic stress exposure. However, it would be important to investigate how these chronic factors (maternal exposure to racism, ACE, trauma, and SES) that have been shown to influence infant behavioral and physiological regulatory capacity affect the acute stress regulation in an experimental setting. This is one of the promising possibilities the new CASP paradigm opens research up to; it is possible to control for the effects of acute maternal stress, with a clear definition and allows to compare different maternal adversities, backgrounds, and preconditions. Large studies will allow cross-over designs, where dyads complete both the caretaker-stress and caretaker-control condition. Further, large studies could compare more than two groups, extending to maternal-healthy caretaker-stress, maternal-depression caretaker-stress compared to two control groups with matched diagnosis.

Remarkably, the findings indicate that even a brief laboratory stressor can affect the dyad in such a significant way that infant behavioral and cardiovascular regulation is compromised. Future research with the caretaker acute stress paradigm (CASP) will add to our understanding on the underlying mechanisms involved in the association between maternal depletion of resources and infant regulation. It would be especially interesting to observe dyads from a high-risk sample such as infants with depressed mothers. Results on the impact of maternal depressive symptoms have been equivocal but based on the literature one could assume a greater challenge of an additional caretaker stressor. However, it would be also within the scope of current literature to assume a better adaption of the infant to a stressed caretaker (for review, see (72)) and subsequently a better adjustment of the dyad to the CASP.

Overall, the CASP offers new opportunities to study the independent effects of maternal stress on the dyad and its interplay with other risk factors. Observations within a controlled laboratory setting will allow us to gain new insight into subtle variations of caregiving under stress in a more objective way than previous studies, extending our understanding of the underlying behavioral and physiological mechanisms associated with maternal stress.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB office at the University of Massachusetts Boston. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

IM, NS, JD, and ET contributed to conception and design of the study. JD and IM organized the database. IM performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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The Impact of Maternal Anxiety on Early Child Development During the COVID-19 Pandemic

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Background: Maternal prenatal anxiety is among important public health issues as it may affect child development. However, there are not enough studies to examine the impact of a mother's anxiety on the child's early development, especially up to 1 year.

Objective: The present prospective cohort study aimed to examine whether maternal trait anxiety, perceived social support, and COVID-19 related fear impacted speech-language, sensory-motor, and socio-emotional development in 12 months old Serbian infants during the COVID-19 pandemic.

Methods: This follow-up study included 142 pregnant women (Time 1) and their children at 12 months (Time 2). Antenatal maternal anxiety and children's development were examined. Maternal anxiety was assessed using the State-Trait Anxiety Inventory (STAI). Child speech-language, sensory-motor, and socio-emotional development were assessed using the developmental scale in the form of an online questionnaire that examined the early psychophysiological child development. Information on socioeconomic factors, child and maternal demographics, clinical factors, and perceived fear of COVID-19 viral infection were collected. Multivariable General Linear Model analysis was conducted, adjusted for demographic, clinical, and coronavirus prenatal experiences, maternal prenatal anxiety levels, perceived social support, speech-language, motor skills, and cognitive and socio-emotional development at the infants' age of 12 months.

Results: The study revealed the influence of the COVID-19 pandemic on maternal trait anxiety. The association between selected independent factors and infants' development was found in a demographically unified sample except for employment and the number of children. There was a correlation between all observed developmental functions. Univariate General Linear model statistical analysis indicated that linear models with selected independent factors and covariates could account for 30.9% (Cognition) up to 40.6% (Speech-language) of variability in developmental functions. It turned out that two-way and three-way interactions had a dominant role on models, and STAI-T Level and COVID-19 related fear were present in all interaction terms.

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Conclusion: Our findings reveal important determinants of child developmental outcomes and underline the impact of maternal anxiety on early child development. These findings lay the groundwork for the following interdisciplinary research on pregnancy and child development to facilitate and achieve positive developmental outcomes and maternal mental health.

Keywords: perinatal mental health, maternal anxiety, infant development, social support, COVID-19 pandemic, COVID-19-related fear

INTRODUCTION

The conditions under which intrauterine development happens and the influences during childbirth and the postpartum period form the child's essential psychophysiological capacity. There is accumulating evidence about the importance of the first 1,000 days of life to a child's overall development (Black et al., 2017). During prenatal and early child development brain adapts in response to a wide range of early experiences, which supports the rapid acquisition of language, cognitive skills, and socioemotional competencies (Luby, 2015; Britto et al., 2017).

The prenatal period is the sensitive period for child development, in which negative associations between prenatal exposure to maternal anxiety and outcomes are observed (Comaskey et al., 2017). In this respect, perinatal maternal health may play an important role and influence the child's early development. A woman's mental health during pregnancy and the first year after birth refers to perinatal mental health. It includes mental health difficulties that occur before or during pregnancy and mental health problems that appear for the first time and can significantly increase during the perinatal period (Rees et al., 2019). Findings in the literature point to maternal mental well-being as crucial for optimal infant health (Ryan et al., 2017).

On the other hand, maternal mental health problems are considered a significant public health issue. Depression, anxiety, and high levels of perceived stress are the most common mental health problems during pregnancy (Hamid et al., 2008; Martini et al., 2015; Ryan et al., 2017; Rees et al., 2019).

Perinatal anxiety refers to anxiety experienced during the pregnancy and/or the first 12 months after birth. It may be significantly associated with postnatal anxiety (Grant et al., 2008). According to previous epidemiological studies, the prevalence of women who experienced high anxiety during pregnancy ranges from 6.8 to 59.5% (Leach et al., 2017). Research on the dynamics of the anxiety manifestation during pregnancy is inconsistent. While some authors reported a significant increase in anxiety during the last trimester of pregnancy (Gunning et al., 2010), others pointed to stable pregnancy-specific anxiety across all three trimesters of pregnancy (Rothenberger et al., 2011). In line with this, it is crucial to notice the difference between general anxiety and pregnancy-specific anxiety. These two entities are considered strictly interrelated, although the mechanisms of interrelation are not fully documented (Huizink et al., 2014). While pregnancy anxiety refers to an emotional state that is mostly situationally or contextually conditioned, general anxiety—trait anxiety, in particular, can be maintained and last in the period after pregnancy. In that way, general anxiety may continue to affect a mother's mental health and influence mother-child interaction (Huizink et al., 2014).

The impact of pregnant woman's anxiety on early child development has been a focus of recent studies. More specifically, interest in studying the link between prenatal anxiety and early childhood development has increased in the past 20 years. Van den Bergh et al. (2005) supported a fetal programming hypothesis and pointed out that the development of the hypothalamo–pituitary–adrenal (HPA) axis, limbic system, and the prefrontal cortex may be affected by maternal prenatal stress and anxiety. It results in cortisol passing through the placenta, affecting the fetus and disturbing ongoing developmental processes. Studies examining the impact of maternal postnatal anxiety on child development have indicated possible findings within three domains: somatic, developmental, and psychological outcomes (Glasheen et al., 2010). Similarly, studies examining the same outcomes about prenatal maternal anxiety suggest that maternal anxiety during pregnancy may also have long-lasting consequences on child development and behaviour (Dunkel Schetter and Tanner, 2012; Huizink et al., 2014). Research evidence indicates that high levels of maternal anxiety symptoms are associated with a wide range of adverse cognitive, behavioural, and neurophysiological offspring outcomes (O'Connor et al., 2014), as well as with temperamental and developmental problems (Hernández-Martínez et al., 2008). Infants of mothers with high trait anxiety have a predisposition to suboptimal nervous system development and may have an increased vulnerability for developing motor problems (Kikkert et al., 2010). On the other hand, research data on the direct impact of perinatal maternal anxiety on children's emotional problems lacks cohesion and indicate that maternal prenatal anxiety has a slight adverse effect on child emotional outcomes (Rees et al., 2019).

In addition, maternal anxiety in pregnancy is also associated with perceived social support (Sharif et al., 2021). Similarly to maternal anxiety, a pregnant woman's lack of perceived support may negatively affect her mental well-being, fetus, and close family members (Aktan, 2012). Social support plays a significant role in stressful life events and includes providing emotional, informational, and practical physical support (financial and material) during the time of need and within a person's social network (Dambi et al., 2018; Sharif et al., 2021). Research on social support during pregnancy has shown that it may be a strong predictor of a healthy pregnancy (Naveed et al., 2018).

Several studies on the population of pregnant women found that social support plays a significant role in maternal well-being, while perceived lack of social support leads to mental health problems (Aktan, 2012; Denis et al., 2015; Sharif et al., 2021).

The mentioned aspects that may affect infant and child development need to be additionally considered to the coronavirus disease 2019 (COVID-19), which has grown into a global pandemic declared by the World Health Organization (WHO) on March 11, 2020 (Cucinotta and Vanelli, 2020). COVID-19 was reported for the first time in Wuhan, China, in December 2019, with increasing global transmission (Api et al., 2020). Data on the COVID-19 in the Republic of Serbia show that the first case of COVID-19 was reported on March 6, 2020, and soon after it, precisely on March 15, 2020, a state of emergency was declared in the whole country (Stašević-Karličić et al., 2020). Psychological impacts of COVID-19 on pregnancy have already been explored in recent studies (Quinlivan and Lambregtse-van den Berg, 2020; Usher et al., 2020; Yan et al., 2020; Motrico et al., 2021). An accompanying phenomenon of the COVID-19 pandemic is the fear of COVID-19 viral infection, which can intensify the level of anxiety (Andrade et al., 2020). Although the symptoms of anxiety manifested by individuals during the epidemic/pandemic may be similar to those expressed in other anxiety situations, it is noticed that there are specific forms of anxiety-related distress responses during viral outbreaks and the COVID-19 pandemic as well (Asmundson and Taylor, 2020). Some major factors which contribute to specificity of pandemic anxiety are the fear of becoming infected and dying, socially disruptive behaviors, and adaptive behaviors (Asmundson and Taylor, 2020; Bernardo et al., 2020; Wang et al., 2020). In other words, the increased risk of death (Aldridge et al., 2020), additionally unemployment and economic losses (Coibion et al., 2020), and numerous restrictions introduced by the countries' governments around the world, lead to negative health consequences (Meyerowitz-Katz et al., 2021), that include pandemic anxiety with its specifics as well (Bernardo et al., 2020). Accordingly, a fair number of studies have been published indicating an increase in anxiety symptoms in pregnant women during the COVID-19 pandemic (Ayaz et al., 2020; Corbett et al., 2020; Durankuş and Aksu, 2020; Kotabagi et al., 2020; Lebel et al., 2020; Moyer et al., 2020; Saccone et al., 2020; Wu et al., 2020; Yue et al., 2021). So far, there are studies, systematic reviews, and meta-analyses in which the prevalence of pregnant women with moderate to severe anxiety during the COVID-19 pandemic is given more precisely (Corbett et al., 2020; Hessami et al., 2020; Lebel et al., 2020; Mappa et al., 2020; Saccone et al., 2020; Fan et al., 2021; Sun et al., 2021; Tomfohr-Madsen et al., 2021). Accordingly, it ranges from: 23.4% found in Brazil (Nomura et al., 2021); the 29% was determined during the initial stage of the COVID-19 pandemic in China (Wang et al., 2020), while 25% was determined by meta-analysis (Ren et al., 2020); the 38% was found in Poland (Nowacka et al., 2021); the elevated level of the trait (38.2%) and state anxiety (77%) was found in Italy (Mappa et al., 2020). Higher prevalence in the range from 53 to 72% was found in other countries (Corbett et al., 2020; Dagklis et al., 2020; Davenport et al., 2020; Hessami et al., 2020; Lebel et al., 2020; Saccone et al., 2020; Sut and Kucukkaya, 2020). In contrast to these studies, a lower prevalence of anxiety among pregnant women (8.4% of whom had moderate anxiety and 5.2% of whom had severe anxiety) was determined in Belgium (Ceulemans et al., 2020), while COVID-19 did not increase anxiety levels in Dutch pregnant women (Zilver et al., 2021).

Generally, the analysis of the most recent systematic reviews and meta-analysis have shown that the prevalence of anxiety in pregnancy during COVID-19 ranges from 30.5 to 42%, the prevalence of depression ranges from 25 to 30%, and prevalence of both anxiety and depression was 18% (Fan et al., 2021; Sun et al., 2021; Tomfohr-Madsen et al., 2021).

Pregnant women may be affected by various aspects of COVID-19 pandemic that can cause negative implications on both maternal well-being and child development, which imposes the need for longitudinal studies of the COVID-19 birth cohort (Quinlivan and Lambregtse-van den Berg, 2020).

Given the clear need for longitudinal studies on the impact of maternal prenatal anxiety on early child development generally, and especially during the COVID-19 pandemic, the present prospective cohort study aimed to examine whether maternal trait anxiety, COVID-19 related fear and perceived social support were associated with speech-language, sensory-motor and socio-emotional development in 12 months old Serbian infants during COVID-19 pandemic. Demographic characteristics of mothers were also controlled in the analyses. Generally, it was hypothesized that maternal trait anxiety and COVID-19 related fear are prospectively and directly associated with infant development and may affect an infant speech-language, sensory-motor and socio-emotional development.

MATERIALS AND METHODS

Study Design, Setting, and Participants

The present ongoing prospective cohort study is a part of a more extensive experimental study that examines maternal anxiety during pregnancy and its associated factors in the context of the COVID-19 pandemic in Serbia. This investigation examines the impact of maternal anxiety during pregnancy on early child development. Between April 2020 and December 2020, 900 pregnant women were included in the cohort. Expectant mothers were recruited consecutively, in the order in which they came for a regular examination during pregnancy on the Clinic for gynaecology and obstetrics "Narodni Front" in Belgrade. Women in the third trimester of pregnancy were asked to voluntarily fill out an anonymous self-administered questionnaire in a pleasant atmosphere in the waiting room during a time-optimal for them. The questionnaire contained socio-demographics, pregnancy-related background, maternal mental health, perceived social support, perceived COVID-19 related fear, and personal contact information related to an e-mail address and/or mobile phone. It is emphasized that personal contact information should be written if the pregnant woman agrees to provide data on her child development later in the longitudinal research. Of the total sample, 209 women did not complete the questionnaire, 187 women partially completed, while 145 women did not meet defined inclusion and exclusion criteria. The inclusion criteria for the study were: normal singleton pregnancy

without complications of any kind; singleton pregnancies with the presence of hypertension, diabetes, or preterm delivery symptoms; spontaneous conception, delivering a phenotypically normal live birth, no pre-and perinatal risk factors. The exclusion criteria for the study were: failure to meet the inclusion criteria, infertility treatment; hospitalization; history of pre-eclampsia, eclampsia, autoimmune diseases, cancer, or any general chronic illnesses except hypertension or diabetes; psychiatric illnesses verified and/or treated before pregnancy; use of tranquilizers or sedatives, tobacco, alcoholic beverages, or any other type of psychoactive substances; non-acceptance of participation in the study. The final sample comprised 359 pregnant women in whom it was possible to examine the presence of anxiety during the COVID-19 pandemic in Serbia. All participants signed their written informed consent prior to the study, and confidentiality of the responses was assured.

The present study included a follow-up assessment of children aged 11.5 to 12.5 months whose mothers participated in a baseline assessment of maternal anxiety during the third trimester of pregnancy. Between May 2021 and September 2021, all mothers whose children aged 11.5 to 12.5 months were invited to participate in the study. Out of the sample of 359 pregnant women, 256 left personal contact information, while 221 of them met the criteria regarding the assessment of their children at the age of 1 year. In order to observe the possible influence of anxiety on early child development, we excluded mothers who had pregnancy complications. Thereby, the sample was reduced to 164 mothers who had normal singleton pregnancies without complications of any kind. Mothers were invited to complete an online questionnaire on their child's development by phone or e-mail. After collecting and analyzing the obtained data, the final analysis showed that 19 mothers did not complete, while three mothers partially completed the questionnaire related to child development. The final sample included $n =$ of 142 mothers who completed the questionnaire related to child development (**Figure 1**). By completing the questionnaire, the mothers gave their consent to participate in the study. The sample was uniform with regard to all demographic factors except employment and the number of children.

The complete study protocol had been approved by the Ethics Committee of the Clinic for Gynecology and Obstetrics "Narodni Front" (Date: 26 March, 2020, No 27/20), in Belgrade, and by the Ethics Committee of the Institute for experimental phonetics and speech pathology (Date: 2 April, 2020, No 45/20), in Belgrade, which operates under the Ethical principles in medical research involving human subjects, established by the Declaration of Helsinki 2013.

FIGURE 1 | Definition of participation process by flow-chart.

Measures

A self-administered anonymous questionnaire included questions related to socio-demographics, pregnancy-related background, maternal anxiety, perceived social support and perceived COVID-19 related fear.

Maternal trait anxiety was measured with the Spielberger State-Trait Anxiety Inventory (STAI), which is a frequently used measure for self-reported anxiety (Spielberger et al., 1983). Spielberger questionnaire form Y was used in our study (Spielberger et al., 2000). The STAI consists of two scales: state anxiety scale (STAI-S) and trait anxiety scale (STAI-T), each containing twenty items. STAI-S measures anxiety as a current state, while STAI-T measures anxiety as a personality trait, and it is considered to be more stable and more long-lasting (Easter et al., 2015). Since STAI-S is relatively transient and variable over time (Floris et al., 2017; Papadopoulou et al., 2017), it was not possible to conduct measurements by applying it in

short time intervals during the COVID-19 pandemic, which would enable obtaining a reliable mean value of the current state of anxiety during the first year of a child's life. Concerning that, we evaluated only the STAI –T, as it measures relatively stable individual differences in propensity for anxiety (Julian, 2011). Participants select responses on a four-point Likert scale, ranging from "almost never," "sometimes," "often," and "almost always." The total score ranges between 20 and 80, with higher scores indicating greater anxiety levels. Some authors use cut-off points to define two-level state and trait anxiety (low and medium/high) (Özpelit et al., 2015; Mappa et al., 2020, 2021). We used three-level cut-off points for reasons described in the literature (Tomašević-Todorovic et al., 2012; Candelori et al., 2015). Accordingly, STAI-T scores were classified as "no or low anxiety" (20–30), "moderate anxiety" (31–44), and "high anxiety" (45–80).

Maternal perecption of social support was assessed with The Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet et al., 1988), the Serbian version of the scale (Pejičić et al., 2018). MSPSS consists of twelve items divided into three subscales that measure the perception of social support from three sources: family, friends and significant others. Responses are rating on a seven-point Likert scale, ranging from 1 ("very strongly disagree") to 7 ("very strongly agree"). The maximum score is 84 and indicates the highest degree of perceived social support. In the study, the total MSPSS score was used in the calculation and interpretation of the results.

COVID-19-related fear was assessed using a single item question "Do you feel a fear of COVID-19 viral infection?" Participants select one of three responses: 1–"I do not feel a fear of COVID-19 viral infection"; 2–"Sometimes, not all the time I feel a fear of COVID-19 viral infection"; and 3-"I do feel a fear of COVID-19 viral infection."

Language, sensory-motor and socio-emotional development in 12 months old infants were assessed by The Scale for Evaluation of Psychophysiological Abilities of Children (Subota, 2003; Rakonjac et al., 2016; Vujović et al., 2019; Bogavac et al., 2021). The Scale for Evaluation of Psychophysiological Abilities of Children (SEPAC) is created according to developmental norms of the child from birth to 7 years. It comprises subtests specific for different months up to the first year of life and different years of age to the seventh year of life. Each subtest consists of three subscales: Speech-language scale, Sensory-motor scale and Socio-emotional scale. The speech-language scale consists of questions through which receptive speech, expressive speech and non-verbal communication are assessed. The sensory-motor scale consists of questions through which motor skills and cognition are assessed. Finally, the socio-emotional scale consists of questions through which a child's experience and self-regulation (child's social behaviour, emotional behaviour, regulation of attention, and thoughts) are assessed. The child's achievements within each scale are assessed with three possible answers: answer "+" indicates that your baby is performing the specified activity; answer "+/–" indicates that your baby sometimes or insufficiently performs an assessed activity, and answer "–" indicates that your baby is not yet performing an assessed activity. For the scoring of the test, answers marked with "+"are scored with 2 points, answers "+/–" with 1 point, and answers marked with "–" are scored with 0 points. In our study, we used a subtest that assesses the psychophysiological abilities up to 12 months of age. It consists of 43 simple, straightforward questions related to the assessment of the following abilities and skills: receptive and expressive speech (13), sensory-motor skills (9), cognition (12), and socio-emotional skills (9). The maximal number of points on subtests is 26, 18, 24, and 18, respectively.

Statistical Analyses

Only women who completed the two questionnaires were included in the analyses. Descriptive statistics were used to determine central tendencies and distributions of variables. To determine the existence of relationships between variables, we conducted a bivariate correlation analysis. To investigate the effects of individual factors on the variables of interest and interactions between factors, we conducted Univariate General Linear Model Analysis. To perform hypothesis testing, a priori contrasts were applied and, depending on results *post-hoc* test. Statistical Package for the Social Sciences version 22.0 was used.

Before any statistical test, appropriate assumptions were checked. For STAI-T and MSPSS, we defined the new variables STAI-T level and MSPSS level, dividing the main variables into three groups. For STAI-T level, range limits are: if STAI-T is $\leq$30 Level is Low (1), if STAI-T is between 31 and 45 Level is Intermediate (2) and for values >45 Level is High (3). For MSPSS level range limits are: Low (1) <35; Medium (2) between 36 and 60; High (3) >61.

RESULTS

Sample Characteristics

The final sample consisted of 142 mothers with a mean age of 29.56 years (SD = 4.88). The majority of participants (n = 88, 61.97%) had Bachelor's degree or higher, while 63.38% (n = 90) of them were employed. There were 50.70% (n = 72) mothers having one child and 49.30% (n = 70) having two or more children. Almost half of the participants (n = 64, 45.07%) reported having a COVID-19-related fear, 39.44% (n = 56) reported having no COVID-19 related fear, while 15.49% (n = 22) reported that they sometimes have a COVID-19 fear. Half of the participants (50.70%, n = 72) had an intermediate level of anxiety, while 49.30% (n = 70) had a high level of anxiety measured on STAI-T. The vast majority of participants (81.69%, n = 116) had an intermediate level of anxiety, while 18.31% (n = 26) had a high level of anxiety measured on STAI-S. All participants reported a high level of perceived social support. Baseline sample characteristics are shown in **Table 1**.

The average STAI-T score was 44.59 ± 4.61. As previously mentioned (**Table 1**), no participants had scores corresponding to low anxiety levels. When observing the findings of social support, it is noticed that the average MSPSS score was 76.70 ± 7.14. Results related to infant's achievement included the estimation of speech-language development, sensory-motor development in which the development of motor skills and

TABLE 1 | Sample description ($N = 142$).

Sample characteristics	Mothers ($N = 142$) Mean (SD) or (%)	
Maternal age (years)	29.56	(4.88)
Years of school education		
<12 years	88	(61.97)
12 or more years	54	(38.03)
Employment status		
Employed	90	(63.38)
unemployed	52	(36.62)
Number of children		
One child	72	(50.70)
Two or more children	70	(49.30)
COVID-19-related fear		
Having a COVID-19-related fear	64	(45.07)
Having no COVID-19 related fear	56	(39.44)
Sometimes have a COVID-19 fear	22	(15.49)
STAI-T		
Low anxiety level	–	–
Intermediate anxiety level	72	(50.70)
High anxiety level	70	(49.30)
STAI-S		
Low anxiety level	–	–
Intermediate anxiety level	116	(81.69)
High anxiety level	26	(18.31)
MSPSS		
Low perceived support	–	–
Medium perceived support	–	–
High perceived support	142	(100)

TABLE 2 | Descriptive statistics on maternal anxiety, perceived social support, and infants' achievement.

Variable	Min.	Max.	Mean	SE	SD
Maternal age	19.00	39.00	29.56	0.409	4.88
STAI-T	31.00	55.00	44.59	0.387	4.614
MSPSS	62.00	84.00	76.70	0.599	7.137
Speech-language development	12.00	26.00	20.27	0.302	3.602
Motor skills	4.00	18.00	13.33	0.296	3.524
Cognition	11.00	24.00	18.99	0.304	3.619
Socio-emotional development	7.00	18.00	14.22	0.246	2.930

cognition was observed as two separate variables, and socio-emotional development. The average speech-language score was 20.27, which is 77.9% of maximal achievement score; the average motor skills score was 13.33, which is 74.06% of maximal achievement score; the average cognition score was 18.99, which is 79.12% of maximal achievement score, and the average socio-emotional score was 14.22 which is 79% of maximal achievement score (**Table 2**).

TABLE 3 | Descriptive statistics for STAI-T and MSPSS related to COVID-19 related fear.

	COVID-19 related fear	*N*	Mean	SD	SE
STAI-T	No	64	43.53	4.75	0.594
	Sometimes	56	45.46	3.95	0.528
	Yes	22	45.45	5.30	1.129
MSPSS	No	64	73.84	7.77	0.972
	Sometimes	56	79.11	5.13	0.6868
	Yes	22	78.91	6.80	1.449

One-Way Anova

Comparing mean values for STAI-T and MSPSS related to fear of getting COVID-19 (**Table 3**) shows that mean values are not equal.

One-Way ANOVA statistical test was used to check the impact of COVID-19 related fear on STAI-T and MSPSS. For STAI-T, homogeneity of variance is not violated, and *post-hoc* test with Tukey-Kramer correction for multiple comparisons (uneven sample size) was used. The MSPSS Games-Howell method was used because of its robustness when homogeneity of variance is violated, and the sample size is unequal.

There was statistically significant difference for STAI-T $F_{(2,139)} = 3.171$, $p = 0.045$. *Post-hoc* test revealed that there was no statistically significant difference between groups.

It was found that there is a statistically significant difference for MSPSS between the observed groups $F_{(2,139)} = 10{,}646$, $p < 0.001$. *Post-hoc* test showed statistically significant difference between groups 1 and 2 ($p = 0.016$), 1 and 3 ($p < 0.001$) and that there was no statistically significant difference between groups 2 and 3 ($p = 0.992$).

Mothers who reported no COVID-19 related fear have lower perceived social support (mean value 73.8) than mothers in the other two groups (**Table 3**).

Correlations

Bivariate correlation analysis revealed a statistically significant correlation between Speech-language and Motor skills, Cognition and Socio-emotional status (**Table 4**). The highest correlation is between Speech-language and Socio-emotional status [$r_{(140)} = 0.744$, $p < 0.001$]. Also, there is a low but statistically significant correlation between the child's socio-emotional status and maternal trait anxiety $r_{(140)} = 0.184$, $p = 0.028$.

The association between factors and developmental abilities (**Table 5**) ranges between weak and medium. If the mean value of eta for all developmental functions is observed to assess the association of individual factors and the child's overall development, then that association is at the level of medium association for STAI-T and weak for the other three factors.

Multifactor Analysis

It was not possible to model the relationship between children developmental abilities (Speech-language, Motor skills, Cognition and Socio-emotional status) and STAI-T, MSPSS,

TABLE 4 | Pearson correlation between variables of interest.

		Speech-language	Motor skills	Cognition	Socio-Emotional status
Speech-Language	Pearson corr.	1	0.273**	0.544**	0.744**
	Sig. (2-tailed)		0.001	0.000	0.000
Motor skills	Pearson corr.	0.273**	1	0.379**	0.276**
	Sig. (2-tailed)	0.001		0.000	0.001
Cognition	Pearson corr.	0.544**	0.379**	1	0.698**
	Sig. (2-tailed)	0.000	0.000		0.000
Socio-Emotional status	Pearson corr.	0.744**	0.276**	0.698**	1
	Sig. (2-tailed)	0.000	0.001	0.000	
Maternal age	Pearson correlation	−0.007	0.046	−0.035	−0.079
	Sig. (2–tailed)	0.938	0.590	0.682	0.353
STAI-T	Pearson correlation	0.163	−0.108	0.159	0.184*
	Sig. (2-tailed)	0.052	0.203	0.059	0.028
MSPSS	Pearson correlation	0.122	0.150	0.091	0.019
	Sig. (2-tailed)	0.149	0.075	0.283	0.825

*Significant correlations are marked in grey. *significance at the level $p < .05$. **significance at the level $p \leq .001$.*

TABLE 5 | Level of association between development abilities and factors.

Developmental function	Level of association η			
	STAI-T level	COVID fear	Number of children	Employment
Communication	0.405	0.475	0.371	0.432
Motor skills	0.449	0.277	0.331	0.449
Cognition	0.515	0.313	0.353	0.266
Socio emotional	0.254	0.378	0.415	0.363
Mean value	0.40575	0.36075	0.3675	0.3775

COVID-19 related fear, employment, maternal age and number of children that mother has, with multivariate GLM because Box's Test revealed that Equality of Covariance Matrices across groups is violated. Box's M = 359.32, $F_{(100,5,441.018)} = 2.833$, $p < 0.001$. Levene's Test of Equality of Error Variances revealed that the assumption of equality is not violated, so we conducted separate univariate GLM tests where dependent variables were Speech-language, Motor skills, Cognition and Socio-emotional status with factors: employment, number of children, COVID-19 related fear, and STAI-T level. Mother age and MSPSS were included in the model as covariates.

To determine if there was statistically significant difference between mean values of groups within interaction terms, new grouping variables were composed for each interaction term (**Appendix A**). One–way ANOVA for dependent variables was conducted. Only interaction terms of dependent variables with Observed Power >0.8 were considered.

Results of Speech-Language Achievement

Univariate GLM analysis for dependent variable SPEECH-LANGUAGE achievement revealed that full linear model (**Appendix B**) could explain 40.6% of variability $F_{(21,120)} = 3.902$, $p < 0.001$, $\eta p^2 = 0.406$ and Observed Power = 1. Maternal age and Employment as a main effects have statistically significant impact on the model. Impact of the Employment can't be analyzed separately because of its interaction with COVID-19 related fear and STAI-T level. The biggest contribution to model has interaction term Number of children * COVID-19 related fear * STAI-T level (Partial eta squared = 0.182).

One-way ANOVA revealed that there was no statistically significant difference between groups of interaction terms Employment * COVID-19 related fear [$F_{(5,136)} = 2.034$, $p = 0.078$] and Employment * STAI-T level [$F_{(3,138)} = 2.199$, $p = 0.091$] but for interaction term Number of children * COVID-19 related fear * STAI-T level, there is statistically significant difference between groups $F_{(11,130)} = 2.839$, $p = 0.002$. *Post-hoc* test with Tukey-Kramer correction was used. It turns out that group of children whose mothers have one child, sometimes fearing getting COVID-19 infection and intermediate level of STAI-T (group 2) have the highest level of speech-language achievement (mean value = 22.67). There is statistically significant difference between this group and group 4 (p2–4 = 0.006). On the other hand, children groups 3, 4, and 12 have minimal speech-language achievements (17.50, 17.56, 17.50, respectively), but there were no statistically significant differences between group mean values except mentioned between groups 2 and 4. Explanation of membership to the variable group is given in Table c in **Appendix A**.

In **Figure 2**, the plot of estimated marginal means of dependent variable Speech-language for statistically significant interactions is presented as an example of interaction terms in all four univariate GLM models.

Results of Motor Skills Achievement

Univariate GLM analysis for dependent variable MOTOR skills achievement revealed that the full linear model (**Appendix B**) could explain 34.7% of variability $F_{(21,120)} = 3.031$, $p < 0.001$, $\eta p^2 = 0.347$ and Observed Power = 0.999. One-way ANOVA for interaction term Employed * COVID-19 related fear * STAI-T level revealed statistically significant difference between groups $F_{(11,130)} = 2.206$, $p = 0.018$. It turns out that children from group 6 had the highest (mean value = 16.00), and children group 11 had the lowest level (mean value 11.42) of Motor skills achievement. *Post-hoc* test with Tukey-Kramer correction revealed that there was no statistically significant difference between particular groups. Explanation of membership to the variable group is given in Table d in **Appendix A**.

Univariate GLM analysis for dependent variable COGNITION achievement revealed that full linear model (**Appendix B**) could explain 30.9% of variability $F_{(21,120)} = 2.555$, $p = 0.001$, $\eta p^2 = 0.309$ and Observed Power = 0.997.

One-way ANOVA revealed a statistically significant difference between groups of interaction term Employed * COVID-19 related fear [$F_{(5,136)} = 2.825$, $p = 0.017$]. *Post-hoc* test with Tukey-Kramer correction was used. It turns out that group 5 has the highest level of cognitive achievement (mean value = 21.5). There is statistically significant difference between this group and groups 3 and 4 (p5–3 = 0.016, p5–4 = 0.021). On the other hand, children group 3 has minimal Cognitive achievement (mean value = 17.44), but there was no statistically significant difference between group mean values except mentioned between groups 3 and 5. Explanation of membership to the variable group is given in Table a in **Appendix A**.

For interaction term Number of children * COVID-19 related fear * STAI-T level, we obtained statistically significant difference between groups $F_{(11,130)} = 2.266$, $p = 0.015$. It turns out that children group 10 had the highest (mean value = 20.625), and children group 12 had the lowest level (mean value 15.25) of Cognition achievement. *Post-hoc* test with Tukey-Kramer correction revealed that there is statistically significant difference between groups 10 and 4. Children group 4 had a mean value of cognition achievement of 16.190. This finding is a bit specific, but in that group were 16 samples while in group 12 were only 4. Explanation of membership to the variable group is given in Table c in **Appendix A**.

Results of Socio-Emotional Achievement

Univariate GLM analysis for dependent variable SOCIO-EMOTIONAL achievement revealed that the full linear model (**Appendix B**) could explain 39.1% of variability $F_{(21,120)} = 3.673$, $p < 0.001$, $\eta p^2 = 0.391$ and Observed Power = 0.999.

One-way ANOVA revealed a statistically significant difference between groups of interaction term Employed * STAI-T level [$F_{(3,138)} = 3.309$, $p = 0.022$]. *Post-hoc* test with Tukey-Kramer correction was used. It turns out that group 4 has the highest level of Socio-emotional achievement (mean value = 15.54). There is statistically significant difference between this group and group 1 (p4–1 = 0.011). On the other hand, children group 1 has minimal Socio-emotional achievement (mean value = 13.40), but there was no statistically significant difference between group mean values except mentioned between groups 1 and 4. Explanation of membership to the variable group is given in Table b in **Appendix A**.

For interaction term Number of children * COVID-19 related fear * STAI-T level, there was no statistically significant difference between groups $F_{(11,130)} = 1.811$, $p = 0.058$. It turns out that children group 2 had the highest (mean value = 16.0), and children group 3 had the lowest level (mean value 12.33) of Socio-emotional achievement. Explanation of membership to the variable group is given in Table c in **Appendix A**.

DISCUSSION

The present prospective cohort study examined whether maternal trait anxiety was associated with speech-language, sensory-motor and socio-emotional development in 12 months old Serbian infants during COVID-19 pandemic. Prenatal maternal anxiety may represent a relevant risk factor that interferes in various ways with child development. There is already quite a bit of evidence on the consequences that prenatal maternal anxiety may produce on the psychophysiological child development (Dunkel Schetter and Tanner, 2012; Huizink et al., 2014; O'Connor et al., 2014; Rees et al., 2019), while the interest in this topic has increased significantly in the past 20 years. The impact of maternal prenatal anxiety on child development needs to be additionally considered to the COVID-19 pandemic, which impacts on pregnancy and maternal mental health have also been studied in the past 2 years (Quinlivan and Lambregtse-van den Berg, 2020; Usher et al., 2020; Yan et al., 2020; Motrico et al., 2021). On the other hand, there are scarce data about longitudinal trajectories of maternal prenatal anxiety on early child development during the COVID-19 pandemic (Barišić, 2020; Quinlivan and Lambregtse-van den Berg, 2020; Araújo et al., 2021).

The present study sought to explore whether maternal prenatal anxiety impacts psychophysiological development in 12 months old Serbian infants during the COVID-19 pandemic. Specifically, the aim was to investigate the prospective impact of maternal prenatal anxiety on infant speech-language, sensory-motor and socio-emotional development at the age of 12 months, controlling maternal age, employment status, the number of children that mother has, COVID-19-related fear, STAI-T, and MSPPS.

Our main findings were as follows: Pregnant women from the sample, who were examined during the third trimester of pregnancy, had intermediate and high levels of trait anxiety, while none had low levels of anxiety. Also, all pregnant women reported a high level of perceived social support. Almost half of the pregnant women reported a COVID-19-related fear, while a group of pregnant women whose number is slightly less than half

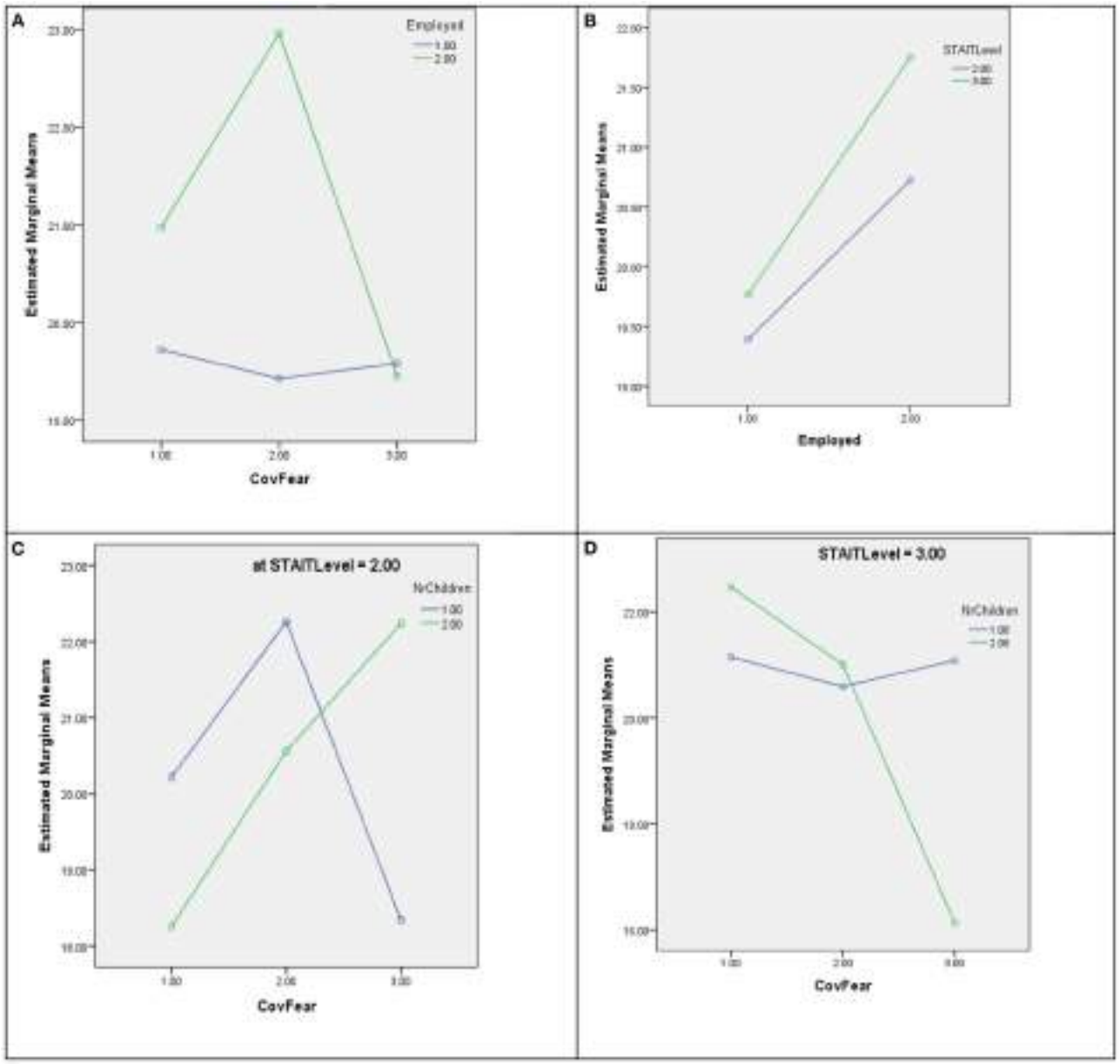

FIGURE 2 | Plot of estimated marginal means of dependent variable speech-language for interactions **(A)** Employed * COVID-19 related fear, **(B)** Employed * STAI-T level, **(C)** Number of children * COVID-19 related fear * STAI-T level where STAI-T level = 2, and **(D)** Number of children * COVID-19 related fear * STAI-T level where STAI-T level = 3. Covariates appearing in the model are evaluated at the following values: Maternal age = 29.5634, MSPSS = 76.7042.

reported that they have no COVID-19 related fear. Only a small percentage of pregnant women reported that they sometimes had COVID-19-related fear. Moreover, pregnant women who reported having a COVID-19 related fear had higher trait anxiety levels. The average developmental achievements in infants aged 12 months were as follows: the highest level of achievement was present in the assessment of cognition, followed by average achievement in socio-emotional development, then in speech and language development, and finally in motor skills. The experimental factors have an impact on infants' development.

Maternal Trait Anxiety During Pregnancy in the Context of COVID-19 Pandemic

The study found intermediate and high levels of maternal anxiety among 142 pregnant women from Serbia. The same findings were observed both on STAI-S and STAI-T scale. It was noticed that none of the study participants had a low level of maternal anxiety during pregnancy. In further analysis of the results, we observed the values of STAI-T, which measure relatively stable individual differences in propensity for anxiety (Julian, 2011), while the STAI-S values are relatively transient

and variable over time (Floris et al., 2017; Papadopoulou et al., 2017). Similarly to findings from the literature relating to the COVID-19 pandemic and mental health consequences (Shigemura et al., 2020; Xiang et al., 2020), and especially the consequences on maternal mental health (Corbett et al., 2020; Mappa et al., 2020; Saccone et al., 2020; Yan et al., 2020), our findings also indicated that the COVID-19 pandemic has a profound impact on maternal prenatal anxiety, and maternal mental health in general. Various factors during the COVID-19 pandemic have been identified that lead to mental health consequences (Berthelot et al., 2020; Liu et al., 2021). However, the exact prevalence of anxiety among pregnant women during the COVID-19 pandemic is currently unknown, although recent research from different countries suggests elevated symptoms of anxiety in this population of women (Liu et al., 2021; Tomfohr-Madsen et al., 2021). Considering the above data on elevated anxiety symptoms in pregnancy during the COVID-19 pandemic, we could partly explain only the participation of pregnant women with intermediate and high levels of anxiety and the absence of pregnant women with low levels of anxiety in our study. On the other hand, all pregnant women were examined in the third trimester of pregnancy, which emerged as the most vulnerable to the manifestation of high anxiety levels compared to the previous two trimesters (Gunning et al., 2010).

The Role of Perceived Social Support

The present study revealed that all pregnant women reported increased social support during the COVID-19 pandemic, which is in line with recent studies (Zhang and Ma, 2020; Hashim et al., 2021). This could be explained by the burdensome circumstances that resulted from the COVID-19 pandemic, since social support acts as a protective factor against the adverse mental health difficulties resulting from epidemics and natural disasters (King et al., 2012), and has been identified as an essential protection against stressful life events (Dambi et al., 2018).

Though certain studies indicate that there is a significant inverse relationship between social support and state and trait anxiety in pregnancy (Aktan, 2012), even during the COVID-19 pandemic (Lebel et al., 2020; Khoury et al., 2021), we did not notice such a relationship in our study, but the opposite one. This might be explained by the hypothesis that explains how the impact of social support on health increases during stressful circumstances (Flannery and Wieman, 1989). On the other hand, although there is large evidence that social support predicts depression and vice versa, there is little evidence to explain the directionality of perceived social support and anxiety (Dour et al., 2014). Especially, there are no precise indicators on the impact on individuals' social aspect and the mental health of pregnant women during the COVID-19 epidemic (Api et al., 2020). Findings from our study showing a high level of perceived social support in pregnant women, despite their high level of anxiety during the COVID-19 pandemic, could be further explained by the role that social support has as an essential coping resource, as well as a mechanism for the maintenance of psychological well-being under conditions of psychological burdens (Bruwer et al., 2008). Also, it is important to consider the fact that there is a strong family bonding in Serbian culture, especially during women's pregnancy when family and friends give strong support to women in every sense.

The Role of COVID-19 Related Fear

Although resent research indicated that the COVID-19 pandemic might cause a significant long-lasting increase in fear (Skoda et al., 2020), in our study, less than half of pregnant women reported having a fear of getting a coronavirus infection (COVID-19-related fear). Our results should be interpreted in line with findings that point to decreasing of COVID-19 fear within 6 weeks from the pandemic outbreak (Hetkamp et al., 2020), but also with evidence indicating that individuals may respond differently to the emotional distress caused by traumatic events such as this pandemic (Killgore et al., 2021).

Pregnant women who reported that they have no COVID-19 related fear had lower STAI-T anxiety levels. One-way ANOVA showed a statistical significance of the difference in average STAI-T values to the presence of COVID-19 related fear. However, *post-hoc* analysis subsequently showed that there was no statistical significance between the groups. However, such findings indicating a connection between fear and trait anxiety are in line with the literature that confirmed this relationship (Paredes et al., 2021).

Developmental Achievements of Infants Aged 12 Months

Child development is a complex maturational and interactive process that includes a gradual progression of perceptual, motor, cognitive, language, socio-emotional and self-regulatory abilities (Sameroff, 2009). There is increasing evidence of the importance of the first 1,000 days of life on later human development (Black et al., 2017; Agarwal et al., 2020). In that light, we also observed the first 12 months of the child's development, the age of the examined children in our study.

Harmonization of developmental abilities is a precondition for orderly child development (Sameroff, 2009). Observing the developmental abilities of infants aged 12 months in our study, we noticed that the highest level of correlation exists between socio-emotional development and speech-language development; then between socio-emotional development and cognition; then between cognition and motor skills, and finally between speech-language and motor skills. Some authors pointed to the connection between the mentioned abilities, which is not simple and direct, but rather complex and multiple (Piek et al., 2008; Wang et al., 2014; Bedford et al., 2016). The links between achievements in cognitive, social communication, and language development were noted, considering the assumed correlation and interdependence of the mentioned abilities (Iverson, 2010; Libertus and Violi, 2016). The highest association between socio-emotional development and speech-language development found in this study may be explained by the close connection between emotion and action, within which communication has a central aspect of action (Saarni et al., 2006). The quality of the maternal-infant relationship has a significant influence on infant development (Johnson, 2013). On the other hand, some authors pointed that a mother's emotional connection with her child has an essential role in predicting social–emotional outcomes and less

cognitive, language, and motor development outcomes in infant development (Le Bas et al., 2021). We assumed that maternal-infant bonding, as one of the predictors of child development (Johnson, 2013), has a significant role even more during the COVID-19 pandemic, and thus reflects infants' socio-emotional development, and speech-language consequently.

The relationship between motor skills and language, cognitive, social, and perceptual development has been intensively studied in recent years (Leonard and Hill, 2014; Leonard et al., 2015; Libertus and Violi, 2016; Libertus and Hauf, 2017; Collett et al., 2019). Interactions between cognition, language, and speech motor skills at an early developmental stage are also shown (Nip et al., 2011). However, the weakest correlation between speech-language and motor skills found in this study may be interpreted with similar findings (Alcock and Krawczyk, 2010), although it is not yet fully understood how the development of motor skills affects the development of speech-language (Libertus and Violi, 2016).

The Potential Impact of Maternal Trait Anxiety on the Early Infants' Development During COVID-19 Pandemic

Bearing in mind that in our study, all mothers during pregnancy had an intermediate or high level of trait anxiety, it was important to examine the impact of anxiety on the early infants' development. The impact of pregnant woman's anxiety on early child development has been well-documented (O'Connor et al., 2002, 2014; Dunkel Schetter and Tanner, 2012; Huzinik, 2014). Also, an essential issue under consideration is the impact of the COVID-19 pandemic upon pregnancy, childhood and adult outcomes (Quinlivan and Lambregtse-van den Berg, 2020). The results of our study pointed to a weak positive correlation between maternal trait anxiety and the child's socio-emotional status, which is in line with the literature (Rees et al., 2019).

In addition, literature data have shown that other factors may also affect the child's development, such as the maternal age, employment, and the number of children the mother has (Brooks-Gunn et al., 2002; Bernal, 2008; Chittleborough et al., 2011; Tearne, 2015; Duncan et al., 2018; Falster et al., 2018). With this in mind, we decided to examine the influence of these factors depending on the levels of trait anxiety, COVID-19 related fear, and perceived social support.

Table 5 shows the association between the independent factors STAI_T level, COVID-19 related fear, Number of children and Employment (nominal type) and the dependent variables Speech and language, Motor skills, Cognition and Socio-emotional achievement (scale type). It is evident that association depends on factor variable combination. For example, STAI-T level has the highest association with Cognition ($\eta = 0.515$) and the lowest with Socio-emotional achievement ($\eta = 0.0.254$), while Employment has the highest association with Motor skills ($\eta = 0.449$) and the lowest with Cognition ($\eta = 0.0.266$) It is important to notice that all independent factors are associated with child's development. Results indicate that part of the variability of developmental abilities can be explained by factors. It implies that the factors have an impact on child development.

Univariate analysis showed that between 30.9 and 40.6% variability of dependent variables Speech-language, Motor skills, Cognition and Socio-emotional achievement could be explained by factors Employed, Number of children, COVID-19 related fear and STAI-T level and covariates Maternal age and MSPSS. It can be concluded from **Table 5** that interaction terms have a dominant impact on models. In all models statistically significant impact of COVID-19 related fear and STAI-T level interaction is present. However, this two-way interaction also occurs as an element of a statistically significant three-way interaction. In the case of all dependent variables, they occur in interaction with number of children. Only in Motor skills Observed Power is <0.8 (0.741). In the case of Motor skills, three-way interaction with Observed Power >0.8 (0.927) occurs between COVID-19 related fear, STAI-T level, and Employed. The interaction of factors and their influence can be easily observed from the example given in **Figure 2**.

If we look at the three-way interaction term Number of children * COVID-19 related fear * STAI-T level found in all four linear models, we notice that the influence of individual factors on achievements within the developmental functions is different. That is, for each of the four development functions, the maximum and minimum achievements are influenced by different combinations of interacting factors values. For example, while children of mothers who have one child are sometimes afraid of COVID-19 and have an intermediate level of STAI-T have the most developed speech and language, children of mothers who have two or more children have no fear of COVID-19 and have a high level of STAI-T show the best cognitive abilities. The obtained results indicate a complex interdependence of the observed factors and their influence on the development of the observed functions in the first 12 months of a child's life. We can say that the mother-child relationship in this period is subject to the influence of various factors, reflecting on the child's development and having complex implications on individual functions.

The conducted research did not answer the question of the individual influence of the analysed factors on the child's development, but it confirmed our hypothesis that the mother's anxiety affects the child's development. COVID-19 related fear has also been shown to have an effect. In that sense, considering that there are no consolidated studies on the possible impacts of COVID-19 on pregnant women's health and their children's development, especially over the long term, maternal anxiety during this period is a problem that needs to be more widely addressed.

CONCLUSION

The study showes that the COVID-19 pandemic affects the level of trait anxiety manifestation in pregnant women and the level of perceived social support. Selected factors as follows: maternal age, the level of maternal anxiety, and the maternal COVID-19 related fear influence the infants' development. This study confirmes our hypothesis that maternal anxiety and fear of COVID-19 have an influence on infant's development. Due to the interaction

between the factors, their individual influence could not be precisely determined. Further focused research should provide an answer to this question.

Generally, this study aims to improve the understanding of the impact of the COVID-19 pandemic on infants' development, which can help to guide appropriate strategies to prevent dysfunctions in the children's development on the one hand, and on the other to promote a stimulating environment for children.

Strengths and Limitations

To the best of our knowledge, there are no studies that monitor the early infant's development under the influence of the mother's mental health during the COVID-19 pandemic. Since this study was conducted during a COVID-19 pandemic, we assume that it resulted without having a group of mothers with a low level of trait anxiety. In that sense, it was not possible to make a more precise conclusion about the influence of maternal anxiety on the infants' development during the COVID-19 pandemic. On the other hand, it is not possible to accurately state the impact of each observed factor on the early infants' development. It is also important to note that the comorbidity of depression/anxiety is very high, and its impact on child's development during the COVID-19 pandemic was not estimated in our study. Also, only the mothers were included in the study, which indicates that without including fathers/partners, the impact of child development could not be determined accurately. The findings from this study suggest that future research is warranted to investigate the longitudinal impacts of maternal and parental mental health on child development during the COVID-19 pandemic, taking into account additional measurement points and modifiable risk factors. The need for systematic monitoring of children at the earliest age was pointed out, and providing the necessary support to pregnant women and fathers/partners during the COVID-19 pandemic.

AUTHOR'S NOTE

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DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of legal and ethical constraints. Public sharing of participant data was not included in the informed consent of the study. Requests to access the datasets should be directed to Miško Subotić, m.subotic@add-for-life.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Clinic for Gynecology and Obstetrics Narodni Front (Date: 26 March, 2020, No 27/20), in Belgrade and by the Ethics Committee of the Institute for experimental phonetics and speech pathology (Date: 2 April, 2020, No 45/20), in Belgrade, Serbia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LJ and MSu: conceptualization and visualization. LJ and MSo: methodology. MSu: formal, statistical analysis, and supervision. LJ, IB, and AD: investigation. AD and IB: data curation. LJ: supervision of the (ongoing) data collection and writing—original draft preparation. MSo, OG, and MK: writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.792053/full#supplementary-material

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Maternal History of Adverse Experiences and Posttraumatic Stress Disorder Symptoms Impact Toddlers' Early Socioemotional Wellbeing: The Benefits of Infant Mental Health-Home Visiting

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Background: The present study examined the efficacy of the Michigan Model of Infant Mental Health-Home Visiting (IMH-HV) infant mental health treatment to promote the socioemotional wellbeing of infants and young children. Science illuminates the role of parental "co-regulation" of infant emotion as a pathway to young children's capacity for self-regulation. The synchrony of parent–infant interaction begins to shape the infant's own nascent regulatory capacities. Parents with a history of childhood adversity, such as maltreatment or witnessing family violence, and who struggle with symptoms of post-traumatic stress may have greater challenges in co-regulating their infant, thus increasing the risk of their children exhibiting social and emotional problems such as anxiety, aggression, and depression. Early intervention that targets the infant–parent relationship may help buffer the effect of parental risk on child outcomes.

Methods: Participants were 58 mother–infant/toddler dyads enrolled in a longitudinal randomized control trial testing the efficacy of the relationship-based IMH-HV treatment model. Families were eligible based on child age (<24 months at enrollment) and endorsement of at least two of four socio-demographic factors commonly endorsed in community mental health settings: elevated depression symptoms, three or more Adverse Childhood Experiences (ACEs) parenting stress, and/or child behavior or development concerns. This study included dyads whose children were born at the time of study enrollment and completed 12-month post-baseline follow-up visits. Parents reported on their own history of ACEs and current posttraumatic stress disorder (PTSD) symptoms, as well as their toddler's socioemotional development (e.g., empathy, prosocial skills, aggression, anxiety, prolonged tantrums).

Results: Maternal ACEs predicted more toddler emotional problems through their effect on maternal PTSD symptoms. Parents who received IMH-HV treatment reported more positive toddler socioemotional wellbeing at follow-up relative to the control condition. The most positive socioemotional outcomes were for toddlers of mothers with low to moderate PTSD symptoms who received IMH-HV treatment.

Conclusion: Results indicate the efficacy of IMH-HV services in promoting more optimal child socioemotional wellbeing even when mothers reported mild to moderate PTSD symptoms. Results also highlight the need to assess parental trauma when infants and young children present with socioemotional difficulties.

Keywords: infant mental health, parent-infant psychotherapy, maternal PTSD, Infant Mental Health-Home Visiting, infant socioemotional development, maternal childhood adversity, toddler socioemotional development

INTRODUCTION

Science illuminates the role of parental "co-regulation" of infant emotion as a pathway to young children's capacity for socioemotional wellbeing, including the ability to express and manage emotions, and manage attention and impulses that facilitate social relationships (Geva and Feldman, 2008). Parents with a history of childhood adversity, such as maltreatment or witnessing family violence, may have greater challenges in co-regulating their infant, thus increasing the risk of their children exhibiting social and emotional problems such as anxiety, aggression, and depression (Ahlfs-Dunn and Huth-Bocks, 2014; Steele et al., 2016). In this paper, we summarize the relationship between maternal psychological wellbeing and infant socioemotional development. Specifically, we examine the influence of maternal early adversity and current symptoms of posttraumatic stress on infant socioemotional wellbeing. Finally, we explore the efficacy of Infant Mental Health-Home Visiting (IMH-HV) (Tableman and Ludtke, 2020) in promoting the socioemotional wellbeing of infants whose mother has a history of early adversity and current symptoms of posttraumatic stress disorder (PTSD).

Infant Socioemotional Development

Emotion regulation is an important aspect of infant socioemotional wellbeing. It acts to reduce negative emotions and, importantly, also serves in "amplification, an intensification of positive emotion, a condition necessary for more complex self-organization" (Schore, 2001b, p. 21). The neuroscience of the development of early childhood emotion regulation largely focuses on parent–child interactions and the parent–infant attachment system. Exchanges between parent and child in the form of emotional or affective communication, sharing emotion, and the caregiver's "empathic understanding" of the child's emotional state are important pathways in the process of emotion regulation (Schore, 2001a; Trevarthen, 2001; Manian and Bornstein, 2009). Ultimately, the synchrony children experience in infancy primes them for emotion regulation, social interactions, and affiliative partnerships later in life (Kinreich et al., 2017). The newborn infant is biologically equipped to engage in "bio-behavioral synchrony" (Feldman, 2012) that also contributes to the development of the attachment relationship with their parent(s). Their biosocial development is supported through daily interactive exchanges, as they learn the language (Oller et al., 2001; Kuhl et al., 2006) and emotion display "rules" (Matsumoto and Hwang, 2013) of the culture in which they are growing.

In studies examining behavioral challenges in children, several indicators of parenting are associated with social competence and resilience, as well as early emotional/behavioral disorders. For example, a secure mother–infant attachment not only promotes resiliency, but also protects against such behavioral issues (Letourneau, 1997; Edwards et al., 2006; Cyr et al., 2010; Riva Crugnola et al., 2014). Higher parental cognitive empathy and reflective functioning, both of which measure the capacity to perceive and understand the emotional states of others, are connected to emotion regulation and social competence in children (Wong et al., 2017; Borelli et al., 2020). Furthermore, higher frequency of shared pleasure moments in early childhood between mother and child have been shown to lower the likelihood of emotional/behavioral problems in children and moderate the possible negative effects of parental psychopathology on the development of children's emotion regulation abilities (Mäntymaa et al., 2015).

Parents who are grossly insensitive to their infant's affective communication overwhelm their infant's capacity to develop organized and effective emotion regulation strategies (Lyons-Ruth et al., 1999). Underdeveloped emotion regulation systems often lead to dysregulated emotions and frequently manifest as child internalizing and externalizing behaviors, including excessive or prolonged tantrums, physical aggression, and/or emotional withdrawal and anxiety (Lyons-Ruth, 1996; Calkins et al., 2007; Chambers and Allen, 2007; Beauchaine and Thayer, 2015; Ostlund et al., 2019).

Maternal Stress and Trauma

An informed approach to understanding the dynamics and developmental implications of early parent–child interactions must also attend to parental wellbeing and psychopathology. The mental health of any primary caregiver can significantly affect early relationships and child development; however, we focus on maternal mental health given the replicated associations between maternal wellbeing and myriad gestational, birth, and caregiving

outcomes (Grote et al., 2010; Kingston et al., 2012; Monk et al., 2012; Van den Bergh et al., 2020). A history of adverse experiences in childhood, traumatic stress, and PTSD can impact adult emotion regulation and sensitive and responsive parenting, and in turn impact young children's social–emotional development.

Adverse Childhood Experiences

Adverse Childhood Experiences (ACEs) generally refer to events prior to the age of 18 that may have been distressing or traumatizing for an individual, including psychological, physical, or sexual abuse, physical and emotional neglect, or witnessing interpersonal violence, among other events (Felitti et al., 1998). The original ACEs study (Felitti et al., 1998) demonstrated the significant connection between cumulative exposure to abuse, neglect, or household dysfunction during childhood and multiple adverse health outcomes in adulthood, including increased risk of depression, an array of physical health issues, and early mortality (Chapman et al., 2004; Felitti et al., 2019). In the perinatal period, higher ACE scores are associated with negative pregnancy and birth outcomes, including high-risk pregnancy behaviors (e.g., alcohol and cigarette use), preterm birth, and low birth weight (Chung et al., 2009; Hudziak, 2018; Racine et al., 2018). Pregnancy and the postpartum period are commonly associated with the initial onset or exacerbation of mental health concerns (Munk-Olsen et al., 2016) and women with a history of childhood adversity are disproportionately at risk for clinically significant symptoms of perinatal depression, anxiety, and PTSD (McDonnell and Valentino, 2016; Narayan et al., 2016, 2018; Oh et al., 2016; Meltzer-Brody et al., 2018; Racine et al., 2018; Atzl et al., 2019; Osofsky et al., 2021). In the current study, we therefore expand upon the existing literature to address intergenerational relationships between experiences of adversity in a mother's own childhood, current maternal PTSD symptoms, and socioemotional and behavioral outcomes for her young child.

Maternal Traumatic Stress

Childhood adversity can also lead to cumulative, chronic stress when the event is on-going in duration or uncontrollable in nature, and children do not have a stable or emotionally available caregiver who can support and protect them or help them make sense of the situation(s) (Lieberman and Van Horn, 2009; Slade, 2014). Mothers who faced more adversity in their own childhoods are more likely to use corporal punishment and to display hostile, intrusive, or frightening parenting behaviors (Jacobvitz et al., 2006; Chung et al., 2009). Condon et al. (2019) suggest that mothers who experienced high levels of adversity and stress early in life may have limited lived experiences to draw from in order to offer their children solace from stressful experiences or teach effective coping skills in the presence of current stressors. Intrusive, withdrawing or hostile parenting styles can have direct effects on the infant and young child, as well as contribute to challenges within the mother–child relationship (Lyons-Ruth, 1996). Maternal ACEs in the form of childhood maltreatment are directly correlated with higher levels of maladaptive socioemotional symptoms in infants (McDonnell and Valentino, 2016). There is evidence that maternal childhood trauma leads to disturbed caregiving behavior which in turn interferes with infants developing a secure attachment (Lyons-Ruth and Block, 1996). Furthermore, a mother's history of ACEs predicts higher behavioral problems and blood pressure levels – a tangible biomarker of stress – in children (Condon et al., 2019). Nevertheless, the impact of maternal childhood adversity and toxic stress on parenting behaviors and child outcomes is probabilistic rather than deterministic. When controlling for concurrent perinatal mental health symptoms, effects of maternal childhood adversity on parenting and child outcomes do not always confer risk (Martinez-Torteya et al., 2014; Muzik et al., 2017; Morelen et al., 2018). However, in toddlers and older children, maternal childhood abuse and adversity more consistently predict risk for emotional and behavioral problems (e.g., Collishaw et al., 2007; Min et al., 2013; Myhre et al., 2014; van de Ven et al., 2020). Thus, a mother's own childhood adversity and caregiving history may directly impact her child's development of emotion regulation, often manifesting as behavioral and emotional regulation challenges. This is even more true in the context of maternal post-traumatic stress disorder. For example, maternal PTSD symptoms predict infant emotional reactivity and regulation deficits (Bosquet Enlow et al., 2011), insecure and disorganized attachment (van Ee et al., 2016), dysregulation in preschoolers (Pat-Horenczyk et al., 2015), and internalizing and externalizing problems in children (Schechter et al., 2011; Glaus et al., 2021).

There are multiple psychosocial routes through which maternal PTSD may affect young children. Prenatal PTSD symptoms can affect child development through prenatal exposure to mothers' disordered stress-response systems and altered epigenetic programming (Glover et al., 2010); however, dysregulated prenatal stress responses are not limited to current stressors and childhood adversity may play a significant role. Bublitz et al. (2014) found that maternal history of severe childhood sexual abuse was associated with increased cortisol awakening response – a biomarker of PTSD – for pregnant women between 25 and 35 weeks' gestation. In the postpartum period, effects of maternal PTSD on child development may be conferred through disruptions to sensitive and responsive caregiving. Higher severity of PTSD symptoms increase risk for maternal negative representations of the parent–child relationship (Schechter et al., 2005; van Ee et al., 2016). Mothers with PTSD may be emotionally unavailable; experience higher levels of parenting stress; endorse higher levels of aggression toward their children; have increased difficulty reflecting on their child's needs; have limited empathic responses to their child's struggles; and display significant difficulties providing sensitive, nurturing care that contributes to security of attachment and healthy child development (Schechter et al., 2008, 2005; Pereira et al., 2012; Muzik et al., 2013; van Ee et al., 2016). Notable child outcomes associated with maternal PTSD and these maladaptive parenting behaviors include difficult temperament, sleep disturbances, and internalizing and externalizing problems, among other challenges (Tees et al., 2010; Hairston et al., 2011; Parfitt et al., 2013; van Ee et al., 2016; Plant et al., 2018). Maternal trauma symptoms have also been found to mediate the relationship between maternal history of childhood trauma/interpersonal violence and child

outcomes (Schechter et al., 2011; Fenerci and DePrince, 2018). However, no study to our knowledge has examined the impact of broader maternal ACEs on maternal PTSD symptoms and child behavioral outcomes, a gap the current study will address.

Both past and ongoing stress and trauma can impact parent mental health, parenting behavior, parent perception of the infant, and infant socioemotional development. Infant mental health interventions can support parents with a history of stress and trauma and in turn buffer the negative effects of stress and trauma on infant socioemotional development.

Infant Mental Health Treatment

The seminal article, "Ghosts in the Nursery" (Fraiberg et al., 1975), spawned the birth of home-based "kitchen table" therapy (Fraiberg et al., 1980) as a preventative intervention model to promote sensitive and nurturing care, reduce maltreatment, and to promote infant wellbeing (Weatherston and Tableman, 2015; Lawler et al., 2017). Fraiberg and colleagues, 1980 documented, with clinical sensitivity and acuity, the myriad of ways a parental history of unresolved childhood loss, separation, abuse, or neglect resulted in the ghosts in the nursery of the traumatized parent, invading the present parent–infant relationship. The very defenses that the parent, when she was a young child, used to ward off the anxiety of uncontained fear (Fraiberg, 1982; Slade, 2014) emerges in parenting in response to the vulnerability of their newborn or young infant. Later termed infant mental health-home visiting (IMH-HV; Tableman and Ludtke, 2020), IMH-HV offers a mix of needs-driven intervention, often combining concrete services, emotional support, developmental guidance, and infant–parent psychotherapy. Weekly, or twice weekly, depending on the needs of the family, the IMH-home visitor meets in the home of the family, with the infant present. The presence of the infant focuses attention on the developing relationship and enables both the parent and the infant to inform the IMH specialist, *via* their interactive exchanges, what is going well and what is challenging. The Michigan Model of IMH-HV is an empirically validated approach to enhancing parenting outcomes (Rosenblum et al., 2020; Julian et al., 2021; Stacks et al., 2021), but research is nascent of its' impact on the socioemotional wellbeing of the infant. In the presence of a containing, responsive therapist, the parent is helped to grieve unmourned losses, give voice to the fears that went unnoticed in their own childhood, and hear and see the needs of their infant (Malone and Dayton, 2015; Weatherston and Ribaudo, 2020). Infant mental health treatment may help to mitigate the impact of parents' painful early relationship history on the current parent–child relationship and infants' wellbeing.

Current Study

The current study has two distinct aims. The first is to examine the association between maternal ACEs, maternal symptoms of PTSD, and maternal perception of their young child's socioemotional difficulties. Our second aim is to examine whether participation in IMH-HV improves child socioemotional outcomes and mitigates the associations between maternal PTSD symptoms and child socioemotional and behavioral difficulties. With regard to aim 1, we hypothesize that mothers who report greater exposure to ACEs during their own childhood will report more symptoms of PTSD at study baseline and will report that their young children demonstrate more behavioral and emotional difficulties. Furthermore, we hypothesize that mothers' PTSD symptoms will mediate the association between maternal ACEs and elevated infant socioemotional and behavioral difficulties. With regard to aim two, we hypothesize that in the context of maternal PTSD symptoms, mothers randomized to IMH-HV treatment will report their toddlers display more positive socioemotional functioning compared to toddlers randomized to the control condition.

MATERIALS AND METHODS

Methods

Participants were 58 mother–infant/toddler dyads who completed baseline and 12-month follow up visits as part of a larger longitudinal randomized control trial (N = 73) testing the efficacy of the relationship-based IMH-HV treatment model. Families were eligible based on child age (<24 months at enrollment) and endorsement of at least two of the following: eligibility for public assistance, probable maternal depression, perceived parenting challenges, or history of maternal childhood adversity (ACE score >3). Eligible parents were >18 years of age, had legal custody of their child at enrollment, and did not endorse symptoms of substance use disorders or psychosis. Diagnoses such as depression, anxiety, attention deficit hyperactivity disorder, etc., were *not* grounds for exclusion. The study was reviewed and approved by the University of Michigan Institution Review Board. The participants provided their written informed consent to participate in this study.

This particular study included dyads whose children were born at the time of study enrollment and completed 12-month follow-up visits. Seven families were enrolled in the study during pregnancy, resulting in no child baseline data. Eight additional families were lost to follow up. Aside from child age, there were not demographic differences between those who were retained in the study and those who were not, suggesting there was no differential attrition. Given the small sample size, it was not possible to use intent-to-treat analyses. Instead, only those participants with data at the 12 month follow-up were included. Families who did not complete later follow-up visits were evenly split across the treatment and control conditions (4 from each). Additionally, some families completed later follow-up evaluation visits even after they ended participation in the intervention, which ended for some families before 12 months largely due meeting mutually agreed upon goals. Further details can be found in Riggs et al. (2021).

At the time of study enrollment, average maternal age was 32.5 years (SD = 5.41) and the average age of the child was 11.9 months (SD = 6.57). The majority of the sample identified as a racial or ethnic minority (62.1%); White mothers comprised 37.9% of the sample. Nearly 40% of the families (n = 22) reported household incomes of less than $40,000 and the average number of ACEs (Felitti et al., 1998) experienced by mothers was 3.64

(SD = 2.40) out of a possible 10, significantly above the national mean ACE score of 1 (Merrick et al., 2018). See **Table 1** for additional demographic characteristics.

Measures

Maternal Adverse Childhood Experiences

The ACEs questionnaire is a 10-point measure used to assess harmful events (i.e., abuse, neglect, or household dysfunction) that occurred prior to the age of 18. The 10 events include psychological abuse, physical abuse, sexual abuse, physical neglect, emotional neglect, parental divorce, family member mental illness, substance abuse by a family member, incarceration of a family member, and domestic violence. At baseline data collection, participants endorsed (yes) or denied (no) exposure to the 10 items. A total score was calculated by summing the endorsed items, with higher total scores indicating a greater number of adverse events. See **Table 2** for a summary of descriptive statistics for the ACE questionnaire.

Maternal Posttraumatic Stress Disorder Symptoms

The PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013; Blevins et al., 2015) is a 20-point self-report measure that assesses symptoms consistent with PTSD diagnostic criteria. Respondents are asked to report on symptoms within the past month, for example, how much they have been bothered by "*Repeated, disturbing, and unwanted memories of the stressful experience?*" or "*Feeling distant or cut off from other people?*" The PCL-5 is scored on a 0–4 Likert scale, increasing in severity from 0 (*not at all*) to 4 (*extremely*), with total scores ranging from 0 to 80. This measure can be used as a screener for a provisional diagnosis of PTSD, wherein the suggested clinical cut-off for total scores falls between 31 and 33. In this study, a total score was calculated by summing the individual items, with higher scores reflecting greater severity of symptoms. Prior reports indicate sound psychometric properties of the PCL-5 (Blevins et al., 2015), and reliability was high in the current sample ($\alpha = 0.94$). PTSD symptoms data was collected at baseline and 12 months.

TABLE 1 | Frequencies (and percentages) for social demographic characteristics (*N* = 58) at baseline assessment.

	n (%)	*M*	SD
Participant demographics			
Mother age		32.65	5.23
Child age in months		11.95	6.19
Household income range			
0–$19,999	9 (15.8)		
$20,000–$39,999	13 (22.4)		
$40,000–$59,999	13 (22.4)		
$60, 000–$79, 999	5 (8.5)		
$80,000 and above	17 (29.2)		
Race/ethnicity			
White	22 (37.9)		
Racial or ethnic minority	36 (62.1)		
Education level			
High school diploma or less	8 (13.8)		
Some college or associates degree	12 (20.7)		
College or Voc. Tech degree	22 (37.9)		
Postgraduate degree	16 (27.6)		
Marital status			
Currently married	47 (81.0)		
Not currently married	11 (19.0)		

One participant did not wish to report income data for her family.

Infant-Toddler Socioemotional Development

The Brief Infant-Toddler Social Emotional Assessment (BITSEA; Briggs-Gowan et al., 2004) is a 44-item parent-report measure for children ages 12–35 months. It is a screener used to assess social, emotional, behavioral problems, and delays in competence as well as to identify children measuring at-risk in multiple areas. Parents rate each descriptive comment about their child (e.g., "My child often gets very upset") from 0 (*not true/rarely*) to 2 (*very true/often*). In this study, the 31-item total Problem Score was utilized, with a possible range of scores from 0 to 62. Higher Problem Scores indicate greater difficulties with child internalizing, externalizing, or regulation capacities. The BITSEA can only be administered after the infant is 12 months old. Because a number of families began treatment prior to the child's first birthday, there was too much missing data at baseline to use in analyses. As such, the BITSEA is only used in study aim 1 to assess elevated social emotional difficulties at 12-months.

The Devereux Early Childhood Assessment

Because the BITSEA is only administered after the infant is 12 months old, we also included the Devereux Early Childhood Assessment-Infant (DECA-I) and the Devereux Early Childhood Assessment-Toddler (DECA-T; Powell et al., 2007) to enable a large enough sample size to accommodate the planned analyses. The DECA-I and DECA-T are standardized parent-report measures of children's emotional and behavioral adjustment. The measure generally assesses positive and protective factors demonstrated by resilient infants and toddlers. There are two subscales that are consistent across both versions of the Devereux Early Childhood Assessment (DECA); the Initiative scale, which measures behaviors used by the infant/toddler to meet their needs, and the Attachment/Relationships scale, which assesses social and emotional behavior and regulation exhibited between the infant/toddler and their caregiver. Example items on the Initiative scale include "*. . .how often did the child try to do things for herself/himself?*" and "*. . .how often did the child try to comfort others?*" Example items on the Attachment/Relationships scale include "*. . .how often did the child seek comfort from familiar adults?*" and "*. . . how often did the child express a variety of emotions (e.g., happy, sad, mad)?*"

For the infant version of the assessment (DECA-I; used for children 0–18 months of age), there are 18 items on the Initiative subscale and 15 items on the Attachment/Relationships subscale. For the toddler version of the assessment (DECA-T; used for children 18–36 months of age), there are 11 items on the Initiative scale and 18 items on the Attachment/Relationships scale. Scoring on both forms of the DECA yield standardized *T*-scores, where scores greater than 60 indicate a strength, scores less than 40 indicate an area of concern, and scores

between 40 and 60 indicate typical socioemotional development. Subscale reliability for both versions of the DECA were acceptable (Cronbach's alpha for the Initiation subscale ranged from 0.68 to 0.85; Cronbach's alpha for the Attachment/Relationships subscale ranged from 0.90 to 0.92).

Analytic Strategy

Data were analyzed using IBM SPSS for Windows, Version 26. Frequencies and percentages were calculated for all categorical variables. Means and standard deviations were calculated for the continuous variables. Before proceeding with the primary study analysis, data were screened for errors and extreme values to ensure that data met assumptions for statistical analysis and to understand factors that may affect interpretation of the findings. Variables were checked for outliers and assessed for normal distribution of differences in the scores; all assumptions for the planned analyses were met.

For our first aim, we conducted a multiple regression mediation model using PROCESS (Hayes, 2013) to explore the relationship between the mothers' baseline experience of childhood adversity, the severity of maternal PTSD symptoms, and infant/toddlers' socioemotional and behavioral outcomes at the 12 month follow up wave. We used the BITSEA Problem score as the measure of socioemotional and behavioral outcomes for this aim, given its wide use as a measure of child socioemotional functioning and excellent psychometric properties.

For our second aim, we conducted a multiple regression moderation model (Hayes, 2013) to explore the impact of treatment condition on infant/toddler socioemotional outcomes and the potential role of maternal PTSD symptoms in this effect. For this aim, we utilized the DECA subscales as our measures of child socioemotional development. This was necessary in order to control for baseline socioemotional development because the DECA can be administered to infants less than 12 months of age, while the BITSEA can only be administered once the child is older than 1 year. Given that many of the families began treatment when their child was less than 1 year, there was not enough BITSEA data available to use to examine pre/post treatment efficacy. DECA Initiation and Attachment subscales were evaluated separately.

RESULTS

Preliminary Analyses

Prior to conducting primary analyses, we examined descriptive and correlational data among our study variables of interest. See **Tables 2**, **3** for additional detail. Overall, maternal experiences of childhood adversity were relatively high compared to population estimates, and ACE scores ranged from 0 to 10 (M = 3.64; SD = 2.40). Although average scores were below the cutoff used to identify probable PTSD diagnoses (suggested cutoff of 33), there was some variability in the sample, with a number of participants endorsing PTSD symptoms scores above the clinical cutoff (n = 17; 23.30% of sample). Maternal PTSD symptom scores reported at the 12-month data collection visit were relatively lower but included a number of participants (n = 8; 12.1% of sample) whose 12-month assessment of PTSD symptoms indicated probable diagnosis of PTSD.

TABLE 2 | Descriptive statistics for key study variables.

	Baseline			12-month follow-up			
Variable	***M***	**SD**	**Range**	***M***	***M***	**Range**	**Possible range**
Maternal measures							
ACE score	3.64	2.4	0–10	–	–		0–10
PTSD score (PCL-5)	22.89	17.42	1–67	14.06	13.73	0–69	0–80
Child measures							
BITSEA Problems score	–	–	–	11.14	5.92	2–27	0–62
DECA Attachment score	50.94	8.54	33–67	51.94	9.86	33–66	
DECA Initiative score	51.72	8.63	33–72	52.35	10.04	32–72	

ACE, Adverse Childhood Experiences questionnaire; PCL-5, PTSD Checklist for DSM-5; BITSEA, Brief Infant-Toddler Social and Emotional Assessment; DECA, Devereux Early Childhood Assessment.

Over a quarter of the sample of toddlers were rated above the socioemotional problems cutoff score at both data collection time points (n = 20; 27.4% of sample), representing a subgroup of children with high levels of socioemotional problem behavior. Child protective and positive socioemotional factors were also examined using the DECA. On the Attachment subscale of the DECA, scores indicated that most children were in the "typical" range at baseline (M = 50.94; SD = 5.92) and 12-month (M = 51.94; SD = 9.86) data collection visits. Some parents rated their children as having "needs" (baseline and 12-month follow up n = 7; 9.6%) or "strengths" (baseline n = 10; 13.7%; 12-month follow up n = 17; 23.3%) on the Attachment subscale. Likewise, when evaluating the Initiative subscale of the DECA, scores indicated that most children in this study were in the "typical" range at baseline (M = 51.72; SD = 8.63) and 12-month data collection visits (M = 52.35; SD = 10.04), with some children rated as having needs (baseline n = 4; 5.5%; 12-month follow up n = 5; 6.8%) or strengths (baseline n = 9; 12.3%; 12-month follow-up n = 17; 23.3%) in this area.

Examination of bivariate correlations among study variables revealed several significant associations among key study variables. See **Table 3** for additional information.

Primary Analyses

Consistent with our first study aim, we examined the association between maternal ACEs, maternal symptoms of PTSD, and toddler socioemotional difficulties. We hypothesized that mothers who reported greater exposure to childhood adversity would report greater symptoms of PTSD (H1). As shown in **Table 3**, this hypothesis was supported. There was a moderate, positive bivariate association between maternal ACE score and baseline maternal PCL-5 score (r = 0.42, p = 0.000),

TABLE 3 | Correlations among key study variables.

Variable	ACE score	PCL-5 baseline	PCL-5 12-month	BITSEA Problems baseline	BITSEA Problems 12-months	DECA Attachment baseline	DECA Attachment 12 months	DECA Initiative baseline
Parent measures								
ACE score (baseline)	–							
PCL-5 (baseline)	0.42***	–						
PCL-5 (12-month)	0.15[c]	0.44***	–					
Child measures								
BITSEA Problems (baseline)	0.39*	0.10[e]	−0.05[f]	–				
BITSEA Problems (12-month)	0.36**	0.45***	0.22[a]	0.53***	–			
DECA Attachment (baseline)	−0.02[f]	0.05[e]	−0.01[f]	−0.56***	0.01[f]	–		
DECA Attachment (12-month)	−0.11[d]	−0.13[c]	0.06[e]	−0.43*	−0.52**	0.34**	–	
DECA Initiative (baseline)	0.08[e]	0.24[a]	0.08[e]	−0.36*	0.05[e]	0.69***	0.15[c]	–
DECA Initiative (12-month)	−0.19[b]	−0.14[c]	0.0[f]	−0.42*	−0.37**	0.35**	0.68***	0.30*

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[a]p ranges from 0.051 to −0.10; [b]p ranges from 0.101 to 0.20; [c]p ranges from 0.201 to 0.30; [d]p ranges from 0.301 to 0.50; [e]p ranges from 0.501 to 0.70; [f]$p > 0.701$.
ACE, Adverse Childhood Experiences questionnaire; PCL-5, PTSD Checklist for DSM-5; BITSEA, Brief Infant-Toddler Social and Emotional Assessment; DECA, Devereux Early Childhood Assessment.

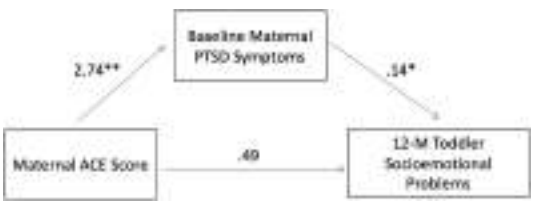

FIGURE 1 | Regression analysis summary for parent variables predicting toddlers' socioemotional problems. $R^2 = 0.25$ ($N = 58$, $p = 0.0004$). *$p = 0.0041$; **$p = 0.0013$.

wherein mothers who reported greater experiences of childhood adversity reported greater symptoms of PTSD when they entered our study. We also hypothesized that toddlers of mothers with greater experiences of childhood adversity would demonstrate more behavioral and emotional difficulties (H1). This relationship was also supported; as shown in **Table 3**, there was a moderate, positive association between maternal ACE score and BITSEA Problem score at baseline ($r = 0.39$, $p = 0.02$) and 12-months ($r = 0.36$, $p = 0.006$). This first hypothesis was also supported within the multiple regression models (see **Figure 1**).

Our second hypothesis was that PTSD symptoms would mediate the association between maternal exposure to childhood adversity and increased risk of child socioemotional and behavioral difficulties in the next generation (H2). Prior to mediation analyses, maternal ACE scores were positively associated with maternal PTSD symptoms measured at baseline and toddlers' socioemotional difficulties as measured by the BITSEA at the 12-month follow-up, such that mothers with more ACEs had greater PTSD symptoms and reported more behavioral and emotional difficulties among their toddlers. Mediational analyses in PROCESS (Hayes, 2013) revealed a significant mediation model [($F(2,55) = 9.2$, $R^2 = 0.25$, $p = 0.0004$], see **Figure 1**. After controlling for the effect of the proposed mediator – baseline maternal PTSD symptoms – the direct effect of ACEs on child emotional problems was no longer significant ($B = 0.20$, $t = 1.57$, $p = 0.123$), and there was an indirect effect of maternal ACEs on the BITSEA Problem score through maternal PTSD symptoms (β = 0.16, bootstrapped 95% CI = 0.07–0.71). Thus, having a higher number of ACEs predicted more PTSD symptoms among mothers, which in turn predicted more child problems.

Our second aim was to examine how participation in an in-home, relationally based intervention impacts child socioemotional development and whether it mitigates the association between maternal PTSD symptoms and child outcomes.

As seen in **Table 4**, the overall moderation model estimating the 12-month DECA Attachment scale was significant [$R^2 = 0.20$, $F(4,53) = 3.23$, $p = 0.02$]. Baseline ratings on the DECA Attachment subscale predicted 12-month ratings on the DECA Attachment subscale ($t = 2.82$, $p = 0.006$). There was a trend-level main effect of treatment on DECA Attachment scores ($t = 1.93$, $p = 0.06$) wherein mothers randomized to the treatment condition rated their toddlers higher on this scale while controlling for baseline levels. This implies that in the full sample, treatment was marginally effective at improving toddler socioemotional outcomes. There was also a significant interaction between treatment condition and maternal PTSD symptoms at baseline ($t = -1.76$, $p = 0.04$). Specifically, mothers randomized to receive IMH-HV treatment who had lower PTSD symptoms at the start of treatment rated their toddlers higher on the DECA Attachment scale compared to mothers with subclinical baseline PTSD symptoms who did not receive treatment. Thus, IMH-HV treatment was most associated with positive child socioemotional development when mothers entered treatment with fewer PTSD symptoms, see **Figure 2**. When mothers entered the study with higher PTSD symptoms suggestive of a probable diagnosis of PTSD, their toddlers had similar scores on the DECA Attachment subscale regardless of treatment condition.

As shown in the lower portion of **Table 4**, the overall moderation model estimating the 12-month DECA Initiative

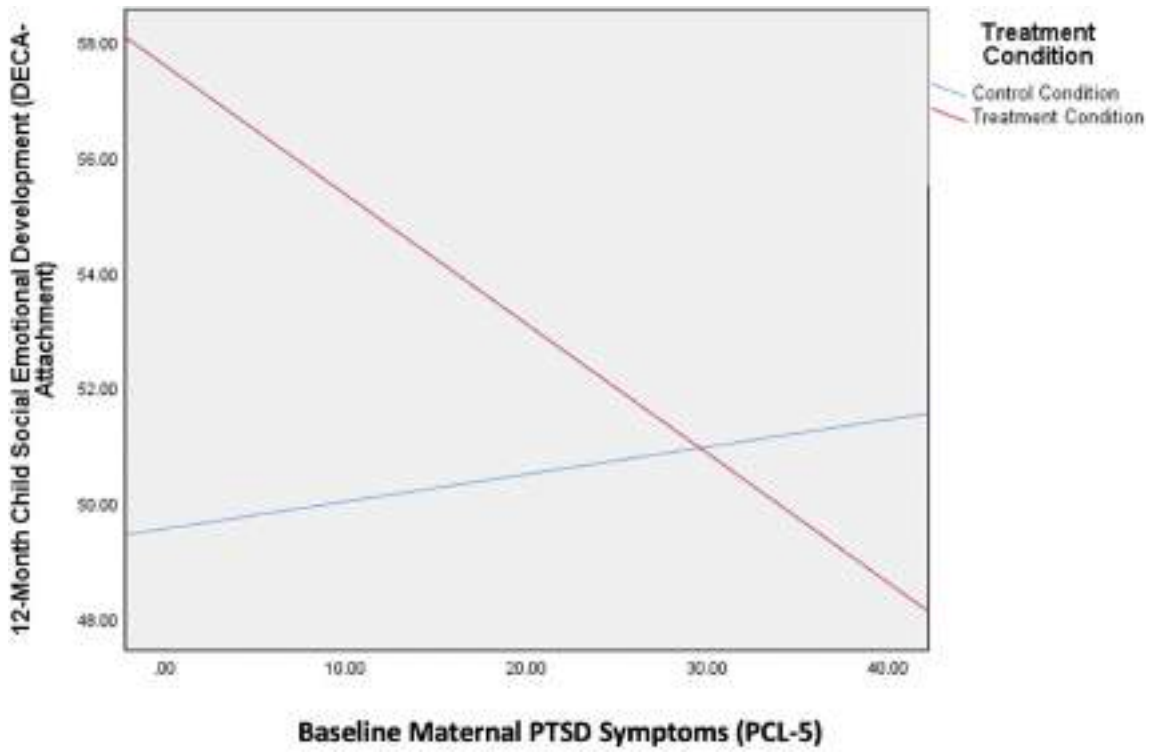

FIGURE 2 | Interaction between maternal PTSD symptom at baseline and treatment condition on child socioemotional development.

scores was also significant [R^2 = 0.18, $F(4,50)$ = 2.73, p = 0.04]. Baseline ratings on the DECA Initiative subscale predicted 12-month ratings on the DECA Initiative subscale (t = 2.72, p = 0.009). Treatment condition was not associated with 12-month rating on the DECA Initiative subscale (t = −0.13, p = 0.89). Baseline maternal PTSD symptoms were a trend-level predictor of DECA Initiative ratings when accounting for the other terms in the model.

There was no significant interaction between treatment condition and baseline PTSD symptoms in the model predicting DECA Initiative scores (t = 0.50, p = 0.62).

DISCUSSION

The current study had two aims. First, we aimed to determine if maternal PTSD symptoms mediate the relation between maternal history of adversity and child outcomes. Second, we aimed to test whether IMH-HV was efficacious in improving child outcomes, particularly in the context of maternal PTSD symptoms. Each result will be discussed below.

Maternal Adverse Childhood Experiences, Posttraumatic Stress Disorder, and Child Outcomes

Our study provides further support for the notion that childhood adversity may increase the likelihood of maternal mental health challenges and thus negative consequences for their offspring. We interpret these associations to be probabilistic, and not deterministic, given the findings that the impact of adversity is mediated by maternal PTSD symptoms, which are amenable to psychotherapeutic intervention. Current symptoms of maternal PTSD were observed to mediate the influence of maternal childhood adversity on infant socioemotional wellbeing suggesting that prenatal screening for maternal symptoms of PTSD is warranted (Erickson et al., 2019). Treating maternal PTSD symptoms sooner rather than later may reduce maternal suffering. Such amelioration affords the developing relationship between mother and infant the opportunity to unfold unhindered by extremely insensitive, misattuned maternal behaviors, such as dissociation, avoidance, or flooding, which can disrupt the sensitive caregiving and the affective communication between parent and infant (Lyons-Ruth et al., 1999).

Importantly, young children presenting with externalizing and internalizing disorders may be adapting to parental behavior in order to sustain the attachment relationship, even if costly to their psychosocial development (Sroufe, 2009; Borelli et al., 2020). Mothers who are experiencing intrusive thoughts while interacting with their infant may demonstrate behaviors that are disruptive to the infants' affective communication, such as dissociation, aversive hostility, or withdrawal (Lyons-Ruth et al., 1999). Infants of mothers who are struggling with PTSD must adapt to caregiving that is more likely to be negative, intrusive, or in other ways persistently insensitive or alarming (Lyons-Ruth, 1996; Schechter et al., 2014). As Fraiberg noted long ago, infants who are routinely unprotected from overwhelming affects and

TABLE 4 | Main and interaction effects of maternal PTSD symptoms and intervention on DECA Attachment and Initiative subscales.

Variables	*b*	SE	*t*	*p*
Model 1	**Child social emotional development – 12-month DECA Attachment**			
Constant	28.53	8.02	–	
Treatment	8.03	4.16	1.93	0.06
Maternal baseline PTSD score	0.05	0.11	0.42	0.67
Treatment by baseline PTSD symptoms (moderator)	−0.27	0.15	−1.76	0.04
Control variables				
Child socioemotional development (baseline)	0.41	0.15	2.82	0.006
Model 2	**Child social emotional development – 12-month DECA Initiative**			
Constant	33.85	8.04	–	
Treatment	−0.55	4.09	−0.13	0.89
Maternal baseline PTSD score	−0.21	0.11	−1.91	0.06
Treatment by baseline PTSD symptoms (moderator)	0.08	0.15	0.50	0.62
Control variables				
Child socioemotional development (baseline)	0.42	0.15	2.72	0.009

Model 1: R^2 = 0.20, F(4,53) = 3.23, p = 0.02.
Model 2: R^2 = 0.18, F(4,50) = 2.73, p = 0.04.
Maternal PTSD symptoms measured by the PTSD Checklist for DSM-5 (PCL-5); Child socioemotional development measured by the Devereux Early Childhood Assessment-Infant (DECA-I) and the Devereux Early Childhood Assessment-Toddler (DECA-T).

frequently left in a state of helpless despair develop psychological defenses against the aversiveness of interaction with the parent (Fraiberg, 1982; Weatherston and Ribaudo, 2020). The substrate of socioemotional health is laid in the first months of life; when the infant experiences frequent lapses in parental responsivity, or when the parent becomes the source of alarm (Hesse and Main, 2000) the infant is more likely to develop defensive strategies such as avoidance or aggression (Fraiberg, 1982) that result in an increased risk of child psychopathology (Lyons-Ruth, 1996; Plant et al., 2018). The data suggests that practitioners who are consulted due to concerns regarding young children with socioemotional problems should pay careful attention to assessing parental mental health, including assessment of subclinical levels of PTSD. Treatment of children's behavior problems in the absence of treating parental mental health may be ineffective. In addition, the association between parental psychopathology and childhood socioemotional problems lends evidence to the need for family systems and dyadic assessment (Shonkoff et al., 2012; Erickson et al., 2019). For instance, psychotherapists providing individual treatment for adults who are parents of young children can promote two generation approaches by encouraging their patients who have a history of early adversity or depression to access IMH-HV services, in addition to their continuing their own psychotherapy. However, it is noted that such an approach would require significant coordination and teamwork, ideally within a reflective consultation/supervision group with the therapists to reduce the risk splitting/fragmentation and confusion for the traumatized parent(s) (Biggart et al., 2017; Green, 2018).

Efficacy of Infant Mental Health-Home Visiting

Building upon previous reports that IMH-HV is an effective intervention that promotes maternal sensitivity, responsivity, and reflective functioning (Rosenblum et al., 2020; Julian et al., 2021; Stacks et al., 2021), the current study explored the effectiveness of IMH-HV for improving child outcomes among mothers with a history of childhood adversity and current PTSD symptoms. Results indicated positive socioemotional outcomes for children of mothers who received IMH-HV compared to the control group, with the best outcomes seen for children of mothers with low to moderate PTSD symptoms who received the intervention. Attention to early intervention and the emerging relationship (Fitzgerald et al., 2011), before early childhood adaptations become traits (Perry et al., 1995), is a hallmark of infant mental health work. Our findings suggest that dyadic intervention for mothers with low to moderate PTSD symptoms helps promote child socioemotional wellbeing. Mothers with low to moderate PTSD symptoms may respond more quickly to IMH-HV intervention than mothers with more severe symptomology. IMH-HV services are designed to provide intervention until the infant's third birthday. This study only examined child wellbeing after 12 months of service. A longer duration of treatment of both individual and dyadic psychotherapy may be warranted for mothers with more PTSD symptomology to effect improvement in children's socioemotional functioning. Some mothers may need a sustained period of intervention to stabilize their symptoms (Stacks et al., 2021). They may need time to experience "being held in the mind of another" (O'Rourke, 2011, p. 170) and understanding their own mental states (Suchman et al., 2018) before they can regulate their own emotions well enough to help their child co-regulate. For mothers with history of relational harm, the "felt sense" of being cared for that fuels mothering may be thin. The therapeutic relationship serves as a corrective emotional experience, but that takes time to develop, especially for mothers with a history of early childhood adversity (Stacks et al., 2021). In addition, once the mother begins to understand her mental states, it will still take time for the child to shift their "expectation" of interactions. The longer they have adapted to a particular attachment template, the longer it may take to develop the confidence in using the parent as a source of comfort (Stovall-McClough and Dozier, 2004; Barlow et al., 2021). It is also possible that children of mothers with severe PTSD symptoms did benefit from the intervention, but that these mothers were not reliable reporters of their infants' symptoms early on and became more insightful as treatment progressed. This reporter-bias would have masked treatment effects in this group. Further research is necessary to examine the efficacy of the model, including the duration and intensity required, to effect dyadic change in the highest risk group.

Importantly, many of the mothers faced systemic inequity and oppression, in addition to interpersonal harm, which

add to the complexity and severity of traumatic stress (Cyr et al., 2010). The challenges of developing a therapeutic alliance with traumatized individuals can be exacerbated when there are obvious differences in social identities, especially when clinicians are uncomfortable addressing racial and ethnic differences (Owen et al., 2017). Further research is necessary to examine the contribution of client and therapist match to therapeutic outcomes.

Contributions and Limitations

Our study has several strengths, including randomization and a control group, low attrition, a racially and economically diverse sample, and longitudinal data. It expands and refines attention to the mounting load of PTSD symptoms on the mother and infants' wellbeing. It provides evidence that IMH-HV is efficacious at improving child socioemotional outcomes and can be especially effective for dyads where the mother has low to moderate PTSD symptoms. However, for mothers with more PTSD symptoms, it's possible that longer durations of treatment may be more effective at reducing mother's dysregulation before the positive impact on the infant is observable.

A limitation of the study is that we relied on self-report of PTSD symptoms, rather than a clinical interview. Because avoidance is a central feature of PTSD, it may be that this led to under-reporting of PTSD symptoms. If this is true, it could impact the results of this study, especially considering that IMH-HV was found to be especially effective for mothers with low to moderate PTSD symptoms. If self-reported PTSD symptom rates were lower due to participant avoidance, it may be that the intervention is effective for those with greater PTSD symptoms than we initially thought. Similarly, we did not ask the mothers to elaborate which traumatic experience they were reflecting upon while answering the PCL-5 questions. Knowing the nature of the traumatic event(s) that contribute to dyadic disruption may offer the capacity for more refined treatment. For instance, there are likely to be qualitative differences in interactions with a baby if parent is reporting PTSD symptoms related to a recent incident of interpersonal violence as opposed to recalling physical abuse in their childhood (Schechter et al., 2014).

Another limitation of the study is the reliance on parental self-report for measures of infant wellbeing. Mothers who are coping with multiple stressors, including PTSD, may have a negative bias which contributes to perceiving the infant as difficult (Romero et al., 2021) or may present as avoidant of their infant's challenges. Future research would benefit from having both parent-reported and observer-rated measures of infant socioemotional development.

Additionally, the gold standard for treatment studies is intent-to-treat analyses, which were not possible in this trial. Thus, the attrition rate may affect the generalizability of the findings. Finally, there is some evidence of the utility of the DECA in samples of preschool children from low-income backgrounds, though the behavioral concerns subscale may not adequately assess culturally and linguistically diverse children in low-income families (Bulotsky-Shearer et al., 2013). Thus, this measure may not have captured the full range of socioemotional concerns or strengths of our population.

Future Directions

Our sample included many women who have faced systemic inequalities and oppression. Experiences with systems of care guided by dominant culture may negatively impact the epistemic trust (Fonagy and Allison, 2014) that contributes to the development of a therapeutic relationship. Infant mental health therapists, though engaged in reflective practice, may unwittingly interfere with the development of a trusting relationship by engaging in microaggressions or being culturally insensitive. Mothers whose history of relational harm intersects with societal harm, may present with co-morbid and severe traumatic life-events (e.g., life-threatening encounter with law enforcement) and thus demonstrate related mental health challenges. They may require longer, more intensive or multi-modal, and interdisciplinary interventions that are culturally responsive and humble, while also recognizing often unacknowledged sources of resiliency and support (Parker, 2021).

A majority of our sample (70%) was married. This study did not specifically address how paternal support contributes to the infant's mental health. Given the influence of the father–infant relationship on infant mental health, *via* the marital relationship and direct interaction with the infant, future studies could reveal the impact of the marital relationship on infant socioemotional wellbeing (Hall et al., 2014; Korja et al., 2016).

In conclusion, this study contributes to the body of research that suggests that maternal mental health influences the socioemotional wellbeing of young children. It provides evidence that IMH-HV is effective in supporting the socioemotional health of infants and young children of mothers, especially for those who experience low to moderate PTSD symptoms. It suggests that a longer period of intervention may be required to impact the mother's capacity to support their infant's socioemotional wellbeing when she struggles with more severe PTSD symptomology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Michigan Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MM and KR obtained funding and oversaw all aspects of the clinical trial. JuR, JL, and JeR conceptualized and

designed the study for this manuscript. JJ organized the database. JuR, JL, JeR, and JJ performed the statistical analyses. JuR wrote the first draft of the manuscript. JuR, JeR, NE, and JL wrote sections of the manuscript. All authors contributed to manuscript revision, and read and approved the submitted version.

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From Early Micro-Temporal Interaction Patterns to Child Cortisol Levels: Toward the Role of Interactive Reparation and Infant Attachment in a Longitudinal Study

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Parental mental disorders increase the risk for insecure attachment in children. However, the quality of caregiver–infant interaction plays a key role in the development of infant attachment. Dyadic interaction is frequently investigated via global scales which are too rough to uncover micro-temporal mechanisms. Prior research found that the latency to reparation of uncoordinated dyadic states is associated with infant behavioral and neuroendocrine regulation. We investigated the hypothesis that this interactive mechanism is critical in predicting secure vs. insecure attachment quality in infancy. We also assessed the predictive quality of infant attachment regarding neuroendocrine reactivity later in childhood. A subsample of N = 58 dyads (n = 22 mothers with anxiety disorders, n = 36 controls) from a larger study were analyzed. At 3–8 months postpartum, maternal anxiety disorders were diagnosed via a structured clinical interview as well as dyadic interaction during the *Face-to-Face-Still-Face* (FFSF) was observed and coded on a micro-temporal scale. Infant attachment quality was assessed with the strange situation paradigm at 12–24 months of age. In an overlapping subsample of N = 39 (n = 13 mothers with anxiety disorder; n = 26 controls), we assessed child cortisol reactivity at 5 to 6 years of age. Generalized linear modeling revealed that longer latencies to interactive reparation during the reunion episode of the FFSF as well as maternal diagnosis at 3–8 months of age predict insecure attachment in children aged 12–24 months. Cox regressions demonstrated that dyads with infants who developed insecure attachment at 12–24 months of age were 48% less likely to achieve an interactive reparation at 3–8 months of age. Mixed models revealed that compared to securely attached children, children who had developed an insecure attachment at 12–24 months of age had an increased cortisol reactivity at 5 to 6 years of age during free play. The results confirm the hypothesis that the development of attachment is affected by experienced micro-temporal interactive patterns besides

diagnostic categories. They also showed that infants of mothers with postpartum anxiety disorders have a more than fivefold increased risk of developing an insecure attachment than the infants of the control group. Moreover, results imply that these patterns may influence neurohormonal regulation even in preschool aged children.

Keywords: maternal anxiety disorder, still-face, interactive reparation, infant attachment, child cortisol reactivity

INTRODUCTION

Attachment theory describes the inherent human need to establish close relationships to other humans from the perspective of the emotional needs of infants. Attachment is discussed as the evolutionary established ensuring of child survival, since the human offspring is specifically in need of long-term care and help (for an overview, see Bowlby, 1969/1982, 1973, 1980). Ainsworth developed the strange situation – an observational experiment for classifying secure, insecure-avoidant and insecure-ambivalent attachment styles (Ainsworth et al., 1978), as well as the later defined disorganized attachment (Main and Solomon, 1986). However, it is not only the relationship quality between children and their parents that is determined by the attachment style. For decades now, the scientific literature has also demonstrated the multi-facetted long-term effects of secure vs. insecure attachment for child development.

To mention a few recent results, securely attached infants manifest higher capacities in processing social information than insecurely attached infants (Biro et al., 2015). The latter exhibit a higher increase in cortisol levels than their securely attached counterparts following the strange situation (Luijk et al., 2010). Securely attached children demonstrate vagal adaption to external demands, such as social stressors, while insecurely attached children do not (Paret et al., 2015). Additionally, Bernard and Dozier (2010) detected a cortisol response following the strange situation for disorganized and not for children with a secure attachment quality. Later in life, securely attached adolescents show a higher empathetic responsiveness (Diamond et al., 2012), whereas insecurely attached children, adolescents and adults exhibit difficulties in regulating stress, more specifically, they show signs for a dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis (Oskis et al., 2011; Pierrehumbert et al., 2012; Kidd et al., 2013). In their review, Beatson and Taryan (2003) concluded that secure attachment serves as a buffer in the relationship between HPA dysregulation and the development of depressive symptoms later in life. Thus, one can conclude "early attachment quality may be a lasting source of vulnerability or protection in children's development" (Carlone and Milan, 2021, p. 603).

Waters et al. (2010) explored the ties between attachment and emotion regulation. They emphasized the importance of emotion understanding in the development of these constructs. Furthermore, Kerns and Brumariu (2014) discussed insecure and disorganized attachment as risk factors for the development of affective disorders and that this association might trace back, in part, to less competent emotion regulation capacities in insecurely attached children. A hypotheses that was recently supported by Verhees et al. (2021), who found a mediation pathway between attachment insecurity, the regulation of positive, as well as negative affect and the development of depressive symptoms in a large longitudinal sample of adolescents.

Emotion regulation capacities are hypothesized to be formed by social interactions children experience in their everyday life (Beeghly and Tronick, 2011). Also, Ainsworth emphasized the importance of caregiving behavior, specifically the caregiver's sensitivity, for the development of a secure attachment. Ainsworth defined sensitivity as the caregiver's ability to perceive, correctly interpret, as well as to promptly and adequately respond to the infant's communicative signals (Ainsworth et al., 1978). Braungart-Rieker et al. (2001) found that both infant affect regulation and maternal sensitivity discriminate between secure and insecure infants and that the association between sensitivity and attachment was partially mediated by infant regulation. Besides these associations to infant attachment (e.g., Fuertes et al., 2009), parental sensitivity has been shown to be of relevance for a wide range of further developmental outcomes, such as the processing of social information (Biro et al., 2015), fear reactivity (Braungart-Rieker et al., 2010), physiological (Moore et al., 2009; Conradt and Ablow, 2010), neuroendocrine (Spangler et al., 1994; Jansen et al., 2010b) and affective regulation (Haley and Stansbury, 2003; Jonas et al., 2015; Rodrigues et al., 2021), social behavior (Kivijärvi et al., 2001; Bernier et al., 2021; Licata-Dandel et al., 2021), as well as cognitive and language development (Malmberg et al., 2016; Rodrigues et al., 2021).

However, as much as the concept of parental sensitivity was and is needed to understand infant attachment, it is both multidimensional and a somewhat rough macro characteristic. Thus, it is limited in uncovering the details of the moment-to-moment interactive mechanisms that may be important in forming a secure attachment throughout the interactive history of a child (compare to Mesman, 2010). One such mechanism may be derived from Tronick's reparation model (Tronick, 2007). In this model, Tronick describes the micro-temporal regulation of affect and distress in caregiver–infant dyads. The interactive partners are described as open and dynamic systems (Ham and Tronick, 2009; DiCorcia and Tronick, 2011), whose interactive states are interdependent, especially in young infants. As their self-regulatory capacities are limited, they rely on the regulatory input of their caregivers. It is a complimentary expanded view shared by other theoretical frameworks (see Cole et al., 2004) that suggest a developmental sequence of increasing self-regulatory capacities. In this sequence, young infants have basic regulatory skills of limited effectiveness (compare to Diener and Mangelsdorf, 1999), then interactively engage with their caregivers who represent external resources of regulation (Spangler et al., 1994), and finally

develop more competent self-regulatory strategies throughout their development. The interactive process is asymmetric (e.g., Beebe et al., 2016) as it is largely led by the caregivers (Cohn and Tronick, 1988) which is somewhat due to the limited capacities of infants. However, in this process, the role of infant interactive behavior is essential as they communicate their biobehavioral status by means of eye-contact, facial expressions, body postures, vocalizations, etc. and consequently invite the caregivers to regulatory scaffolding. The caregivers, in turn, may perceive, correctly interpret, as well as promptly and adequately respond to the infant's signals (compare "sensitivity," Ainsworth et al., 1978), and thus externally regulate the biobehavioral status of their infant. According to Tronick (1989) this process is mutually regulated.

Paradoxically, this regulatory process in itself is stressful. Due to misinterpretations of the caregiver or the limited interactive capacities of the infant, the speed of exchange, etc., uncoordinated dyadic states (so-called mismatches) repeatedly occur in small time intervals. These mismatches produce inconsistencies between the regulatory need of the infant and the regulatory input of the caregiver, which Tronick describes as micro-stressors. These stressors are overcome as soon as the caregiver is able to provide a regulatory input that corresponds to the infant's regulatory need, or the infant adjusts to the caregiver's actions – a process called interactive reparation. Thus, the reparation model describes the dyadic regulation as mutual adaptive process in which the dyad oscillates between coordinated states (matches) and mismatches on a micro-temporal scale. It is this dynamic process, which is thought to shape not only infant regulatory strategies but also a wide range of developmental domains, such as attachment (DiCorcia and Tronick, 2011). Indeed, interactive reparation was demonstrated to be associated to infant neuroendocrine (Müller et al., 2015) and psychological regulation (Provenzi et al., 2015). Furthermore, Beebe et al. (2010) revealed, that a moderate level of interactive contingency, which may be described as the occurrence of mismatches that are quickly repaired to matches, predicted infant secure attachment, whereas both low (failure to reparation) and high (few mismatches) levels of contingency predicted insecure attachment. This result fits well with the idea, that a perfectly matched interactive pattern between caregivers and children is neither possible nor desirable as it would prohibit the opportunities to internalize dyadically scaffolded regulation strategies by transforming micro-temporal stressors into non-stressful states (DiCorcia and Tronick, 2011). Nonetheless, to the best of the author's knowledge, the role of interactive reparation regarding the development of secure vs. insecure attachment has not been investigated. As Provenzi et al. (2018) state, "more research on the interconnections between macro-analytical concepts in caregiver–infant research, such as sensitivity and attachment, and micro-analytical processes is desirable" as "[. . .] future investigations on the relations between macro- and micro-analytical concepts would not only connect different methodological approaches but also enhance our understanding of the dynamics in developmental trajectories" (page 18).

Besides the associations between parental sensitivity and infant and child attachment, it is well known, that parental mental disorders may lead to unfavorable effects on child behavioral (Kingston and Tough, 2014), cognitive (Murray et al., 2003) and psychopathological (Goodman et al., 2011) development and that parental psychopathology may interfere with the development of a secure attachment style (Wan and Green, 2009). Although most studies have concentrated on maternal depression (e.g., Goodman et al., 2011) there is also some empirical and growing evidence about the associations between parental anxiety and child development (Glasheen et al., 2010; Goodman et al., 2016; Reck et al., 2018b; Polte et al., 2019). Specifically, for this current study and to the best of the authors' knowledge, there is only one study demonstrating that maternal anxiety may predict insecure attachment in children (Stevenson-Hinde et al., 2011). As it is assumed that the attachment quality and regulatory capacities are associated to and organized by interactive history, it is only natural to conclude, that the association between parental anxiety and child attachment would be mediated by interactive characteristics. Indeed, dyads in which the mother suffers from anxiety show specific problematic interactive patterns (for an overview see Kaitz and Maytal, 2005; Goodman et al., 2016). Besides reduced maternal sensitivity (Warren et al., 2003; Kertz et al., 2008; Feldman et al., 2009; Stevenson-Hinde et al., 2013), dyads with anxious mothers also show micro-temporal differences compared to non-anxious mothers, as for example less contingent maternal interactive patterns (Beebe et al., 2011), as well as changed infant patterns of positive and negative affective displays (Reck et al., 2018a).

However, compared to the effects of parental depression, the evidence regarding the effects of parental anxiety on interactive patterns is less consistent. Several studies identify specific rather than general interactive impairments in dyads with anxious mothers: Grant et al. (2009), for example, did not find an association between maternal anxiety and maternal sensitivity. A finding that is shared by the results of Murray et al. (2007) regarding mothers with social phobia. However, they specifically observed that the mothers were more anxious and were less engaging when interacting with a stranger. Moreover, they encouraged their infants less to interact with the stranger. Additionally, the infants of mothers with social phobia were less responsive to the stranger. The results of Murray et al. (2012) did not reflect general differences regarding interactive patterns between dyads with social phobic mothers and controls in a non-threat interaction task, too. Contrary, in disorder-specific challenges, some parenting difficulties were observable for the clinical group. These difficulties, however, did not seem disorder specific. Accordingly, Kertz et al. (2008) report, that anxious mothers only demonstrate less sensitivity in social tasks. Hence, it may be erroneous to assume general interactive deficits in these dyads. Results suggest the associations between maternal anxiety and child behavioral regulation along with mental development are moderated by caregiving behaviors (as shown for sensitivity in Grant et al., 2010a,b). Notably, these studies refer to prepartum anxiety and their results are discussed considering the fetal programming hypothesis (see van den Bergh et al., 2017). However, we suggest the applicability of this idea to the postpartum period as shown by Kertz et al. (2008) as well as Richter and Reck (2013) for infant regulatory problems and

aim to control for prepartum effects in our models in particular. It also seems highly unlikely that the associations between child attachment and long-term consequences are mono-causal. They are rather more likely determined by mutually moderating risk-constellations and factors. For example, the effect of insecure attachment on cortisol response seems more pronounced in infants of depressed mothers (Luijk et al., 2010). Furthermore, insecurely and disorganized attached children seem more prone to develop behavioral and cognitive deficits when exposed to parenting distress or maternal depression than securely attached children (Tharner et al., 2012; Carlone and Milan, 2021).

The aim of this study is to identify the most important predictors for (1) the development of insecure vs. secure attachment considering the effects of micro-temporal reparation processes along with parental anxiety in the postpartum period, prepartum distress and their interaction effects, and (2) child cortisol-reactivity considering the long-term effects of infant secure vs. insecure attachment, maternal anxiety in the postpartum period and the interaction between these factors. Though these analyses were exploratory in nature, according to current literature, we expected infant attachment quality to be mainly predicted by interactive measures (e.g., Stevenson-Hinde et al., 2013).

STUDY 1

Materials and Methods

Procedures

The current secondary analyses consist of two subsamples derived from a larger longitudinal sample previously described elsewhere (Reck et al., 2013, 2018a,b; Richter and Reck, 2013; Tietz et al., 2014; Müller et al., 2015, 2016; Zietlow et al., 2019). The independent ethics committee of the medical faculty, Ruprecht-Karls-University, Heidelberg, Germany approved the study protocol prior to the first assessment. After the study procedures had been fully explained to the caregivers, we obtained written informed consent to participate in the study.

The data for the first part of the study were collected from 2006 to 2010. At 3–8 months postpartum, the caregiver–infant interaction was videotaped in laboratory during a standardized interaction experiment, namely, the Face-to-Face-Still-Face paradigm (FFSF). The FFSF was designed by Tronick et al. (1978) and in its most prevalent form (Mesman et al., 2009) consists of three episodes, i.e., the play, the still-face and the reunion episode, in which each episode lasts 120 s. Throughout the procedure, the infant is secured in a booster seat. The initial play episode is a face-to-face-interaction between the caregiver and the infant. The caregivers are instructed to play with their infants as they would at home, however, without the use of toys and/or pacifiers. At the end of the play episode, the caregivers are instructed to react to an acoustic signal by turning their head aside and silently count to ten (transition). Next, they turn their head back around but look slightly above their infant's head, however, without engaging in any gestures, facial expressions, or vocalizations for the next 120 s (still-face). Finally, during the reunion episode, the caregivers are required to resume face-to-face-play with their infant for the last 120 s. After the FFSF, we carried out the German version of the Structured Clinical Interview for DSM-IV Disorders (Wittchen et al., 1997). Furthermore, questionnaires regarding sociodemographic and psychological variables were handed out to fill out at home. Around 1 year postpartum, the dyads were invited to revisit the lab for the strange situation (Ainsworth et al., 1978) for 12- to 24-month olds. The strange situation is designed to elicit exploration and attachment behavior in the child, and thus enable the observation and evaluation of attachment security. Like the FFSF, this procedure was videotaped. The strange situation is, like the FFSF, a standardized behavioral experiment that involves a sequence of eight episodes each lasting approximately 3 min, in which a caregiver and her child are repeatedly separated, reunited and a strange person is introduced. Attachment is classified based on the infant's behavior. The reunion episodes (episodes 5 and 8) are coded concerning proximity seeking, contact maintaining, proximity avoidance and resistance to contact.

Measures

Maternal Mental Disorders

Mental pathology during the postpartum period was assessed via the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, Wittchen et al., 1997). The SCID-I was a widely used semi-structured interview for the diagnosis of selected disorders. It was the diagnostic gold standard at the time. According to the DSM-IV, anxiety disorders included generalized anxiety disorder, panic disorder with and without agoraphobia, agoraphobia without history of panic disorder, specific phobias, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and anxiety disorder not otherwise specified.

Recollected Prepartum Distress

Prepartum distress was assessed retrospectively via a self-report instrument, namely the Prenatal Emotional Stress Index (PESI; Möhler et al., 2006). The PESI assesses emotional distress during pregnancy separately with 11 items per pregnancy trimester. The items assess anxiety, sadness, joy, distress, and tension via a visual analog scale ranging from 0% to 100%. The item values (2 items with reversed polarity) are averaged for each trimester, resulting in three PESI scores ranging from 0% to 100%. Measures for internal consistency were taken from the larger study sample ($N = 111$): We bootstrapped ($N = 1.000$ samples) 95% confidence intervals for McDonald's ω (Hayes and Coutts, 2020) which revealed a good to excellent reliability ($\omega = [0.88;0.94]$ for the first, $\omega = [0.88;0.95]$ for the second and $\omega = [0.91;0.95]$ for the third trimester). We selected the PESI score for the third trimester as independent measure. Thus, we used the measure with the least memory bias.

Dyadic Interaction

Two trained and reliable coders coded the interactive behaviors of the infants and caregivers during the FFSF using the Noldus Observer Video-Pro coding system with 1-s time intervals. They were blinded to the hypotheses of the study and maternal

diagnostic status. They used the German translation and revision of the microanalytical Infant and Caregiver Engagement Phases (ICEP-R; Reck et al., 2009). The engagement phases combine information from the face, direction of gaze and vocalizations of the infants and caregivers. For the infant, the following engagement phases can be coded: negative engagement (further divided into withdrawn and protest), object/environment engagement, social monitor, and social positive engagement. For the caregiver, the engagement phases are negative engagement (further divided into withdrawn, hostile and intrusive), non-infant focused engagement, social monitor/no vocalizations or neutral vocalizations, social monitor/positive vocalizations, and social positive engagement. 10% of the video tapes from the larger longitudinal sample (n = 9 of N = 91) were randomly selected and coded by both of the two independent study coders to assess the inter-rater reliability. The coders were unaware of which videos were used for reliability. The inter-rater reliability was determined using Cohen's κ (Cohen, 1960). The achieved values of Cohen's κ (κ = 0.82 for the infant codes; κ = 0.73 for the maternal codes) were similar to those reported in previous studies (Tronick et al., 2005; Reck et al., 2011). Positive social matching states were defined as the caregiver and infant simultaneously exhibiting the same affective-behavioral state as follows: the caregiver is in positive engagement or social monitor/positive vocalizations and the infant is in positive engagement or social monitor. We calculated the independent measures – the latency to interactive reparation – as the time interval from interaction onset to positive social match onset, that is, the initial mismatch duration of the respective FFSF episode in seconds. As the reunion episode is particularly informative regarding the regulatory quality of the interaction (Weinberg and Tronick, 1996), we selected the latency to interactive reparation during the reunion episode as independent measure.

Attachment Quality

Two trained and reliable coders annotated the videos of the strange situation paradigm. They were blinded to the hypotheses of the study and the maternal diagnostic status. Infants were classified as secure, insecure-avoidant, insecure-ambivalent or disorganized according to their behavior throughout the strange situation paradigm, and especially in the reunion episodes (see above). The disorganized category was assigned, if the attachment behavior was no longer organized or directed toward the caregiver (Simonelli and Parolin, 2017). The 25% of the video recordings from the larger longitudinal sample (n = 19 of N = 77) were randomly selected and coded by both of the two independent study coders to assess inter-rater reliability. The coders were not able to distinguish if they were coding videos for the reliability assessment or for the general study purpose. The inter-rater reliability was determined using Cohen's κ (Cohen, 1960). The achieved values of Cohen's κ (κ = 0.82) were similar to or higher than those reported in previous studies (Behrens et al., 2016; Smith et al., 2016). As we were interested in predicting secure vs. insecure attachment quality, we binary coded all secure patterns as "0 = secure" and all insecure and disorganized patterns as "1 = insecure/disorganized."

Sample

In this project, we focused on the primary caregiver, which in most cases is the mother (e.g., Harmon and Perry, 2011). Mothers were included in the clinical group, if they were diagnosed with at least one of the following anxiety disorders according to the DSM-IV (American Psychiatric Association, 2000) in the postpartum period: panic disorder with agoraphobia, agoraphobia without history of panic disorder, generalized anxiety disorder, social phobia, obsessive compulsive disorder, posttraumatic stress disorder and anxiety disorder not otherwise specified. A specific phobia was not considered as a sufficient condition due to lowered clinical relevance. However, if the specific phobia did not occur as single diagnosis but occurred as a comorbidity to other clinically significant anxiety disorders, we did not exclude the respective cases. Mothers were excluded from the clinical group if an acute or former psychosis, a current or former bipolar disorder, current substance abuse or acute suicidal tendency was diagnosed. Despite initial screening efforts to exclude mothers with any other comorbid psychological disorder, the occurrence of comorbid disorders after screening did not exclude a mother, if it was ascertained that the comorbid disorder constituted a secondary diagnosis. Healthy controls were included if they didn't have any current or antecedent axis I diagnosis according to the DSM-IV.

Initially, 122 mothers with their infants were recruited for the larger study. All mothers were of Caucasian ethnicity. n = 14 mothers were excluded due to meeting diagnostic exclusion criteria. For the first subsample, we excluded n = 50 cases as one of the main variables was missing: n = 18 interactive measures at 3–8 months and partly overlapping n = 37 attachment measures at 12–24 months. Consequently, for the first subsample the clinical group comprised n = 22 mothers with an anxiety disorder while n = 36 mothers were included in the control group.

Data Analysis

We used R (R Core Team, 2021, v. 4.1.1) in combination with RStudio® (RStudio Team, 2021, v. 1.4.1717) for Microsoft Windows 10® for all analyses. We used the following packages: "haven" (Wickham and Miller, 2021, v. 2.4.3), "tidyverse" (Wickham et al., 2019), "naniar" (Tierney et al., 2021, v. 0.6.1), "psych" (Revelle, 2021, v. 2.1.6), "MBESS" (Kelley, 2020, v. 4.8.0), "survival" (Therneau and Grambsch, 2000; Therneau, 2021;, v. 3.2.13).

To ascertain that list-wise case exclusions were valid for our analyses, we evaluated if missing values occurred at random. Thus, we tested the missing-completely-at-random (MCAR)-condition by carrying out Little's MCAR test (Little, 1988) once for each subsample. Moreover, for each subsample, we evaluated the comparability between the clinical and the control group regarding sociodemographic and birth-related variables. Depending on the measurement level, we used *OR*, *U*, and *t*-tests for this analytic step. In case of significant differences and dependent on the measurement level, we Spearman- or Pearson-correlated the potential confounder with the other study variables to ascertain if it needed to be controlled for in the main analyses.

The analyses regarding the first part of the study refer to the predictive quality of maternal diagnostic status and dyadic

interaction regarding infant secure vs. insecure attachment by controlling for effects of prepartum distress. Thus, we used a series of hierarchical generalized binomial regression models with logit-link-function and likelihood-ratio coefficient tests.

For solely descriptive reasons, we added a series of hierarchical Cox regressions on the dummy-coded and time-dependent event "first match". The time variable was the latency to interactive reparation in seconds. The initial predictors were maternal diagnostic status, dummy-coded attachment quality of their infants and prepartum distress. The coefficients were tested via *z*-statistic. These retrospective analyses used attachment quality as strata and the prior assessed interactive quality as outcome. Though these analyses do not inform about the predictive quality of attachment, they inform about the interactive quality of infants later classified as securely vs. insecurely attached. Despite the Cox regressions, the hierarchical model tests started with full-factorial models including all two-way and three-way interaction terms. The hierarchical set of Cox regressions started exclusively with main effects. Terms were excluded from the models if they failed to significantly contribute to explaining the dependent variables. The procedures ended with the model that only contained significant predictors.

Regarding the binomial and the Cox regressions, the relative risks and hazard ratios, respectively, serve as estimators of effect sizes. Empirical *p*-values are reported two-tailed. The critical α-errors of the two confirmative analyses sets (i.e., Study 1: binomial regressions; Study 2: mixed models) were Holm–Bonferroni adjusted (Holm, 1979) regarding multiple testing. This sequential procedure controls the family-wise error-rate by adjusting the critical α-level for each of the individual hypotheses. Thus, the critical α is set to 0.025 for the first and 0.05 for the second model series. The α-errors were not adjusted for the descriptive Cox regression. For the full statistical procedure see the knitted R-markdown in the **Supplementary Data Sheet 1**. Due to the sensitive nature of the current data, it is available on request only.

Results

Preliminary Analysis

For the MCAR-test we considered the following variable categories: Sociodemographic variables (e.g., maternal age), birth-related date (e.g., gestation age), questionnaire data (PESI and questionnaires not described in the current study), interaction data (ICEP-R, Reck et al., 2009) and developmental data not described in the current study (Bayles Scales of Infant and Toddler Development – III; Bayley, 2006). The MCAR-test turned out non-significant ($\chi^2 = 1.352$, $df = 1.330$, $p = 0.328$). Thus, we concluded that the list-wise case exclusions were valid for our analyses.

Sample Description

In the clinical sample ($n = 22$), $n = 14$ mothers had multiple anxiety disorders (median = 2). $n = 8$ women were diagnosed with two, $n = 4$ mothers with three and $n = 2$ women with four anxiety disorders. Overall, there were $n = 10$ mothers with a panic disorder or agoraphobia. $n = 6$ women fulfilled the criteria for a social phobia. Obsessive-compulsive disorders were diagnosed in $n = 8$ mothers, while $n = 1$ woman had a posttraumatic stress disorder. There were $n = 12$ mothers with a generalized anxiety disorder and $n = 1$ woman with an anxiety disorder not otherwise specified. $n = 6$ of the mothers were diagnosed with an additional specific phobia as a disorder comorbid to other clinically significant anxiety disorders. $n = 16$ women reported that at least one anxiety disorder had an onset already prior to pregnancy. Another $n = 3$ mothers had an onset during pregnancy and an additional $n = 3$ mothers after birth. As reported above, there were some women with comorbid disorders in our sample: $n = 1$ mother had a comorbid major depressive episode, $n = 1$ woman had a dysthymia, $n = 1$ case had a somatoform disorder and $n = 1$ mother was diagnosed with a comorbid binge eating disorder. The full sample description and tests on comparability between subgroups is reported in **Tables 1A,B**. There were no differences between the two subgroups ($p > 0.14$) on sociodemographic variables except for the number of children ($p = 0.02$): Mothers in the control group had more children (median = 2) than mothers in the clinical group (median = 1). However, as the Spearman-correlations ($\rho < 0.17$) with the study variables were non-significant ($p > 0.21$), we refrained from controlling the number of children in the models.

Descriptive Statistics of Study Variables

In our sample, $n = 37$ infants were classified as securely attached while $n = 13$ infants were insecure-avoidant, $n = 1$ infant insecure-ambivalent and $n = 7$ infants were disorganized. Thus, the insecurely attached group comprised $n = 21$ infants. In mean, it took dyads 8.9 s to achieve a match during the reunion episode ($SD = 20.0$ s) ranging between 0 and 109.2 s. $n = 9$ dyads did not achieve a match at all, thus decreasing the list-wise *n* in models with the raw latency to reparation as a predictor.

Regarding distress during pregnancy, the correlations between the first and second trimester ($r = 0.89$, $p < 0.01$, 95% CI = [0.82; 0.94]), between the second and third trimester ($r = 0.85$, $p < 0.01$, 95% CI = [0.75; 0.91]) and between the first and third trimester ($r = 0.69$, $p < 0.01$, 95% CI = [0.52; 0.81]) revealed a medium-to-high inter-scale consistency, thus supporting the choice to concentrate on only one of these measures. Our sample reached an overall PESI-mean during the third trimester of pregnancy of $M = 30.2\%$ ($SD = 24.3\%$), ranging between 0% and 85.5%. $n = 3$ women did not fill out the questionnaires. However, as the distress during pregnancy was not our primary predictor, we did not generally exclude these dyads. Notably, the list-wise *n* varies depending on the inclusion of the PESI-score in the models.

Main Analysis

The series of hierarchical generalized logistic regressions on secure vs. insecure attachment revealed a final model (AIC = 55.947) consisting only of two predictors, i.e., maternal diagnostic status and latency to interactive reparation. All other predictors (i.e., prepartum distress and all interaction terms) were stepwise eliminated as they did not significantly contribute to the model ($p > 0.025$, for details see **Table 2** comparing the first and the final model of the series as well as the **Supplementary Table 1** demonstrating the excluded models 2–5). Maternal anxiety disorders were revealed as strong predictors of insecure

TABLE 1A | Maternal and infant parametric demographics and tests on comparability of subgroups 3–8 months postpartum (Study 1).

	Overall			Control		Anxiety		Test statistics	
	Range	*M*	*SD*	*M*	*SD*	*M*	*SD*	$\|t\|$	*p*
Maternal age (years)	22.0–42.0	33.1	5.2	33.4	5.4	32.6	4.9	0.57	0.57
Gestation age (weeks)	36.3–41.9	39.4	1.3	39.5	1.3	39.3	1.3	0.52	0.60
APGAR (10 min)	8.0–10.0	9.9	0.5	9.9	0.4	9.8	0.5	0.82	0.41
Infant age at FFSF (months)	2.8–7.2	3.7	1.1	3.6	1.1	3.9	1.1	1.04	0.30
Infant age at SST (months)	13.2–22.7	19.2	1.4	18.9	1.6	19.6	1.0	1.49	0.14

t, t-value; p, empirical α-error; M, mean; SD, standard deviation; FFSF, Face-to-Face-Still-Face paradigm; SST, Strange Situation Test.

TABLE 1B | Maternal and infant non-parametric demographics and tests on comparability of subgroups 3–8 months postpartum (Study 1).

	Overall		Control		Anxiety		Test statistics	
Maternal education	*n*	%	*n*	%	*n*	%	*W*	*p*
High or low secondary qualification	14	24.1	8	22.2	6	27.3	413.0	0.77
University entrance qualification	11	19.0	7	19.4	4	18.2		
University degree	33	56.9	21	58.3	12	54.5		
Number of children	[a]		[b]		[c]			
One infant	33	56.9	16	44.4	17	77.3	529.0	0.02
Two infants	19	32.8	15	41.7	4	18.2		
Three or more infants	6	10.3	5	13.9	1	4.5		
Marital status							*OR* 95% *CI*	*p*
Married	40	72.7	26	76.5	14	66.7	0.62 [0.16;2.47]	0.54
Not married	15	27.3	8	23.5	7	33.3		
Infant sex								
Female infants	34	58.6	19	52.8	15	68.2	0.53 [0.14;1.79]	0.28
Male infants	24	41.4	17	47.2	7	31.8		

[a] *Median = 1.*
[b] *Median = 2.*
[c] *Median = 1.*
Valid %, percentage of valid values; W, statistical value of Wilcoxon test for independent samples (U test); p, empirical α-error; OR, odds ratio; 95% CI, 95% confidence interval of test statistic.

attachment: With an odds ratio of OR = 5.446 ($p = 0.010$), they increased the risk for insecure attachment by more than fivefold. However, latency to reparation seems to add to the effect of diagnostic category: With an OR = 1.042, this predictor increases the risk for insecure attachment by 4.2% for each passing second ($p = 0.022$).

For the series of descriptive hierarchical Cox regressions on the time-dependent event "match," we created a dummy-coded variable "match" whereas "1" was coded for "match achieved during FFSF-interaction" and "0" was coded for "no match achieved during FFSF-interaction". Moreover, we recoded the raw values of latency to interactive reparation in two ways: (1) We coded the measure to 1 s, if dyads already started with a match in the interaction, not to lose these specific dyads in the analyses. (2) We coded the measure to 120 s (the maximum observation period) for all dyads not achieving any match during the early interaction to integrate them as censored data in the analysis. The final model ($LR = 4.9$, $df = 1$, $p = 0.03$) only consisted of one factor: i.e., infant attachment quality (see **Figure 1**). The other two factors, i.e., maternal diagnostic status and prepartum distress were stepwise eliminated as they did not significantly contribute to the model ($p > 0.22$, for details see the **Supplementary Table 2**). With a hazard ratio of $HR = 0.52$ (95% CI = [0.28; 0.94]; $p = 0.03$), attachment quality was revealed as a strong factor, meaning that at 12–24 months insecurely attached infants were 48% less likely to having achieved a match in the interaction 3–8 months postpartum.

STUDY 2

Materials and Methods

Procedures

The data for the second part of the study 5–6 years postpartum was collected from 2010 to 2014. During a lab visit, child

TABLE 2 | First and final generalized binomial regression models on infant attachment out of hierarchical backward procedure.

Predictors	Model 1				Final model			
	OR	95% *CI OR* lower bound	95% *CI OR* upper bound	*p*	*OR*	95% *CI OR* lower bound	95% *CI OR* upper bound	*p*
Intercept	0.075	0.003	1.050	/	0.161	0.050	0.411	/
Anxiety disorder	0.378	0.000	65.418	0.021	5.446	1.437	23.166	0.010
Interactive reparation	0.817	0.425	1.150	0.029	1.042	1.005	1.110	0.022
Prepartum distress	1.034	0.888	1.186	0.039	/	/	/	/
Anxiety disorder * interactive reparation	1.637	0.895	5.031	0.204	/	/	/	/
Anxiety disorder * prepartum distress	1.019	0.873	1.216	0.442	/	/	/	/
Interactive reparation * prepartum distress	1.015	0.993	1.056	0.853	/	/	/	/
Anxiety disorder * interactive reparation * prepartum distress	0.982	0.943	1.007	0.164	/	/	/	/

Coding of attachment outcome: 0 = secure, 1 = insecure.
OR, odds ratio; CI, confidence interval; p, empirical α-error.
Model 1: AIC = 53.962, fitted probabilities numerically 0 or 1 occurred.
Final model: AIC = 55.947.

cortisol-reactivity was assessed via salivary samples taken immediately before, 20 and 40 min after a socioemotional stressor: engagement with unfamiliar peers and a clown. Two caregiver–child pairs from the same study, who did not know each other, were asked to enter an empty room with a carpet and two chairs located in each corner opposite the other. Pairs were chosen to have children of the same gender. The caregivers were asked to sit on the chairs and fill in questionnaires while the children were invited to sit in the middle of the room and play on a carpet with some gender appropriate toys located there. After a few minutes an attractive toy was placed in the middle of the carpet, and it was coded who grabbed it first. Then, a clown entered the room, told a story, and invited the children to play with him. The whole procedure lasted 20 min. The cortisol baseline was assessed on two consecutive days at home.

Measures

Salivary Cortisol

For the assessment of salivary cortisol, children sucked on a cotton ball until it was saturated. The saliva was then expressed and stored at −20°C until analysis. To account for possible effects of circadian rhythm on cortisol reactivity, we attempted to have the visits to the laboratory, as well as the baseline assessments at home always at around the same time of the day. Moreover, since cortisol reactivity is strongly associated with daytime napping or feeding, the caregivers were instructed to keep their children well rested and well fed on their usual routine in order not to confound the cortisol assessment. The baseline measures were averaged over both assessments. Sampling, storage, transport and analysis of cortisol samples took place according to standard protocols (Schwartz et al., 1998). The limit of detection of the used assay was 0.15 ng/ml. Intra-assay variances were 5.95%

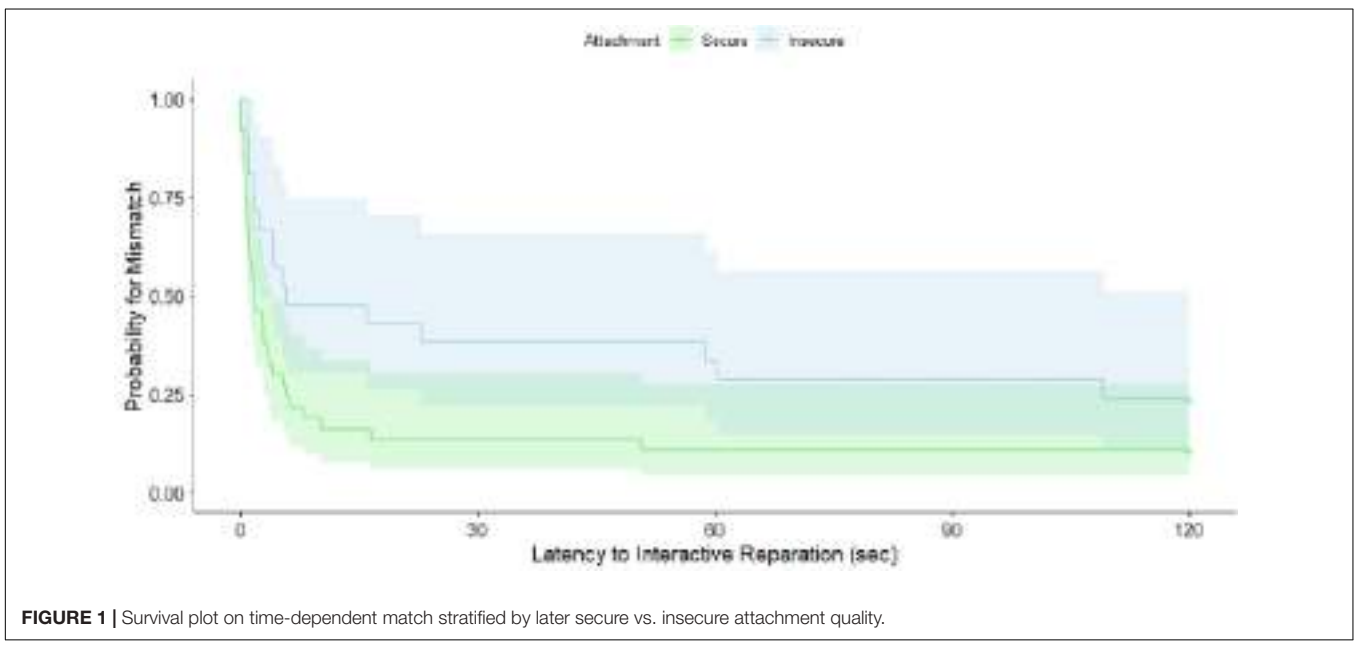

FIGURE 1 | Survival plot on time-dependent match stratified by later secure vs. insecure attachment quality.

volume for 2.6 μg/100 ml, 1.59% for 17 μg/100 ml and 4.62% for 26.6 μg/100 ml.

Sample

Besides the dyads excluded due to diagnostic criteria or missing attachment measures (n = 51), in the second subsample, we lost further n = 23 dyads missing the follow-up at 5–6 years postpartum. Additionally, n = 9 children had missing cortisol values during the stress paradigm (n = 7) or at baseline (n = 9). Thus, for the second subsample, n = 26 mothers were included in the control group, while the clinical group comprised n = 13 mothers.

Data Analysis

We used the following packages: "ggplot2" (Wickham, 2016), "survminer" (Kassambara et al., 2021, v. 0.4.9), "lme4" (Bates et al., 2015), "lmerTest" (Kuznetsova et al., 2017) and "writexl (Ooms, 2021, v. 1.4.0)."

The analyses regarding the second part of the study refer to the predictive quality of the dummy-coded attachment quality and the maternal diagnostic status during the postpartum period on child cortisol-reactivity by controlling for cortisol baseline. Thus, we used a series of hierarchical mixed models on the three nested cortisol measures during the socioemotional stressor. The main effects were tested via F-statistic. The hierarchical model tests started with full-factorial models including all two-way and three-way interaction terms. Terms were excluded from the models if they failed to significantly contribute to explaining the dependent variables. The procedures ended with the model that only contained significant predictors.

Regarding the mixed models effect sizes are reported as partial ω^2, which is a population-based estimator of explained variance. Empirical p-values are reported two-tailed. The critical α-errors of the two confirmative analyses sets (i.e., Study 1: binomial regressions; Study 2: mixed models) were Holm Bonferroni adjusted (Holm, 1979). This sequential procedure controls the family-wise error-rate by adjusting the critical α-level for each of the individual hypotheses. Thus, the critical α is set to 0.025 for the first and 0.05 for the second model series.

Results

Preliminary Analysis

For the MCAR-test, we considered the following variable categories: sociodemographic variables (e.g., maternal age), birth-related date (e.g., gestation age), questionnaire data (PESI and questionnaires not described in the current study (e.g., the Child Behavior Checklist, Arbeitsgruppe-Deutsche-Child-Behavior-Checklist, 2002), interaction data (Coding Interactive behavior, Feldman, 1998), cortisol data and developmental data not described in the current study (Kaufman Assessment Battery for Children; Melchers and Preuß, 2009). The MCAR-test turned out non-significant (χ^2 = 1.188, df = 1.132, p = 0.119). Thus, we concluded that the list-wise case exclusions were valid for our analyses.

Sample Description

In our clinical sample (n = 13), n = 8 mothers had multiple anxiety disorders (median = 2) during the postpartum period. n = 4 women were diagnosed with two, n = 3 mothers with three and n = 1 woman with four anxiety disorders. Overall, there were n = 6 mothers with a panic disorder or agoraphobia. n = 4 women fulfilled the criteria for a social phobia. Obsessive-compulsive disorders were diagnosed in n = 6 mothers, while n = 1 woman had a posttraumatic stress disorder. There were n = 6 mothers with a generalized anxiety disorder and n = 1 woman with an anxiety disorder not otherwise specified. n = 2 of the mothers were diagnosed with an additional specific phobia. n = 10 women reported that at least one anxiety disorder had an onset already prior to pregnancy. Another n = 1 mother had an onset during pregnancy and an additional n = 2 mothers after birth. As reported above, there were some women with comorbid disorders in our sample: n = 1 mother had a comorbid major depressive episode, n = 1 woman had a dysthymia and n = 1 mother was diagnosed with a comorbid binge eating disorder. For the follow-up sample, the mother with the somatoform disorder was lost. n = 7 mothers still suffered from an anxiety disorder 5–6 years postpartum. The full sample description and tests on comparability between subgroups is reported in **Tables 3A,B**. There were no differences between the two subgroups ($p > 0.09$) except for marital status ($p < 0.01$): Mothers in the control group were more frequently married than mothers in the clinical group. However, as the Spearman correlations ($r < 0.16$) with the study variables were non-significant ($p > 0.36$), we refrained from controlling marital status.

Descriptive Statistics of Study Variables

In our sample, n = 28 infants were classified as securely attached, while n = 8 infants were insecure-avoidant and n = 3 infants were disorganized. Thus, the insecurely attached group comprised n = 11 infants. The descriptive statistics for cortisol measures are demonstrated in **Table 4**. In mean, the samples were taken around 2 pm (M = 13.9) with a standard deviation of SD = 1.8 h

TABLE 3A | Maternal and infant parametric demographics and tests on comparability of subgroups 5–6 years postpartum (Study 2).

	Overall			Control		Anxiety		Test statistics	
	Range	*M*	*SD*	*M*	*SD*	*M*	*SD*	|*t*|	*p*
Maternal age (years)	27.0–48.0	39.8	5.3	40.0	5.0	39.2	5.9	0.45	0.66
Infant age at SST (months)	13.2–22.5	19.2	1.6	18.9	1.9	19.6	1.0	1.18	0.25
Child age at follow-up (years)	5.1–6.5	5.7	0.4	5.7	0.4	5.8	0.3	0.89	0.38

t, t-value; p, empirical α-error; M, mean; SD, standard deviation; SST, Strange Situation Test.

TABLE 3B | Maternal and infant non-parametric demographics and tests on comparability of subgroups 5–6 years postpartum (Study 2).

	Overall		Control		Anxiety		Test statistics	
Maternal education	***n***	**%**	***n***	**%**	***n***	**%**	***W***	***p***
High or low secondary qualification	9	23.1	6	23.1	3	23.1	187.5	0.55
University entrance qualification	8	20.5	4	15.4	4	30.8		
University degree	22	56.4	16	61.5	6	46.2		
Number of children	[a]		[b]		[c]			
One child	7	20.0	4	16.0	3	30.0	221.5	0.09
Two children	16	45.7	11	44.0	5	50.0		
Three or more children	12	34.3	10	40.0	2	20.0		
Marital status							***OR* 95% *CI***	***p***
Married	31	88.6	25	100.0	6	60.0	0.00 [0.00; 0.49]	<0.01
Not married	4	11.4	0	0.0	4	40.0		
Infant sex								
Female infants	26	66.7	15	57.7	11	84.6	0.26 [0.02;1.55]	0.15
Male infants	13	33.3	11	42.3	2	15.4		

[a] *Median = 2.*
[b] *Median = 2.*
[c] *Median = 2.*
W, statistical value of Wilcoxon test for independent samples (U test); p, empirical α-error; OR, odds ratio; 95% CI, 95% confidence interval of test statistic.

and ranging from 9 am to around 4 pm. Moreover, the baseline was taken in mean at 7:30 pm (M = 19.5) with a standard deviation of SD = 0.9 h and ranging from 5 pm to 8:45 pm. Due to the high range of sample times, we checked associations to the cortisol measures. However, all correlations ($r < 0.17$) were non-significant ($p > 0.30$). Thus, we refrained from controlling for time of day.

Main Analysis

The series of hierarchical mixed models on cortisol measures revealed a final model ($REML$ = 233.1) with three predictors: time, cortisol baseline and attachment quality. All other predictors, maternal diagnostic status during the postpartum period and all interaction terms were stepwise eliminated as they did not significantly contribute to the model ($p > 0.24$, for details see the **Supplementary Table 3**). The inferential statistics are demonstrated in **Table 5**. The descriptive statistics of the main effects of attachment quality and time are depicted in **Figures 2**, **3** as well as in **Table 6**. The cortisol levels of children with an insecure attachment quality at 12–24 months were higher during the stress paradigm at the age of 5 to 6 years compared to the ones of securely attached children. This effect explains around 4% of variance in cortisol measures ($\omega^2 = 0.04$), while time explained about 8% of variance ($\omega^2 = 0.08$). Still, most of the variance is explained by cortisol baseline with about 9% ($\omega^2 = 0.09$).

TABLE 4 | Descriptive statistics of cortisol measures in ng/ml.

	M	*SD*	*SE*	*Min*	*Max*
Measure immediately before stressor	1.45	0.91	0.15	0.47	5.40
Measure + 20 min after stressor	1.28	0.80	0.13	0.44	4.25
Measure + 40 min after stressor	1.03	0.47	0.07	0.26	2.45
Baseline 1	0.80	1.13	0.18	0.12	5.72
Baseline 2	0.58	0.40	0.06	0.17	2.16
Mean baseline	0.69	0.69	0.11	0.18	3.63

M, mean; SD, standard deviation; SE, standard error; Min, minimal value; Max, maximum value.

DISCUSSION

The present study aimed at testing the hypotheses that prepartum distress, maternal anxiety disorders in the postpartum period as well as latency to reparation predict infant secure vs. insecure attachment and possibly moderate each other's effect. To the best of the authors' knowledge, there is only one other study to date that has demonstrated associations between maternal anxiety, interactional behavior and insecure attachment in a sample of 4.5 year-olds and their mothers (N = 98, Stevenson-Hinde et al., 2013). These results showed that maternal anxiety was a significant predictor of maternal sensitivity measures which in turn predicted attachment security. Compared to these macro-temporal analyses of interaction behaviors, our perspective is that while maternal sensitivity may be an important predictor of attachment, in particular micro-temporal processes such as latency to reparation may represent critical key mechanisms in this context (compare Mesman, 2010). Maternal sensitivity is a macro-temporal measure in which the entire interaction is judged to be sensitive or insensitive on a rank ordered scale. Thus, it is likely that one misses to register the actual details of mother–infant engagement just in time which could lead to secure or insecure attachment quality. So far, there are only a few studies that have focused on micro-temporal processes (e.g., Beebe et al., 2010); the vast majority of studies use global rating systems to analyze interactive paradigms in this context (e.g., Stevenson-Hinde et al., 2013). Of course, micro- and macro-temporal parameters may be interrelated – thus,

TABLE 5 | Mixed model on cortisol measures.

	Sum of squares	Mean squares	Numerator *df*	Denominator *df*	*F*	*p*
Attachment quality	1.685	1.685	1	36	5.916	0.020
Time	3.349	1.674	2	76	5.878	0.004
Cortisol baseline	3.432	3.432	1	36	12.047	0.001

Df, degrees of freedom; F, F-statistic; p, empirical α-error.

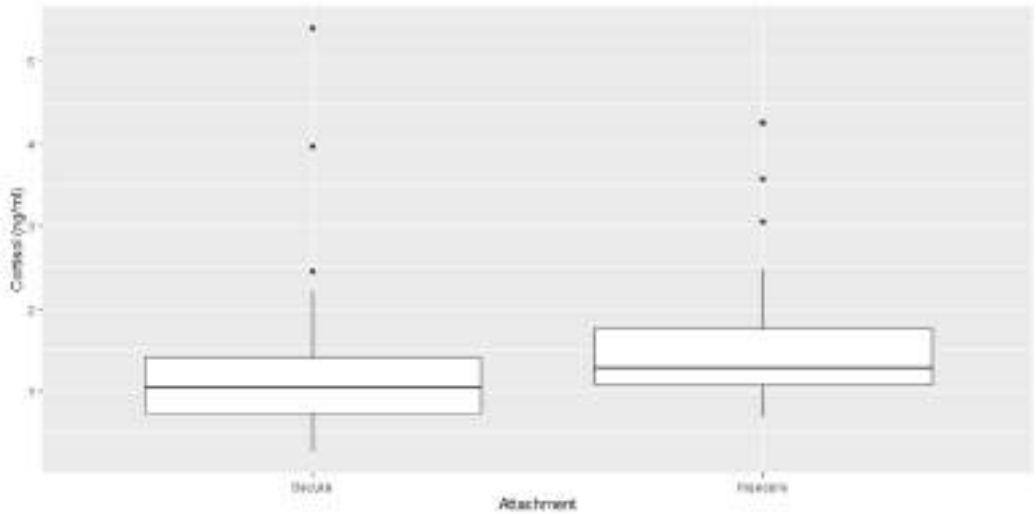

FIGURE 2 | Box-plots regarding the main effect of attachment quality on cortisol measures.

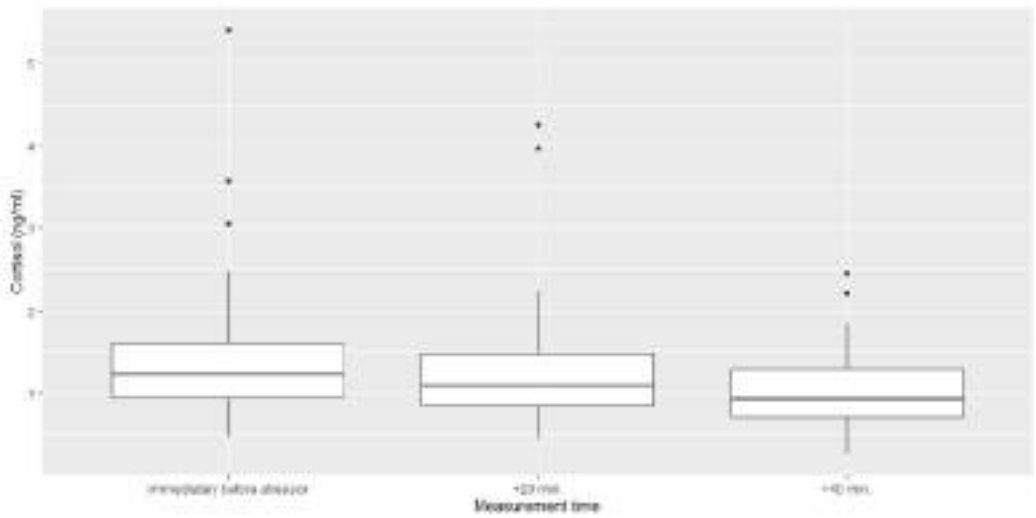

FIGURE 3 | Box-plots regarding the main effect of time on cortisol measures.

we assume that in dyads with sensitively interacting mothers, interactive reparation also succeeds more often (Noe, 2008). However, it is our perspective, that especially the micro-temporal mechanisms may hold the key to understanding the dynamic nature of these multifaceted processes (compare Provenzi et al., 2018). In our study, we examine the micro-temporal process of interactive reparation as a possible interactive mechanism underlying security of attachment. Using regression analysis on a set of possible predictors, as expected we found that apart from maternal diagnostic status, latency to reparation was the only other significant predictor for attachment insecurity.

To predict infant attachment security, not only maternal sensitivity but also infant affect regulation plays an important role. Braungart-Rieker et al. (2001), for example, were able

TABLE 6 | Descriptive statistics on main effects of attachment and time on cortisol measures in ng/ml.

Attachment	*M*	*SD*	*SE*	*Min*	*Max*
Secure	1.15	0.72	0.08	0.26	5.40
Insecure	1.52	0.81	0.14	0.68	4.25
Time					
Measure 1	1.45	0.91	0.15	0.47	5.40
Measure 2	1.28	0.80	0.13	0.44	4.25
Measure 3	1.03	0.47	0.07	0.26	2.45

M, mean; SD, standard deviation; SE, standard error; Min, minimal value; Max, maximum value.

to show that both aspects discriminate between secure and insecure infants. As proposed by DiCorcia and Tronick (2011), interactive reparation – the mutual adaptive process of the dyad oscillating between coordinated and uncoordinated states – seems to shape not only infant attachment security but also – more fundamentally – infant regulatory strategies. Also other studies show that for dyadic co-regulation, sensitive reactions of the caregivers are crucial not only for healthy development (e.g., Malmberg et al., 2016) but likewise for behavioral and physiological reactions (e.g., Haley and Stansbury, 2003; Conradt and Ablow, 2010). As maternal sensitivity is of great importance for infant attachment security, infants of insensitive mothers might frequently lack sufficient regulatory scaffolding with possible long-term consequences for child development (Leclère et al., 2014). And it is our understanding that this regulatory scaffolding is essential in the development of emotion regulation, and thus a secure attachment quality (Kerns and Brumariu, 2014). This is also in line with results of Beebe et al. (2010) showing that very high or very low interactive contingency was linked to insecure attachment in infancy in a sample of anxious mothers. Contingency can be interpreted as a measure of matched states and points toward the same direction as our results. Thus, our findings highlight the importance of specific micro-interactional patterns of mother–child interaction for infants' regulation (Müller et al., 2015) and the development of a secure attachment quality. Consequently, the interactive dysregulation could be partly responsible for the increased risk of developing mental disorders later in life (compare Verhees et al., 2021). Nevertheless, child emotion regulation and their later psychopathological development was not assessed in the current study. Future projects should focus these factors when investigating developmental dependencies between early interactive patterns and child attachment.

Furthermore, our results also showed that infants of mothers with postpartum anxiety disorders have a more than fivefold increased risk of developing an insecure attachment than the infants of the control group. This is in line with previous studies indicating higher attachment insecurity in children of anxious mothers (Stevenson-Hinde et al., 2011). Concerning the mechanism of transmission, e.g., for social anxiety it was demonstrated that particular this disorder goes along with insecure attachment patterns. Consequently, attachment patterns are often transmitted from mother to offspring (for review, see Martins and Gaffan, 2000) by verbal and non-verbal interactions (Ward and Carlson, 1995; Meins et al., 2001). However, in this study we did not assess maternal attachment patterns. Future studies should consider this mediating factor when investigating the development of infant attachment quality. Notably, the effect of anxiety disorder was independent of prepartum distress which turned out not to predict infant attachment quality in our data. This was somewhat surprising given the established effects of fetal programming (van den Bergh et al., 2017), however, this may be due to the fact that in our study prepartum distress was assessed retrospectively and via self-report and not via biological measures such as salivary cortisol. Future studies should consider controlling for prepartum distress via more reliable and objective measures. Moreover, the effect of maternal disorder was not moderated by our dyadic interaction measure as observed in other studies (e.g., Grant et al., 2010a,b). However, it is possible that this is due to the micro-temporal nature of our measurement: This measure may be more sensitive to influences that escape the detection threshold of macro-temporal scales. Thus, it may represent a more direct measure of spontaneous behavior as compared to parental sensitivity measures. Possibly, the behavioral quality we observe here fits better as mediating variable in the association between maternal disorder and infant attachment. Additionally, the power to detect moderation effects may have run too low in our models. Besides increased sample sizes, future studies should investigate the idea of mediation pathways in this context as the work of Stevenson-Hinde et al. (2013) suggests for macro-temporal measures.

In a second part, this study aimed at evaluating possible links between infant attachment quality as well as maternal anxiety disorders in the postpartum period and stress reactivity at preschool age. The results showed increased cortisol levels in insecurely attached children during a stress paradigm compared to securely attached children. This finding is consistent with other studies that have shown associations between attachment security and cortisol reactivity throughout life (Bernard and Dozier, 2010; Oskis et al., 2011; Pierrehumbert et al., 2012; Kidd et al., 2013). However, it is important to emphasize here that the relationship between attachment security and cortisol reactivity in preschool age is moderated by a wide variety of factors, e.g., maternal psychopathology. The study by Luijk et al. (2010), for instance, showed that the association between insecure attachment and cortisol reactivity is stronger in children of depressed mothers. In our study we did not find a significant interaction effect between maternal diagnostic status and attachment on cortisol reactivity in preschool aged children. One reason could be, that our clinical sample consisted of women with various and different anxiety disorders. Hence, it remains unclear whether disorder-specific effects accounted for this null finding. Future studies should consider focusing on more homogenous clinical samples. Another reason could be that we missed to observe a cortisol peak due to too short observational intervals or an ineffective stress paradigm. However, as Gunnar et al. (2009) point out, on average, psychological stress paradigms do not generally induce a cortisol reactivity in developmental studies. Thus, a decrease in cortisol means is a frequent result in infant and child studies (Gunnar et al., 2009; Jansen et al., 2010a). It must be noted that the lack of observable mean cortisol peaks does not imply that the analysis of respective cortisol values is useless. Rather, it has been argued

that their analysis may uncover potential risk factors that account for individual differences and may adversely affect developmental trajectories. Our study suggests that one of these risk factors is represented by infant insecure attachment.

Limitations

First, besides a rather small sample size, and thus low statistical power especially at the 5-6-year follow-up, mothers with different and multiple anxiety disorders were included in our clinical sample. However, the sample size did not allow subgroup analyses on disorder-specific effects. Moreover, according to the DSM-5 (Falkei and Wittchen, 2015), obsessive compulsive disorders are no longer classified as anxiety disorders. Therefore, special attention needs to be paid to these disorders with regard to the outcome variables in future research. Moreover, in respect to the small sample size, the analyses are rather complex. Thus, results should be regarded with cation and focused for replication attempts in future studies. Second, our sample is characterized by an overproportion of academic degrees, whereby our data is not representative for the overall population. Consequently, besides the occurrence of anxiety disorders or not, the sample comprises families with rather low risk-constellations. Third, infant salivary cortisol was assessed prior to, immediately after and 20 min after the stress paradigm. Due to few samples or the limited time frame, it is possible that we missed the cortisol peak. Fourth, it is important to mention the limited control of effects by meantime events between the measurements as well as by the wide age ranges of the infants in both the interaction and attachment assessments. Last, as the study design was observational, causality assumptions are not appropriate.

CONCLUSION

Taken together, our empirical results emphasize the importance to further investigate early interactional micro-temporal markers for infant and child development. Our results underline that latency to reparation is linked to infant attachment security and this in turn influences the child's stress reactivity up to preschool age. During interactions, infants experience that their success or failure in repairing mismatches affects the meanings they make about themselves in the world in relation to others and to themselves (Beeghly et al., 2011): Successful reparation leads to a sense of self as effective and a sense that we – my interactional partner and me – can overcome mismatches or failures and the certainty of being able to trust the other person. Unsuccessful reparation leads to a sense of failure and a distrust of the partner. And it is this sense of trust or distrust that leads to secure or insecure attachment. Therefore, early intervention and prevention programs may be of vital importance. Our results point toward the direction that, in addition to the treatment of clinical symptoms in parents, a promising approach might be to focus on the flexibility of interactional patterns, which is represented by latency to reparation, instead of just positive interaction patterns. As the process of interactive reparation occurs in a clearly detectable time range (seconds; see also Weinberg et al., 2006; Weinberg et al., 2008) video interventions (Reck et al., 2004; Downing et al., 2014) may turn out as useful tools for increasing the flexibility in the flow of dyadic interplay between mismatching and positive matching states. The results suggest, this might improve attachment security in infancy and children's regulatory capacities and mental health in the longer-term (Beatson and Taryan, 2003).

DATA AVAILABILITY STATEMENT

The anonymized raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Faculty of the Ruprecht-Karls-University, Heidelberg, Germany. Written informed consent to participate in this study was provided by the participants or the participants' legal guardian/next of kin respectively.

AUTHOR CONTRIBUTIONS

MM contributed to the conceptualization, methodology, formal analysis, writing – original draft, review – editing, and visualization. A-LZ contributed to the writing – original draft and review – editing. NK contributed to the attachment coding and writing – review and editing. CW and NN contributed to the writing – review and editing. ET contributed to the supervision and writing – review and editing. CR contributed to the investigation, project administration, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.807157/full#supplementary-material

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Birth Experience Mediates the Association Between Fear of Childbirth and Mother-Child-Bonding Up to 14 Months Postpartum: Findings From the Prospective Cohort Study DREAM

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Objective: To explore the longitudinal associations between prepartum fear of childbirth (FOC), birth experience, and postpartum mother-child-bonding, and the potential mediator role of the birth experience.

Design: Women from the prospective cohort study DREAM completed questionnaires during pregnancy, 8 weeks, and 14 months after the birth.

Participants: A community sample of $n = 645$ pregnant women from a large city in Eastern Germany participated in the study.

Results: In a regression analysis, FOC predicted negative birth experience ($\beta = 0.208$, $p < 0.001$) which in turn predicted poorer mother-child-bonding both at 8 weeks ($\beta = 0.312$, $p < 0.001$) and 14 months postpartum ($\beta = 0.200$, $p < 0.001$). FOC also predicted mother-child-bonding at 14 months postpartum ($\beta = 0.098$, $p < 0.05$). Of note, this association was mediated by birth experience both at 8 weeks, indirect effect ab = 0.065, 95% CI [0.036, 0.098], and 14 months postpartum, indirect effect ab = 0.043, 95% CI [0.023, 0.067]. These effects remained stable even when adjusting for potential confounders.

Key Conclusions: This study suggests that the association between FOC and mother-child-bonding is mediated by birth experience, pointing to the importance of a woman's positive subjective experience.

Implications for Practice: Findings reveal two targets for peripartum interventions for women at risk for poor mother-child-bonding, namely the implementation of FOC screenings during pregnancy, and birth experience as mediating factor between FOC

and mother-child-bonding. Focusing on the mother's subjective birth experience could aid to identify women at risk for impaired bonding who might need additional support.

Keywords: fear of childbirth, pregnancy, childbirth experience, mother-child-bonding, mediation analysis, DREAM study

INTRODUCTION

With an estimated pooled prevalence rate of 14% (1), severe fear of childbirth (FOC), also referred to as tokophobia, is a common phenomenon among pregnant women, with most of the research focusing on populations from Scandinavia, Australia, and the UK (2–5). Prevalence rates for FOC vary significantly between countries and seem to have increased during the last years (1, 6). This development is especially problematic as prepartum FOC is associated with various negative outcomes for mother and child, one of them being a mother's negative postpartum rating of the birth experience (3, 7–11). Negative birth experiences have an estimated prevalence rate of 7–34% (12) and may lead to a decrease in women's self-esteem and self-efficacy, a feeling of disempowerment, and mental health problems (13). Hodnett (14) concluded in her systematic review that positive expectations seem to lead to a more positive evaluation of the birth (15), whereas negative expectations may lead to a negative evaluation (16, 17). A possible explanation for FOC predicting a more negative birth experience points to the role of endocrine stress parameters during pregnancy for the course of labor. Findings suggest that cortisol awakening response and higher plasma levels of adrenalin (which could both be influenced by FOC) interfere with uterine contractions during labor (18) and thus in turn predict a more negative birth experience (19). This explanation could be applying especially to primary FOC which describes a woman's fear before her first childbirth (20). However, endocrine stress parameters can also be influenced by the birth environment: less optimal, but modifiable circumstances (e.g., the sterile surroundings of a hospital, the perceived stress of overworked staff, and the consequences on the communication with them) may increase women's biological stress response even if they are not affected by FOC (21, 22). By slowing down labor and increasing fetal distress, this biological stress response can further increase the possibility of medical interventions (23), such as instrumental vaginal birth or emergency cesarean section, which are also a risk factor for a negative birth experience (24, 25). Multiparous women who experienced one of those procedures as traumatic at their last birth may therefore fear the recurrence of these events during their next birth, which is referred to as secondary FOC (26–29).

Prepartum FOC seems to not only predict the level of fear during birth, but is also associated with higher levels of postpartum FOC (30–32). Accordingly, several studies have proposed the idea of a vicious cycle (33): during birth, women experience what they were already afraid of, which in turn predicts their postpartum fear and first interaction with their new-born. In support of this, Pazzagli et al. (34) found a moderate linear association between FOC and postpartum parenting stress. Further, the results of a qualitative study interviewing Swedish midwives suggest that FOC predicts both difficulties with breastfeeding and poorer mother-child-bonding (35). Although mother-child-bonding disorders have been identified as a risk factor for impaired emotional, behavioral, and cognitive development of the child (36, 37), to the best of our knowledge, there is only one quantitative study examining the association between prepartum FOC and postpartum bonding. The findings suggest a negative association between FOC and mother-child-bonding 6 weeks, but not 6 months postpartum (38) which prompts the additional question of the longitudinal development of this association.

Another factor influencing maternal bonding may be birth experience as it can have short- and long-term effects on the mother's postpartum well-being (39, 40) which in turn plays a crucial role for early bonding experiences (41). A systematic review by Bell et al. (42) also shows an association between a negative birth experience and poorer maternal postpartum caregiving. So far, the number of studies on the implications of birth experience for mother-child-bonding is small, and studies are limited to the link between symptoms of birth-related posttraumatic stress disorder (PTSD) and mostly poorer mother-child-bonding (43–47). Due to the high correlation between a subjective negative birth experience and birth-related PTSD (43), it seems likely that a negative birth experience could also predict poorer mother-child-bonding.

Other studies have focused on the mother's recalled labor pain (48) or distress during birth (45) and found significant associations with maternal bonding. As an explanation Kennell and Klaus (49) hypothesized that after a negative birth experience, mothers may be preoccupied with their own physical and emotional needs and engage less with their babies, thereby weakening mother-child-bonding.

However, the association between a women's subjective rating of her birth experience and postpartum mother-child-bonding remains understudied. If these two are indeed inter-related, enabling a positive birth experience could be a successful way to ensure a stronger bond between mother and child, thereby increasing the chance of positive child outcomes (50, 51).

At this point, a potential link between prepartum FOC, birth experience, and postpartum mother-child-bonding needs further clarification. Especially the role of a negative birth experience could be of major importance as it might emphasize prior vulnerabilities of the mother, like FOC, and increase the risk of impaired mother-child-relationships (52), therefore acting as a possible mediator between the two variables.

This study aims to explore the longitudinal associations between prepartum FOC, birth experience, and mother-child-bonding 8 weeks and 14 months postpartum. Furthermore, it

will be analyzed whether the association between prepartum FOC and postpartum mother-child-bonding is mediated by birth experience.

MATERIALS AND METHODS

Design

This study is based on data from the prospective cohort study Dresden Study on Parenting, Work, and Mental Health ("**DR**esdner Studie zu **E**lternschaft, **A**rbeit und **M**entaler Gesundheit"; **DREAM**). The DREAM study examines parental work participation, role distribution, stress factors, and how these affect peripartum outcomes and the long-term mental and somatic health of the family. Recruitment started in 2017 and finished at the end of 2020. Currently the study consists of six measurement points: T1 during pregnancy, T2 8 weeks after the anticipated birth date, T3 14 months, T4 2 years, T5 3 years, and T6 4.5 years after birth. Participants comprise a community sample of $N = 3{,}865$ parents from Dresden, Germany and surroundings who are expecting a child and are mainly recruited at information events of obstetrical clinics. Detailed information on the design of the study can be found in the study protocol (53).

Sample

The present study is based on version 5 of the quality-assured data files and included data of women who gave birth to one child and completed T1, T2, and T3. At time of data extraction (17th March 2020), $n = 2{,}027$ women were included in the cohort. The study's retention is presented in a flow chart in **Figure 1**. Data from T1 were excluded when the questionnaire was completed after childbirth to ensure that prepartum FOC was measured. Additionally, data of participants who did not complete T2 or T3 within a given timeframe were excluded, because previous research has shown that the rating of the birth experience and mother-child-bonding may also depend on the time point of the questionnaire (54, 55). Therefore, data from T2 were excluded if completed earlier than 6 weeks or later than 16 weeks postpartum, and data from T3 were excluded if completed earlier than 12 months or later than 16 months after childbirth. The final sample consisted of $n = 645$ women.

Measures

FOC was assessed using the German version of the Fear of Birth Scale [FOBS; (56)] during pregnancy (T1). The FOBS is a validated, shorter alternative (57, 58) to the widely used Wijma Delivery Expectancy Questionnaire [WDEQ-A; (59)]. The original version consists of a two-item visual analog scale in which expectant mothers are asked about their feelings concerning the approaching birth. The two items are anchored by the terms *calm/worried* and *no fear/strong fear*. In the DREAM study, each item generates scores of 0–100 with possible values being increments of 10. The two scores are then averaged to form a total score, where higher values indicate more fear. The reliability of the FOBS in the current study was excellent (Cronbach's $\alpha = 0.90$).

Birth experience was assessed at T2 (8 weeks after the expected birth date) using the German version of the Salmon's Item List [SIL; (60)], a validated 20-item questionnaire that encompasses the four dimensions fulfillment, physical discomfort, emotional distress, and negative emotional experience. The items of the SIL are presented as positive and negative anchors and women are asked to rate each item on a scale from 0 to 6 depending on their feelings during the birth. The sum of all items generates the total score ranging between 0 and 120. In the original version of the SIL, higher scores indicate a more positive birth experience, but in the current analyses the items were reversed in terms of a better understanding so that higher scores indicate a more negative birth experience. The reliability of the SIL was excellent (Cronbach's $\alpha = 0.92$).

Mother-child-bonding was assessed using the German version of the frequently used Postpartum Bonding Questionnaire [PBQ; (61, 62)] which screens for bonding disorders and contains 25 items on the four subscales "impaired bonding," "rejection and anger," "anxiety about care," and "risk of abuse." The PBQ asks parents (here: mothers) to think of the most difficult time with their child and to state how often they experienced each situation, with six possible answers ranging from *never* (0) to *always* (5). Item scores are added to form the scores for each subscale and a total score ranging from 0 to 125. Higher values indicate more bonding difficulties. For this study, we used data from T2 and T3. The reliability of the PBQ was excellent for both T2 and T3 (Cronbach's $\alpha = 0.90$).

The following eight variables were selected as potential confounders, because they have been associated with FOC, birth experience, and mother-child-bonding in previous research: maternal age, parity, education, financial hardship, partnership satisfaction during pregnancy, maternal depressive symptoms during pregnancy, birth complications, and infant health status after birth. Except for financial hardship, birth complications, and infant health status after birth, which were measured at T2, all potential confounders were measured at T1 during pregnancy.

Education was measured by an item, which asks about the professional qualification. Participants were then divided into one group without a university degree and one group with a university degree (bachelor's degree or higher).

Financial hardship was measured by an item, which asks about financial problems during pregnancy or after the birth. It is part of a questionnaire asking about former and current critical life events and their burden based on the Life Event Questionnaire from the Avon Longitudinal Study of Parents and Children (63).

Partnership satisfaction was measured by the validated German short version of the Partnership Questionnaire (64) which comprises three subscales with three items each and an additional item assessing the general happiness of the partnership. The four possible responses range from *never/very rare* (0) to *very often* (3). The total score is generated by summation of all items and ranges from 0 to 27. The reliability of the PFB-K in the current sample was good (Cronbach's $\alpha = 0.80$).

Maternal depressive symptoms were measured by the German version of the Edinburgh Postnatal Depression Scale [EPDS; (65, 66)] which assesses symptoms of depression during the past week. It consists of ten items with four possible responses respectively that are scored on a scale from 0 to 3. The total score is generated by summation of all items and ranges from 0 to

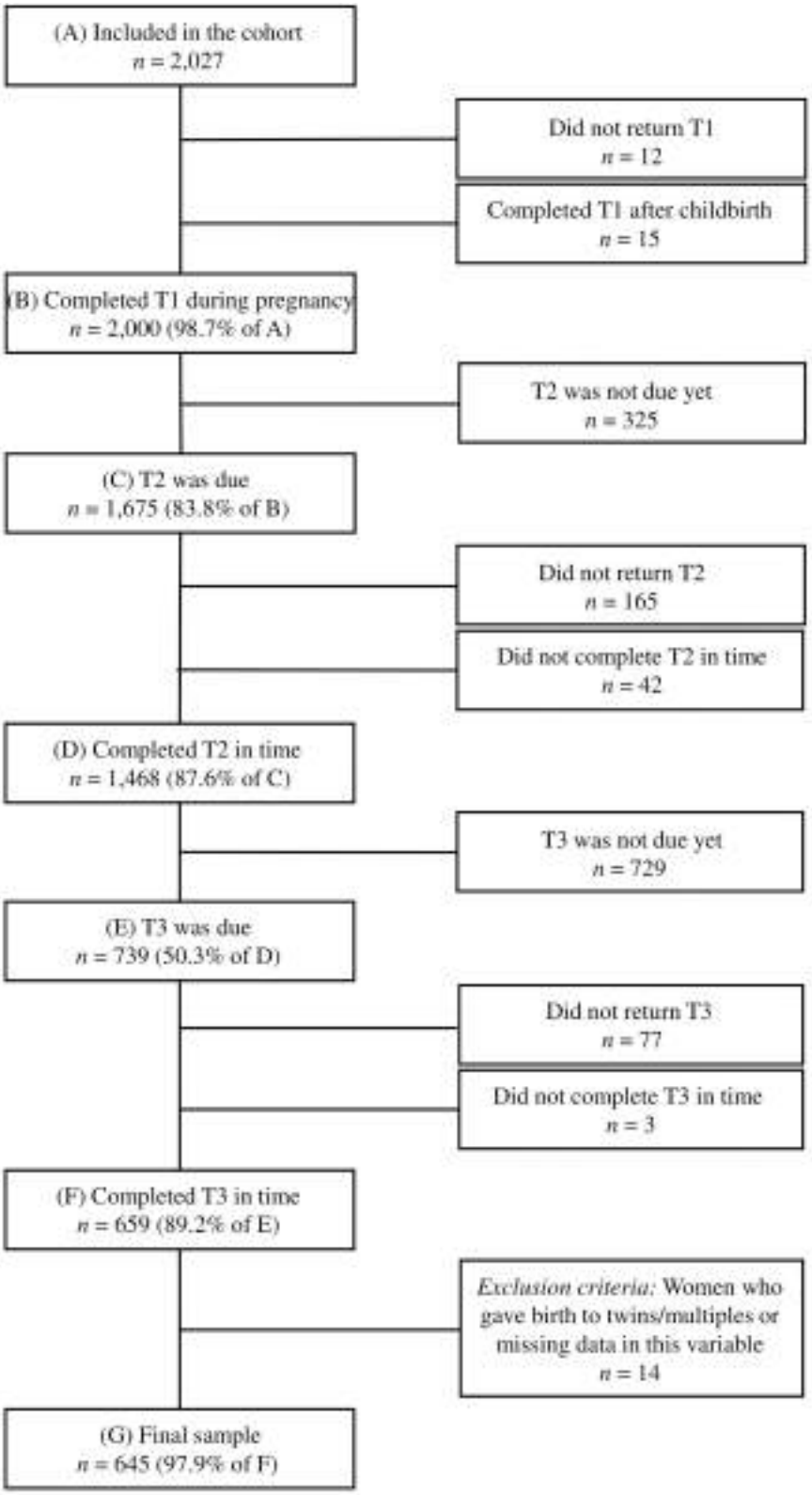

FIGURE 1 | T1, during pregnancy; T2, 8 weeks after the anticipated birth date; T3, 14 months after the birth.

30. The reliability of the EPDS in the current sample was good (Cronbach's $\alpha = 0.83$).

Birth complications and health status of the infant after birth were measured by questions based on the maternity records and the child's medical records. Complications during birth included the number of severe complications concerning the mother, e.g., failure to progress in labor, hemorrhage, perineal tear, vaginal/labial/clitoris tear, or premature or difficult abruption of the placenta. The infant's health status was measured dichotomously as complications during the first 3 days after birth (e.g., icterus, infection, hypoglycemia) which led to a hospitalization of the child.

Data Analysis

All analyses were conducted using IBM SPSS Statistics (Version 27.0). First, data were adjusted and checked for outliers. When items from psychometric scales were missing, they were replaced by the woman's mean value in cases where <20% of the items were missing. Second, descriptive analyses (N, rates in %, mean, SD) for the sociodemographic characteristics of the sample and FOC, birth experience, mother-child-bonding, and the potential confounders were computed. Additionally, correlations between all variables were examined to identify statistically significant confounders. Third, associations between FOC, birth experience, and mother-child-bonding and the potential mediator role of birth experience were analyzed via ordinary least squares regression within the SPSS modeling tool PROCESS (67). The tool computes standardized path coefficients and the standardized total, direct, and indirect effect in a mediation model. For the confidence intervals and inferential statistics bootstrapping with 5,000 iterations and heteroscedasticity consistent standard errors (68) were used. The level of significance was set to $p < 0.05$ with 95% confidence intervals (CI). Due to missing data, *n* varied slightly between analyses.

For the interpretation of the mediated effect we followed the recommendations of Zhao et al. (69) and Rucker et al. (70) who suggest to only consider the indirect effect ab to detect mediation. According to the authors, a significant total effect between the predictor and the outcome is not a requirement for mediation, thus it was reported but not interpreted.

Ethical Statement

All parts of the study were approved by the Ethics Committee of the Faculty of Medicine of the Technische Universität Dresden (No: EK 278062015). The couples were informed about the aims and procedures of the DREAM study, the pseudonymization of their data, and their right to withdraw from the study at any time. All participants provided written informed consent.

RESULTS

Sample Characteristics

The final sample at T3 (14 months postpartum) consisted of $n = 645$ women (**Table 1**). The mean age of the women during pregnancy was 30.1 years ($SD = 3.9$). Most were born in Germany

TABLE 1 | Sample description.

Sample characteristics	Total ($n = 645$)	
	M (SD)	**Range**
Maternal age at T1 (in years)	30.1 (3.9)	15–42
Week of pregnancy at T1	30.7 (5.8)	11–41
Age of child at T2 (in weeks)	8.5 (1.9)	6–16
Age of child at T3 (in months)	13.8 (0.5)	13–16
Fear of childbirth (FOBS score; T1)	36.6 (22.8)	0–100
Birth experience (SIL score; T2)	42.0 (21.0)	0–108
Mother-child-bonding (PBQ score; T2)	13.0 (10.2)	0–93
Mother-child-bonding (PBQ score; T3)	14.0 (9.9)	0–102
Depressive symptoms (EPDS score; T1)	5.5 (4.0)	0–23
Partnership satisfaction (PFB-K score; T1)	21.6 (4.0)	5–27
	***n*[a]**	**%[b]**
Country of birth		
Germany	621	96.6
Other	22	3.4
Education		
No university degree	254	39.5
University degree	389	60.5
Partnership status		
Partner	637	99.4
No partner	4	0.6
Parity		
Nulliparous	507	79.3
Primiparous	114	17.8
Multiparous	18	2.9
Employment status[c]		
Full-time employed	284	44.1
Part-time employed	114	17.7
Maternity leave	93	14.4
Number of birth complications		
0	347	53.8
1	218	33.8
2	67	10.4
≥ 3	13	2.0
Infant health status during the first 3 days		
Healthy	572	89.2
Hospitalized due to complications	69	10.8
Financial hardship		
No financial problems	488	78.3
Financial problems during pregnancy after birth or	135	21.7

FOBS, Fear of Birth Scale; SIL, Salmon's Item List; PBQ, Postpartum Bonding Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; PFB-K, short version of the Partnership Questionnaire; T1, during pregnancy; T2, 8 weeks after the expected birth date; T3, 14 months after birth.

[a]n varies slightly due to missing data of some participants. [b]Valid percent. [c]Multiple answers possible.

(96.6%), in their third trimester of pregnancy (76.6%), expecting their first child (79.3%), and living in a stable partnership (99.4%). Compared to the general population in Dresden, the women in the sample had higher education, with 60.6% holding a university degree (71). The mean scores of the FOBS, SIL, and PBQ at T2 and T3 were all below the suggested clinically relevant cut-offs, indicating low FOC, positive birth experiences, and strong mother-child-bonding, respectively.

Dropout Analyses

Dropout analyses were conducted for the predictor, the mediator, all potential confounders, and sociodemographic characteristics for completers vs. non-completers. Compared to completers, non-completers more often had no university degree (54.2 vs. 39.5%, $\chi^2(1, n = 715) = 5.76$, $p = 0.016$) and had a 7.40 points, 95% CI [1.51, 13.01], higher mean FOBS score than completers, $t(708) = 2.62$, $p < 0.05$, indicating more FOC. There were no differences between completers and non-completers regarding any other variable (tables on request).

Association Between FOC, Birth Experience, and Mother-Child-Bonding

First, correlations between all variables were computed (see **Table 2**), revealing small to medium correlations between FOC, birth experience, mother-child-bonding, and several potential confounding variables.

Second, associations between FOC, birth experience, and mother-child-bonding were examined using ordinary least squares regression within PROCESS. **Figure 2A** shows that higher FOC scores significantly predicted a more negative birth experience ($\beta = 0.208$, $p < 0.001$) which in turn significantly predicted poorer mother-child-bonding at T2 ($\beta = 0.312$, $p < 0.001$). While FOC had no significant direct effect on mother-child-bonding at T2, the effect was mediated by the birth experience, completely standardized indirect effect ab = 0.065, 95% CI [0.036, 0.098]. **Figure 2B** shows that a more negative birth experience also significantly predicted poorer mother-child-bonding at T3 ($\beta = 0.200$, $p < 0.001$). In this model, FOC had a significant direct effect on mother-child-bonding ($\beta = 0.098$, $p < 0.05$), but the effect was also mediated by the birth experience, completely standardized indirect effect ab = 0.043, 95% CI [0.023, 0.067].

Confounding variables which correlated with the two outcome variables can be found in the correlation matrix of **Table 2**. When maternal education, prepartum depressive symptoms, birth complications, and parity were included as confounders in the regression model with mother-child-bonding at T2 (see **Figure 2C**), higher FOC was still a significant predictor for a more negative birth experience, which in turn was still a significant predictor for poorer mother-child-bonding. FOC had no direct effect on mother-child-bonding at T2, but the mediated effect remained significant. The same was true for the regression model with mother-child-bonding at T3, which included the confounders maternal education, prepartum depressive symptoms, financial hardship, and partnership satisfaction (see **Figure 2D**). The associations between FOC and birth experience as well as birth experience and mother-child-bonding remained significant, but FOC had no significant direct effect on mother-child-bonding. Instead, the effect was significantly mediated by birth experience.

DISCUSSION

This study aimed to explore the longitudinal associations between prepartum FOC, birth experience, and mother-child-bonding. We found that FOC significantly predicted a more negative birth experience, which in turn significantly predicted poorer mother-child-bonding at 8 weeks and 14 months postpartum. However, FOC did not have a direct effect on mother-child-bonding. Instead, the association was mediated by birth experience.

Association Between FOC and Birth Experience

FOC was a significant predictor for a more negative birth experience, even when adjusting for maternal education, parity, depressive symptoms during pregnancy, and birth complications (Model at 8 weeks postpartum) and maternal education, depressive symptoms during pregnancy, financial hardship, and partnership satisfaction (Model at 14 months postpartum). This finding is in line with previous research: On the one hand, endocrine stress parameters during pregnancy, like cortisol awakening response and higher plasma levels of adrenalin (which could both be influenced by FOC), may disrupt labor by interfering with uterine contractions (18) and thus in turn predict a more negative birth experience (19). On the other hand, in the current study the association between FOC and birth experience was still significant when adjusting for birth complications, suggesting that the objective birth process is only one of many explanations for the subjective postpartum birth evaluation. The way a woman's expectations of childbirth affect her perception, recall, and therefore her re-interpretation of the birth, seems to be at least equally important as the course of labor and medical interventions (32, 72). Some studies have argued that women should be encouraged to have more realistic expectations of birth to reduce negative experiences and posttraumatic stress responses (73). Instead of having a birth plan, the idea of a birth flow chart is suggested, which considers various possible events and outcomes during labor and birth (74). In contrast, other researchers highlight the importance of women's belief in birth as a natural process and their own body's capability as a way to reduce FOC and medical interventions during birth (75). Clearly, more research is needed to identify the optimal strategy for preparing women for labor and birth.

Association Between Birth Experience and Mother-Child-Bonding

A more negative birth experience was a significant predictor for poorer mother-child-bonding, both at 8 weeks and 14 months postpartum. However, the association was stronger 8 weeks postpartum, suggesting that the impact of birth experience on mother-child-bonding weakens over time. These results are consistent with previous research (42, 45), although, to the

TABLE 2 | Correlation matrix including the predictor, mediator, outcome, and potential confounders.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. FOBS	–											
2. SIL	0.21***	–										
3. PBQ (T2)	0.13**	0.32***	–									
4. PBQ (T3)	0.14**	0.22***	0.61***	–								
5. Age	0.05	0.07	−0.00	−0.03	–							
6. Parity	−0.02	−0.21***	**−0.16*** **	0.06	0.30***	–						
7. Education	−0.07	0.08*	**0.13****	**0.11****	0.19***	−0.01	–					
8. EPDS	0.41***	0.14**	**0.18*****	**0.21*****	0.02	0.09*	−0.08	–				
9. PFB-K	−0.04	−0.06	−0.06	**−0.12****	−0.07	−0.27***	0.07	−0.20***	–			
10. Birth complications	−0.05	0.12**	**0.09***	0.03	0.03	−0.14**	−0.00	−0.07	0.05	–		
11. Financial hardship	0.06	−0.03	0.04	**0.10***	−0.10*	0.07	−0.16***	0.22***	−0.02	−0.05	–	
12. Infant health	0.02	0.05	0.00	−0.00	0.00	−0.08	−0.03	0.02	0.07	−0.05	0.07	–

All associations were calculated using Pearson correlation coefficient, except for the association between dichotomous variables, which were calculated using phi coefficient. Significant correlations of potential confounders with the outcome variables, PBQ (T2) and PBQ (T3), are printed in bold. FOBS, Fear of Birth Scale; SIL, Salmon's Item List; PBQ, Postpartum Bonding Questionnaire; T2, 8 weeks after the anticipated birth date; T3, 14 months after the birth; EPDS, Edinburgh Postnatal Depression Scale; PFB-K, short version of the Partnership Questionnaire.

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

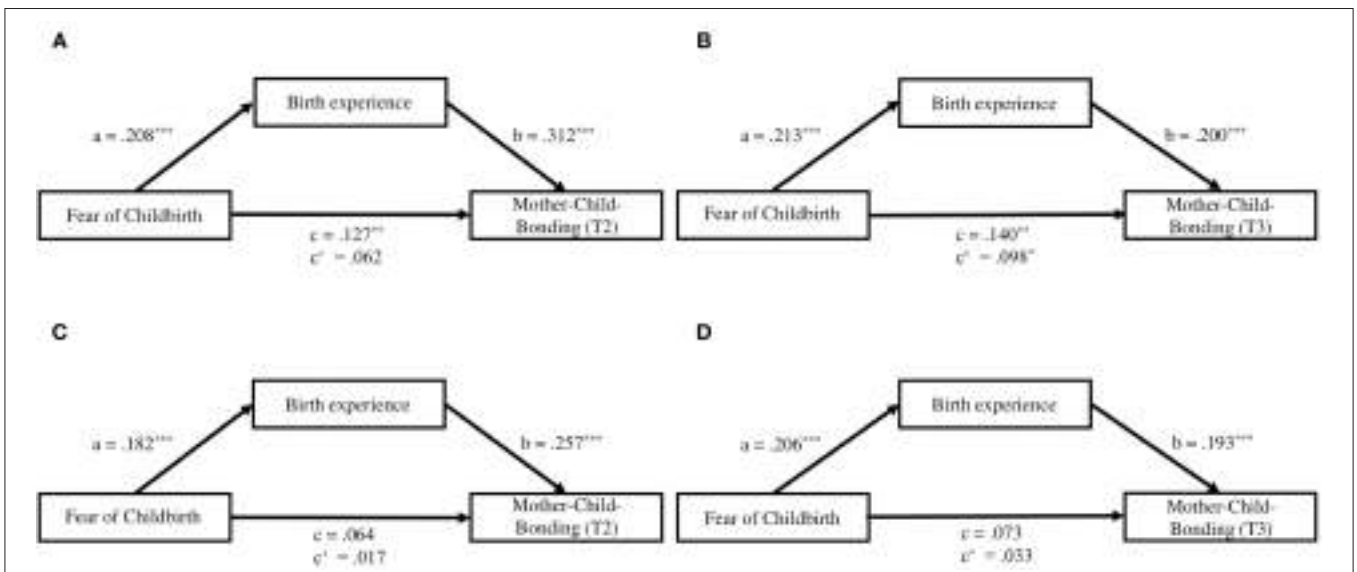

FIGURE 2 | (A) Standardized regression coefficients for the association between fear of childbirth, birth experience, and mother-child-bonding at T2. **(B)** Standardized regression coefficients for the association between fear of childbirth, birth experience, and mother-child-bonding at T3. **(C)** Standardized regression coefficients for the association between fear of childbirth, birth experience, and mother-child-bonding at T2, controlling for maternal education, parity, prepartum depressive symptoms, and birth complications. **(D)** Standardized regression coefficients for the association between fear of childbirth, birth experience, and mother-child-bonding at T3, controlling for maternal education, prepartum depressive symptoms, financial hardship, and partnership satisfaction. c, total effect; c', direct effect.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

best of our knowledge, there are no studies which examine the longitudinal development of the relationship between the subjective birth experience and mother-child-bonding. Thus, our findings emphasize the importance of a positive birth experience for the long-term bond between mother and child. Additionally, our findings support the hypothesis that not only clinically relevant birth-related PTSD symptoms may lead to poorer mother-child-bonding, but a subjectively rated negative birth experience may have the same effect. One might hypothesize that a negative birth experience influences mother-child-bonding via similar mechanisms as birth-related PTSD, because both imply negative feelings about the birth. Thus, a negative birth experience could also contribute to maternal avoidance of contact with the infant to prevent her from thinking about the negative or traumatic birth and re-experiencing it (76, 77). Furthermore, a negative birth experience may lead to a sense of failure in the mother and weaken her feeling of self-efficacy, thereby reducing her emotional availability toward the child, resulting in poorer mother-child-bonding (13, 78, 79).

Association Between FOC and Mother-Child-Bonding and Mediator Role of Birth Experience

Except for 14 months postpartum when not considering the confounders, FOC was not a significant predictor for mother-child-bonding. At first glance, this finding contradicts previous research, which identified an association between FOC and constructs similar to postpartum mother-child-bonding. Especially the results of Klabbers et al. (38) who found a significant correlation between FOC and mother-child-bonding 6 weeks postpartum, seem to differ from our results. However, our data also showed a significant correlation 8 weeks and 14 months postpartum. It was only in the mediation analysis that it became apparent that FOC does not seem to be a direct significant predictor of mother-child-bonding, especially when considering various confounders. This is in line with further analyses by Klabbers et al. (38), in which they found no mean group differences in mother-child-bonding between women with low and high FOC, although no confounding variables were considered here. Instead, the relationship seems to be mediated by the birth experience, which, to the best of our knowledge, has not been considered in any previous studies. This indicates that FOC only influences the mother's bonding with her child via the birth experience, which is in line with the hypothesis of the vicious cycle of FOC (33): a mother who suffers from severe fear of the upcoming birth has a higher risk of experiencing a negative or traumatic birth which in turn may lead to high FOC and difficult maternal adjustment postpartum. Our study suggests that this could also affect bonding with the child even 14 months after birth.

Strengths and Limitations

Using data from the prospective-longitudinal cohort study DREAM, we examined the longitudinal associations between FOC, birth experience, and mother-child-bonding from pregnancy to 14 months postpartum. By studying a large sample of German women, this study also contributed to the literature on FOC in Germany which is still scarce as most research focusses on populations from Scandinavia, Australia, and the UK (3, 4). Additionally, to the best of our knowledge, this was the first study that examined the association between the subjective birth experience and mother-child-bonding. Many of the previous studies have investigated the association between mother-child-bonding and symptoms of birth-related PTSD which is much less common (80, 81) than a negative birth experience [prevalence rates of 3–4% for PTSD as compared to 7–34%; (12)]. This was also the first study to examine the mediator role of birth experience for the association between FOC and mother-child-bonding, thereby further emphasizing the importance of a positive birth experience for the mother and the child. For all analyses, potential confounders were included, and only validated instruments were used to measure FOC, birth experience, and mother-child-bonding.

Nevertheless, when interpreting the results, one should keep in mind the limitations of this study. Firstly, women who dropped out of the study had higher FOC and more often had no university degree than the women in the final sample. One explanation for the higher level of FOC could be that these women were more impaired and therefore dropped out of the study, which would mean that our results underestimate the effect of FOC on birth experience and mother-child-bonding. However, completers and non-completers did not differ from each other in their birth experience, their prepartum depression scores, their partnership satisfaction, or financial hardship, making it unlikely that their impairment was the reason to drop out. Additionally, the women who participated in the study had relatively low FOC levels. Although the mean scores were similar to populations in Sweden and Australia (4, 56, 57), they were still far from the clinically relevant cut-off of 50 (56), indicating a relatively healthy sample. In general, our sample was very privileged and well educated [see study protocol, (53)], as most women were in a stable partnership, had low levels of prepartum depression, and relatively high levels of bonding with their children as the mean scores were far from the clinically relevant cut-off of 26 (82). Therefore, the current findings cannot necessarily be generalized to more impaired or clinical samples, but rather be seen as valuable insights for community samples. Finally, even though the characteristics of our sample may be an indicator for relatively low general psychiatric morbidity, we cannot exclude the possibility that apart from prepartum depression, other psychiatric comorbidities could have affected our results (83).

Research and Practical Implications

Future research on the association between FOC, birth experience, and mother-child-bonding is needed to replicate these findings in more diverse samples including single mothers, less educated women, clinically impaired women, higher proportions of migrants, and LGBTQIA+ couples. Additionally, it should be tested whether there are differences in the described associations for nulliparous and multiparous women as parity was a significant confounder in our analyses. Regarding the improvement of women's birth experiences through altering their prepartum expectations, it should be investigated whether different strategies need to be followed for women with and without FOC. More precisely, women with FOC may profit from strengthening the belief in birth as a natural process, which their body can master, to escape the vicious circle described by Zar et al. (33). Instead, women without FOC may profit more from preparing for various unforeseen events during labor and birth and not narrowing their attention to one possible outcome specified in a birth plan. Further, the putative mechanisms by which a negative birth experience influences mother-child-bonding remain yet to be determined; some of them might be similar to those of birth-related PTSD.

Findings clearly point to the need for FOC screenings in pregnancy to identify women at risk for a negative birth experience and connected postpartum mental health difficulties. However, such screenings are not part of routine clinical practice in Germany yet (84). This might partly be due to the fact that this topic may play a subordinate role in the education of midwives and obstetricians, but also due to the immense time pressure clinicians experience during prenatal appointments, which may

not leave enough room for additional questions. As a first step, FOC screenings should be included in national guidelines as a mandatory aspect of prenatal care. The FOBS is a validated instrument, which could be used for this purpose because it can be completed and interpreted quickly and is therefore suitable for the busy routines in modern practices. A further challenge, which needs to be addressed, is the effective referral of pregnant women with FOC to a specialist offering targeted intervention, like antenatal psychoeducation (85).

Additionally, women who experienced their birth as negative or traumatic need to be identified, as these mothers may need additional support in caring for and interacting with their babies as they are processing their birth experience. For this reason, it should also be investigated whether postpartum partner support can have a moderating effect on the development of bonding difficulties in mothers following a negative birth experience (86). Thus, widening the perspective to a family context rather than only focusing on the mother herself could reveal additional effective approaches for building healthier families.

CONCLUSION

In this study, FOC significantly predicted a more negative birth experience suggesting that a woman's expectation of her birth might be equally important for her birth evaluation as the course of labor and medical interventions. For this reason, it could be helpful to implement FOC screenings during the routine pregnancy check-ups to refer the affected women to a specialist offering a suitable intervention. Furthermore, in this study, a negative birth experience significantly predicted poorer mother-child-bonding at 8 weeks and 14 months postpartum, although the association was stronger at 8 weeks postpartum. This stresses the importance of support for women who perceived their birth as negative and might therefore be preoccupied with emotionally processing their experience and not able to properly bond with their babies. The results of this study also suggest that the association between FOC and mother-child-bonding is mediated by the birth experience, which further emphasizes the importance of a positive birth experience for all women. It could be promising to replicate and test these findings in more diverse samples, as well as comparing them to nulliparous and parous women.

DATA AVAILABILITY STATEMENT

The dataset analyzed during the current study is not publicly available due to legal and ethical constraints, as the study's informed consent did not include public sharing of participant data. The dataset is available from the corresponding author on reasonable request. Requests to access the datasets should be directed to lara.seefeld@ukdd.de.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by the Ethics Committee of the Faculty of Medicine of the Technische Universität Dresden (No: EK 278062015). All participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LS, VW, and SG-N contributed to the conception and the design of the study. VW and MK conducted data cleaning and data preparation. LS and VW performed the statistical analyses. LS wrote the first draft of the manuscript. VW, MK, SK, and SG-N wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Maternal Mood and Perception of Infant Temperament at Three Months Predict Depressive Symptoms Scores in Mothers of Preterm Infants at Six Months

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Postpartum depression is more prevalent in mothers and fathers of preterm infants compared to parents of full-term infants and may have long-term detrimental consequences for parental mental health and child development. The temperamental profile of an infant has been postulated as one of the important factors associated with parental depressiveness in the first months postpartum. This study aimed to examine the longitudinal relationship between depressive symptoms and perceived infant temperament at 3 months corrected age, and depressive symptoms at 6 months corrected age among mothers and fathers of infants born preterm. We assessed 59 families with infants born before the 34th gestational week using the Edinburgh Postnatal Depression Scale (EDPS) and the Infant Behavior Questionnaire-Revised. We found that mothers' scores on EPDS and infants' Orienting/regulation at 3 months corrected age predicted mothers' EPDS scores at 6 months corrected age. In particular, higher depressive scores were related to higher depressive symptoms at 6 months corrected age, whereas higher infant Orienting/regulation was related to lower depressive symptoms at 6 months corrected age. Due to the low internal consistency of EPDS at 6 months for fathers, we were unable to conduct similar analyses for fathers. Our results point to the importance of considering both early indices of maternal mood as well as mother-reported measures of preterm infant temperament in the attempts to predict levels of maternal depressiveness in later months of an infant's life. Further studies are urgently needed in order to better understand the associations between depressiveness and infant temperament in fathers, and with more consideration for the severity of the effects of infant prematurity.

Keywords: postpartum depression, preterm infants, mothers, fathers, temperament

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INTRODUCTION

Despite rapid advances in obstetric and neonatal care, prematurity, i.e., a birth before the 37th gestational week, remains a major health and developmental risk factor for affected children and contributes to increased distress in their parents (Wolke et al., 2019). Multiple emotional reactions of parents to their preterm infants' hospitalization in a neonatal intensive care unit have been

described, including feelings of helplessness and being out of control, uncertainty as to the infant's survival and health status, sadness, and extreme distress (Lasiuk et al., 2013; Trumello et al., 2018). Studies on the impact of preterm birth on parental mental health point to increased risk of depression and post-traumatic stress disorder as well as increased levels of anxiety and parenting stress, especially in mothers of preterm infants (Kersting et al., 2004; Karatzias et al., 2007; Vigod et al., 2010; Helle et al., 2015; Pace et al., 2016; Anderson and Cacola, 2017; Yildiz et al., 2017; Garfield et al., 2021; Genova et al., 2022). The rates of paternal depression and anxiety seem to be lower than maternal ones, but still elevated when compared to fathers of full-term infants (Treyvaud, 2014; McMahon et al., 2020; Weigl et al., 2020; Baldoni et al., 2021; Genova et al., 2022).

Literature on longer-term trajectories of perinatal depression in parents of preterm infants is still limited and existing results are mixed. Some studies have found no evidence for prolonged risks for parental mental health, at least considering the trajectories of parenting stress (Schappin et al., 2013). Others point to gradually declining, yet elevated levels of depression symptoms in mothers (Miles et al., 2007; Poehlmann et al., 2009) or in both mothers and fathers until at least the infant's corrected age of 6 months (Pace et al., 2016). In addition, some evidence has been found for the connections between prematurity/low birth weight (LBW) and parental depression to last much longer. For instance, according to Barkmann et al. (2018), very low birth weight predicts elevated levels of parental depressiveness even up to 5 years postpartum. Finally, a recent study by Genova et al. (2022) points to general decrease in depressiveness between 3 and 12 months postpartum in mothers and fathers, although with some differences, both in the severity of depressiveness and in the reduction in depressive symptoms over time, between parents of extremely LBW and very LBW infants.

The increased risk for postpartum depression should raise our particular concern as the links between perinatal parental depression and a child's mental health and developmental problems later in life have been well documented in preterm children (Cheng et al., 2016; Trumello et al., 2018; Neri et al., 2020; Pisoni et al., 2020), adding to the already complex array of challenges to child development related to biological immaturity, neonatal complications, quality of the early experience, etc. (Aarnoudse-Moens et al., 2009). One of the important factors that has recently received considerable attention from researchers as potentially related to compromised parental mental health (especially in terms of risk of depression), is infant temperament as perceived by the parents.

More and more studies point to preterm birth or its neurological complications as related to less optimal infant temperamental profile (Takegata et al., 2021), or even to "difficult" temperament (Washington et al., 1986; Larroque et al., 2005). Preterm birth is a multifold risk for child development (Wolke et al., 2019). Biological immaturity, medical complications, pain exposure, and exposure to overwhelming sensory input in the NICU are among the risk mechanisms that can alter a child's neurobehavioral functioning (Als et al., 2004; Feldman, 2009; Valeri et al., 2015; Grunau, 2020). For example, exposure to procedural pain and pain-related stress in neonatal period was found associated with the alterations in brain architecture and function (see Gaspardo et al., 2018, for review), which, in turn, may be related to poorer regulatory competencies in later developmental periods. Montirosso et al. (2016) described epigenetic mechanisms through which early NICU-related stress might be associated with temperamental difficulties at 3 months of age.

Studies using Mary Rothbart (2004, 2011) psychobiological, developmental, and dimensional approach to temperament, defined as "biologically rooted individual differences in reactivity and self-regulation in emotional, activational, and attentional processes" (Fu and Pérez-Edgar, 2015, p. 193), clearly point to specificities of preterm children's temperament. Noteworthy in this approach is that reactivity is captured by the dimensions of Negative affectivity and Surgency, whereas self-regulation is reflected in the dimension of Effortful control (Orienting/regulation in infancy) (Fu and Pérez-Edgar, 2015). Furthermore, each of the three higher-order dimensions consists of a number of lower-order temperamental traits (dimensions).

In the study by Cosentino-Rocha et al. (2014), preterm birth was associated with higher scores on high-intensity pleasure and perceptual sensitivity and lower scores on discomfort, cuddliness, and attentional focusing in children aged 18 months to 5 years. The study by Tamm et al. (2020) in the group of very preterm infants showed that early MRI-diagnosed brain abnormalities were predictive of lower parental ratings of child's temperamental features as measured by the Infant Behavior Questionnaire-Revised-Short form (Putnam et al., 2014): High Intensity Pleasure and Vocal Reactivity, High Intensity Pleasure and Cuddliness as well as Fear and Sadness at 3 months corrected age. According to a meta-analysis conducted by Cassiano et al. (2020), preterm children get lower scores in Attentional Focusing and higher scores in Activity dimensions compared to full-term children. Compromised temperamental profile in turn was found to be predictive of long-term behavioral problems (Cassiano et al., 2016, 2019; Lee and Lee, 2017; Martins et al., 2021).

Associations between maternal depressive symptoms and infant behavior and temperament have been broadly documented (e.g., McGrath et al., 2008). However, the study results do not explain the mechanisms which underlie this association, and the direction of the relationship remains unclear (e.g., Murray et al., 1996; Pauli-Pott et al., 2004; Britton, 2011; Eastwood et al., 2012; Aktar et al., 2017). And this is particularly true for preterm infants. Some studies show that the temperamental profile of preterm infants is predictive of maternal depressive symptoms. For example, according to results from Quist et al. (2019), gestational age was predictive of maternal depressive symptoms, but only in interaction with fussiness. Contrary directions were found in studies which point, that maternal depression can alter the perception of child behavior. The study by Voegtline et al. (2010), showed the stability of increased symptoms of depression and anxiety at 2 and 6 months in mothers of late preterm infants, which was related to higher maternal ratings of infant negativity at 6 months.

More research is required to better understand the relationship between parental depression and child temperament. This is especially true in parents of preterm infants due to higher

prevalence of depressive symptoms in mothers and fathers, altered temperamental profiles in infants, and numerous challenges in parent-infant interactions related to both parental (e.g., Misund et al., 2016) and infants' (e.g., Harel et al., 2011; Poehlmann et al., 2011) contributions in this population. Additionally, investigating the association between the course of parents' depressive symptoms and infant temperament might be of crucial clinical importance, as depression in the postpartum period may have long-term detrimental consequences for parental well-being (Hermens et al., 2004; Vigod et al., 2010; Helle et al., 2015) and child development (Latva et al., 2008; Cheng et al., 2016; Slomian et al., 2019).

In the current study, we aimed to analyze the relationship between the intensity of depressive symptoms (depressiveness) in parents of preterm infants and parents' perceived infant temperament at 3 months corrected age (CA). Furthermore, our intention was to verify whether both the intensity of depressiveness and the infant's temperamental dimensions, as assessed by parents at 3 months, were predictors of parental scores on the dimension of depressiveness at 6 months of the infant's CA. Taking into consideration the available research data briefly summarized in the introductory section, and Rothbart's model of temperament, we hypothesized that:

(1) The level of depressiveness will be higher in mothers than in fathers, both at 3 and 6 months infants' CA.
(2) The level of depressiveness of both mothers and fathers will decrease between 3 and 6 months of the infant's CA.
(3) Measures of infants' temperament as assessed by mothers and fathers will be positively correlated.
(4) Infant's Negative affectivity at 3 months CA will be positively related to the maternal and paternal level of depressiveness at 3 and 6 months CA, whereas indices of temperamental self-regulation (Orienting/regulation in the case of infants) and Surgency/extraversion at 3 months CA will be negatively related to both maternal and paternal depressiveness at 3 and 6 months CA.

In addition, an exploratory analysis was planned to explain possible contribution of parental depressiveness scores and parent-reported infant's temperament at 3 months to maternal and paternal levels of depressiveness at 6 months CA.

MATERIALS AND METHODS

General Information

This study was part of a larger longitudinal project on relational and biological antecedents of self-regulatory capacities of preterm infants in the first year of their lives, in which data were collected at 1, 3, 6, and 12 months infants' CA. For the purposes of the current study, only the data collected at 3 and 6 months will be used as these are specifically targeted at assessing parental levels of depressiveness and infant temperament. Our focus was on families with infants born before the 34th gestational week, hospitalized for at least 7 days in the neonatal unit, as their experiences might considerably differ from those of late preterm infants.

Participants

A convenience sample of sixty-four infants (30 girls) born before the 34th gestational week in two tertiary care hospitals in Warsaw between July 2008 and February 2010 was enrolled. The parents were invited via written information about the study distributed by the neonatal unit staff just before each infant's discharge from the hospital. The inclusion criteria also comprised both parents' consent to participate in all assessment meetings, and parents being above 19 years of age. Infants from multiple pregnancies as well as those born with additional metabolic or genetic syndromes, congenital malformations, or tumors were excluded. The study was approved by the research ethics committee of the Faculty of Psychology, University of Warsaw, and conformed to the Declaration of Helsinki. In the original project, a control group of 31 full-term infants was also included but will not be presented here as our focus is not on comparison between the groups but specifically on the interplay of factors that might explain the intensity and persistence of depressive symptoms in parents of preterm infants, and the possible links with infants' temperament.

The preterm group consisted of two subgroups in line with the WHO degrees of prematurity: 33 infants met the criteria for extreme prematurity (EPT), and 31 infants were born very or moderately preterm (VPT and MPT, respectively). Four families resigned from the study (3 from the EPT and 1 from the VPT group) by the time the infant reached 3 months CA. Apart from that, one family could not participate in the assessment for a period of 3 months for medical reasons. As no statistically significant correlations were found between infants' gestational week and either parental depressiveness scores (at 3 and 6 months) or infants' temperamental dimensions, both groups of preterm infants were merged for further analysis in this study. Group characteristics are presented in **Table 1**. Mean gestational age of the infants at birth was 28.746 weeks ($SD = 3.15$; $Mdn = 29$), mean birth weight was 1,290.8 g ($SD = 519.475$; $Mdn = 1{,}200$), mean length of hospitalization was 60 days ($SD = 34.115$; $Mdn = 34$), and the mean number of skin breaking/painful procedures was 91 per hospital stay ($SD = 95$; $Mdn = 45$). The socio-economic status of the families was controlled for, and all the families reported that their financial situation was either average or above average. Most parents had at least 12 completed years of education, and 70% of mothers and 56.7% of fathers had a higher education diploma. Mothers were between 20 and 41 years of age ($M = 31.5$, $SD = 4.2$, $Mdn = 31$), while fathers were between 20 and 52 ($M = 33.8$, SD = 5.26, $Mdn = 33$).

It is worth noting that, at the time when the infants were hospitalized, the two neonatal units adopted various elements of neurodevelopmental care such as special nests surrounding and supporting the infant's body, blankets shielding an isolette to minimize excessive and abrupt light exposure, etc. The units also offered psychological support for the parents and employed a team of physiotherapists and speech therapists to provide developmentally appropriate care for the infants.

Furthermore, participation in the project as such might have served as an additional supportive measure because it involved two home visits by a nurse and a psychologist (at the infant's CA of 1 and 3 months), with plenty of time for parents to

TABLE 1 | Group characteristics.

	N	%	Mean	SD	Median	Min	Max
Total number of infants	59	100.00					
Girls	30	50.85					
Boys	29	49.15					
Infant's gestational week at birth			28.75	3.15	29.00	22.00	34.00
Infant's birthweight in grams			1, 290.80	519.48	1, 200.00	495.00	2, 440.00
Infant's duration of hospital stay after birth			59.70	34.12	54.00	7.00	147.00
Prevalence of neurological complications:							
IVH of at least 3rd grade	8	13.56					
PVL	5	8.47					
Prevalence of retinopathy of prematurity of at least 3rd grade	14	23.73					
Prevalence of necrotizing enterocolitis (NEC)	6	10.17					
Prevalence of chronic lung disease	29	49.15					
Days on mechanical ventilation			10.76	15.84	4.00	0.00	63.00
Number of skin-breaking/stressful procedures during the whole hospital stay			91.45	94.97	45.00	5.00	384.00
Mother's age (years)			31.37	4.17	31.00	20.00	41.00
Father's age (years)			33.71	5.33	33.00	20.00	52.00
Mother's education (number of completed years)			15.73	2.28	17.00	8.00	19.00
Father's education (number of completed years)			15.10	2.78	17.00	11.00	20.00

IVH, intraventricular hemorrhage; PLV, periventricular leukomalacia.

share their concerns with the study team, and the provision of feedback on the infants' developmental progress and parent-infant interactions.

Procedure

As already mentioned, families were first approached at around the time of their infant's discharge from the hospital. Written informed consent was obtained from all adult participants, and the parents were asked to complete a socio-demographic questionnaire. In addition, the medical records of each child were analyzed by a project leader, a neonatologist, and a neonatal nurse in order to retrieve data on infants' gestational age at birth, birthweight, days of mechanical ventilation and hospitalization, number of neonatal skin-breaking procedures, and complications of prematurity (see section "Measures").

At 3 months CA, a home visit was scheduled for each family, at a time convenient for them. The appointments with the families were arranged by a research team member via a phone call, based on prior written consent from both parents. Mothers and fathers were asked to independently rate their infant's temperament and complete a screening tool for postnatal depression. Information on any changes in the infant's health status and family socio-economic status was updated. This phase of the project was completed no later than 4 months CA, mostly at 3 months and 15 days.

At 6 months CA families were invited to a baby lab at the Faculty of Psychology of the University of Warsaw and were asked to repeat completion of a postnatal depression screening tool. Apart from that, interviews with parents were also conducted with a focus on each infant's functioning across a range of typical domains (sleep patterns, feeding, arousal regulation, developmental milestones, and health, etc.). The second visit was supposed to be arranged no later than within 15 days from the time when infants were 6 months CA, and, in fact, the mean CA was 5 months and 29 days (SD = 12.00).

Measures

Socio-Demographic Questionnaire

Data on parental age, level of education (number of completed years of formal education), housing, financial situation, employment, and number of other children in the family were collected.

Data From Medical Records

The following data were extracted from the infants' medical records: birthweight, gestational age, small for gestational age (yes/no), number of days in hospital, number of days on mechanical ventilation, neurological complications (intraventricular hemorrhage/which grade, periventricular leukomalacia, and other), number of skin-breaking procedures during hospital stay, necrotizing enterocolitis (yes/no), retinopathy of prematurity (which grade), bronchopulmonary dysplasia (yes/no), and infection (yes/no), etc.

Infant Behavior Questionnaire–Revised

The Polish version of IBQ-R (Gartstein and Rothbart, 2003; Polish adaptation Dragan et al., 2011) is a 186-item parent – report measure of infant temperament based on Rothbart's approach. It can be used between the ages of 3 and 12 months, and measures 14 temperamental dimensions that load three major factors: Surgency/extraversion (comprising the scales of Approach, Vocal Reactivity, High Intensity Pleasure, Smiling and Laughter, Activity Level, and Perceptual Sensitivity), Negative affectivity (comprising the scales of Sadness, Distress to Limitations, Fear, and Falling Reactivity/Rate of Recovery from Distress), and Orienting/regulation (comprising the scales

of Low Intensity Pleasure, Cuddliness, Duration of Orienting, and Soothability). Each item is rated on a 7-point scale (from 1 – never to 7 – always), and parents are asked to report on behaviors observed during the last week. In addition, parents can choose "does not apply" option, and no numerical score is assigned to a given item in such a case. Scale scores are computed as the mean score of all scale items applicable to the child, as reported by the caregiver. Similarly, the score for each of the three major factors is represented by the mean score of the relevant scales. The internal consistency for the 14 temperamental dimensions was performed on a bigger sample of infants and turned out to be satisfactory, with Cronbach's alphas ranging from 0.73 to 0.89 for maternal ratings, and from 0.71 to 0.90 for paternal ones (Dragan et al., 2011).

Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS; Cox and Holden, 2003; Polish translation by Bielawska-Batorowicz) is a 10-item self-report measure for identifying the risk of postnatal depression in women, with each item rated on a 4-point scale from 0 to 3 and referring to the last 7 days. The higher the score, the higher the level of depressiveness. Although Brouwers et al. (2001) have confirmed that this measure contains a subscale of depression and a subscale of anxiety, they still recommend the use of a total score, as this seems to be a better measure of both anxiety symptoms and depressive symptoms than when subscales are used. The EPDS has also been widely used in research on fathers but with rather mixed results. Cut points of 9/10 and 12/13 have been suggested to identify a risk of minor vs. major depression. More recently, a cut-off value of 11 or higher has been found to maximize combined sensitivity and specificity (Levis et al., 2020). In the current study, we will use this measure as a continuous variable representing the level of a subject's depressiveness.

The Polish version of EPDS had high internal consistency for the assessments of mothers at 3 months CA, Cronbach's alpha = 0.88, and acceptable at 6 months CA, Cronbach's alpha = 0.78. The internal consistency for the assessment of fathers was also high at 3 months CA, Cronbach's alpha = 0.80, and lower than acceptable at 6 months, Cronbach's alpha = 0.67.

Statistical Analyses

First, we used a non-parametric test to compare mothers' and fathers' EPDS scores at 3 months CA. Second, we tested whether mothers' EPDS scores changed from 3 to 6 months CA. Third, we compared mothers' and fathers' ratings of infants' temperament at 3 months CA. Then, we performed correlation analysis to search for possible predictors of mothers' EPDS scores. In order to determine whether infants' perceived temperament at 3 months CA predicted mothers' EPDS scores at 6 months CA, controlling for mothers' EPDS scores at 3 months CA, we conducted a regression analysis. Due to the low internal consistency of EPDS at 6 months CA for fathers, analyses with those scores were not performed.

RESULTS

Mothers' and Fathers' Scores on the Edinburgh Postnatal Depression Scale and Infant Behavior Questionnaire–Revised

Table 2 presents descriptive statistics for EPDS and IBQ-R scores. Mothers scored significantly higher than fathers on the EPDS at 3 months CA, $U = 1344.00$, $z = -2.01$, $p = 0.044$. A related-samples Wilcoxon signed rank test revealed that there was a statistically significant difference between mothers' EPDS scores at 3 and 6 months postpartum, $T = 417.00$, $z = -2.49$, $p = 0.013$. Mothers' EPDS scores decreased between 3 and 6 months of children's CA.

There were no significant differences between mothers' and fathers' assessments of their infants' Negative affectivity or Surgency/extraversion; both ps > 0.05. Regarding Orienting/regulation, there was a trend approaching significance, suggesting higher scores of mothers than fathers, $U = 1314.00$, $z = -1.89$, $p = 0.059$.

Correlations Between Mothers' and Fathers' Edinburgh Postnatal Depression Scale and Infant Behavior Questionnaire–Revised Scores

Table 3 presents the results of correlation analyses for mothers' and fathers' depressive symptoms (EPDS scores) and their perceptions of their infants' temperament (IBQ-R scores). The correlations between mothers' and fathers' ratings of their infants' temperament were either non-significant or very weak. Mothers' ratings of their infants Negative affectivity and Orienting/regulations were correlated with their EPDS scores. There was no such association for fathers.

Notably, no statistically significant correlations were found between mothers' and fathers' EPDS scores at 3 months CA.

As the IBQ-R Negative affectivity and Orienting/regulation scores as assessed by mothers, and the mothers' EPDS scores at 6 months CA, were significantly correlated, we conducted

TABLE 2 | Mothers' and father's EPDS scores at 3 and 6 months CA and IBQ-R scores at 3 months CA: Descriptive statistics.

	Mdn	Min	Max	Q1	Q3
EPDS M 3 MCA	6.00	0.00	27.00	4.00	10.00
EPDS F 3 MCA	5.00	0.00	22.00	3.00	9.00
EPDS M 6 MCA	5.00	0.00	19.00	4.00	8.00
EPDS F 6 MCA	5.00	0.00	14.00	3.00	6.00
IBQ-R Surgency/extraversion M	3.90	1.99	5.54	3.47	4.39
IBQ-R Negative affectivity M	3.49	2.79	4.70	3.22	4.75
IBQ-R Orienting/regulation M	4.81	3.38	6.18	4.34	5.15
IBQ-R Surgency/extraversion F	3.84	2.48	5.49	3.36	4.28
IBQ-R Negative affectivity F	3.39	2.45	4.22	3.17	3.68
IBQ-R Orienting/regulation F	4.52	3.08	5.88	4.26	4.96

EPDS, Edinburgh Postnatal Depression Scale; MCA, months corrected age; M, mother, F, father; IBQ-R, Infant Behavior Questionnaire-Revised.

TABLE 3 | Correlations (τ_b) between mothers' and fathers' EPDS scores at 3 and 6 months corrected age and IBQ-R scores at 3 months corrected age.

	EPDS M 3 MCA	EPDS F 3 MCA	EPDS M 6 MCA	IBQ-R Surg/extr M	IBQ-R Neg aff M	IBQ-R Orient/reg M	IBQ-R Surg/extr F	IBQ-R Neg aff F
EPDS F 3 MCA	0.07							
EPDS M 6 MCA	**0.43****	0.10						
IBQ-R Surg/extr M	0.00	−0.03	−0.07					
IBQ-R Neg aff M	0.09	0.06	**0.19***	0.09				
IBQ-R Orient/reg M	−0.13	0.02	**−0.23***	**0.35****	−0.05			
IBQ-R Surg/extr F	0.01	−0.04	0.02	**0.24***	−0.07	0.05		
IBQ-R Neg aff F	**−0.20***	0.04	−0.13	−0.11	0.12	0.05	0.10	
IBQ-R Orient/reg F	0.02	−0.07	−0.11	**0.24****	−0.01	0.15	**0.40****	0.00

*EPDS, Edinburgh Postnatal Depression Scale; MCA, months corrected age; M, mother; F, father; IBQ-R, Infant Behavior Questionnaire-Revised; Surg/extr, surgency/extraversion; Neg aff, negative affectivity; Orient/reg, orienting/regulation. Bold text indicates a statistically significant correlation; *p < 0.05; **p < 0.001.*

TABLE 4 | Regression: maternal EPDS scores, infant negative affectivity, and infant Orienting/regulation at 3 months as predictors of EPDS scores at 6 months.

Model	Coefficients							
	B	B SE	Beta	*p*	95% CI for *B*		Collinearity statistics	
					LL	UL	Tolerance	VIF
(Constant)	2.76	0.68		0.000	1.39	4.12		
ESDP 3 m.	0.49	0.07	0.66	0.000	0.34	0.63	1.00	1.00
(Constant)	4.55	4.63		0.330	−4.73	18.83		
ESDP 3 m.	0.44	0.07	0.60	0.000	0.30	0.58	0.95	1.05
Neg aff 3 m.	1.77	0.93	0.18	0.063	−0.10	3.64	0.97	1.03
Orient/reg	−1.59	0.65	−0.23	0.018	−2.89	−0.28	0.97	1.03

EPDS, Edinburgh Postnatal Depression Scale; Neg aff, negative affectivity; Orient/reg, orienting/regulation; CI, confidence interval; LL = lower limit; UL = upper limit; VIF, variance inflation factor.

regression analyses with these two dimensions of infant temperament perceived by the mothers at 3 months CA as predictors of the mothers' depressive symptoms at 6 months CA.

Regression: Infant Temperament Predicting Depression Symptoms

We tested whether infants' Negative affectivity and Orienting/regulation at 3 months CA as perceived by the mother predicted mothers' depressive symptoms at 6 months CA, controlling for mothers' depressive symptoms at 3 months CA (see **Table 4**).

In the first step, we entered the control variable: mothers' scores on the EPDS when the infant was 3 months CA. These scores were significantly positively associated with EPDS scores at 6 months CA, and explained 44% of variance, $R^2 = 0.438$.

In the second step, we entered the IBQ-R Negative affectivity scores and the IBQ-R Orienting/regulation at 3 months CA. The relation between Negative affectivity at 3 months CA and EPDS scores at 6 months CA was not statistically significant, $p > 0.05$. The IBQ-R Orienting/regulation scores at 3 months CA were significantly positively associated with the EPDS scores at 6 months. Orienting/regulation scores at 3 months CA predicted lower EPDS scores at 6 months CA. The overall model was statistically significant and explained 53% of variance in EPDS scores at 6 months CA, $R^2 = 0.53$, $F(3, 54) = 19.87$, $p < 0.001$.

DISCUSSION

This study aimed to examine the associations between the levels of parental depressive symptoms and preterm infants' parents – reported temperament at 3 months, and the risk of maternal and paternal depression at 6 months postpartum. We found an association between self-reported depressive symptoms at 3 months and infant temperament assessment in mothers. Moreover, maternal depressiveness combined with the infant's temperamental characteristics assessed by mothers at 3 months turned out to be predictive of depressiveness scores at 6 months.

In line with the large body of research, we found higher levels of depressiveness in mothers compared to fathers at 3 months postpartum. It should be emphasized, however, that we have measured depressiveness which is not equivalent to identifying clinically significant depression. The EPDS is a screening tool, not a diagnostic one. Our participants represented a full range of scores with the mean far below the suggested cut point for the risk of major depression. Further studies are, therefore, needed on groups of preterm infants' parents with clinical diagnosis of mood disorders.

Moreover, contrary to the results of other authors (Neri et al., 2020; Thiel et al., 2020), we have not found a statistically significant correlation between maternal and paternal depressiveness scores. In addition, due to the low internal consistency of EPDS for the assessment of fathers at 6 months,

these results could not be used in the analyses. This, in turn, prevented us from checking correlations with maternal depressiveness scores at 6 months, and made a comparison of paternal levels of depressiveness at 3 and 6 months ineligible. Despite our problems with internal consistency of EPDS for fathers at 6 months CA, one of the reasons for this apparently surprising result of not finding correlations between maternal and paternal scores at 3 months CA might be the nature of EPDS as such. Further studies should address this issue with the item by item analysis of maternal and paternal scores on bigger samples. Although EPDS was validated as a measure of postpartum mood in men (Matthey et al., 2001), our results add to the growing literature which emphasizes the need for using gender-specific tools in screening for perinatal depression (Carlberg et al., 2018; Walsh et al., 2020; Yogman, 2021). More and more authors point to the specificity of paternal depression and paternal depressive symptoms, which are not included in EPDS, e.g., irritability, abnormal illness behaviors, heightened anxiety, or addictions (Kim and Swain, 2007; Baldoni and Giannotti, 2020; Walsh et al., 2020; Garfield et al., 2021). Using gender-specific tools could shed more light on the specificity of depressive symptoms in mothers and fathers of preterm infants.

The level of postpartum depressiveness in mothers in our sample was higher at 3 than at 6 months. This is in line with studies showing that the severity of maternal depressive symptoms decreases over time (Miles et al., 2007; Pace et al., 2016; Garfield et al., 2021). However, it is noteworthy that despite the fact that the risk of depression tends to decline over time in the majority of women, about 30% of mothers affected by postpartum depression remain depressive throughout the first year of the child's life and beyond (Vliegen et al., 2014). The percentage of mothers who meet the criteria of depression many months after delivery turned out to be even higher in women with depression in life history. The risk for depression has been proven to be higher in mothers of preterm infants compared to mothers of full-term infants not only shortly after delivery but also throughout the following months (Vigod et al., 2010; Neri et al., 2020). Moreover, although the directions of these associations are complex, researchers point to the links between preterm infants mothers' postpartum depression and the chronicity of maternal mental health problems (Miles et al., 2007; Pace et al., 2016), paternal depression (Carlberg et al., 2018; Neri et al., 2020), and less than optimal child developmental outcomes (Cheng et al., 2016; Narayanan and Nærde, 2016). For this reason, investigating factors predictive of the persistence of maternal depressiveness is of crucial importance for clinical practice and early intervention addressed to families of preterm infants. Further studies are needed to disentangle possible links between trajectories of maternal and paternal depressiveness and all the different factors related to the severity of infant's prematurity and the comorbid medical complications.

We did not find any significant differences in infants' temperamental characteristics obtained from mothers and fathers. This result is in line with studies showing similarities between maternal and paternal assessments of infant's temperament (Sechi et al., 2020; Vismara et al., 2021). The reliability of parental perceptions may indicate that regardless of the specificity of and possible differences in experiences mothers and fathers shared with their infants, the parental assessments of the infant's temperament were related to the child's actual behaviors. On the other hand, the correlations between maternal and paternal assessments of infants' temperament were rather weak in our study, quite contrary to previous research findings (Dragan et al., 2011). This may point to a presumably complex nature of parental perceptions of preterm infants' temperament, and calls for including observational or at least independent measures of temperament when assessing this at-risk group.

According to our results, Orienting/regulation, but not Negative affectivity, as assessed at 3 months predicted maternal depressiveness at 6 months, which means that our hypothesis as to the links between maternal perceptions of infant temperament and self-reported depressiveness has only partly been supported. In accordance with our hypothesis, heightened scores in EPDS, combined with assessing the child as low on Orienting/regulation at 3 months, turned out to be predictive of mothers' depressiveness at 6 months. At the same time, we haven't found any support for Negative affectivity, as assessed at 3 months, to be a predictor of maternal depressiveness at 6 months. This is quite in contrast to the results obtained by Sechi et al. (2020) for parents of full-term infants, where maternal depression and anxiety symptoms were positively correlated with Negative affectivity, but not with Orienting/regulation, at 3 and 12 months.

Our results point to behaviors that may be particularly significant for mothers of preterm infants in the context of postpartum depression. Data on early preterm infants' temperament indicate that in the first weeks and months of life, preterm infants may be less rhythmic, more difficult to soothe, more withdrawn, and spend less time in alert states, which may hinder rewarding experiences in early parent-infant interaction (Eckerman et al., 1995; Hughes et al., 2002). The Feldman and Eidelman (2007) confirmed a slower maturation of preterm infants' autonomic nervous system and decreased capability to maintain alert states. The authors described the double interactional risk linked to the attention regulation in preterm infants as lower infants' interactional availability and compromised maternal ability to coordinate their interactional behaviors with the fragile infant. Maternal depressiveness turned out to be associated with both mothers' interactional behaviors and infants' vagal tone. These results may show that preterm birth, maternal depressiveness, and mothers' as well as infants' interactional behaviors constitute a multitude of factors that put preterm children and their parents at risk.

Our results add to this knowledge and confirm the complexity of the mechanisms underlying early mood problems in parents of preterm infants. They contribute to the literature on risk mechanisms of postpartum depression in parents of preterm infants by linking parental mood with the temperamental profile of preterm infants. They also show possible links between preterm infant temperament and the chronicity of postpartum depressiveness. Our results further suggest that special clinical attention should be given during screening to those mothers of preterm infants whose depressiveness at 3 months co-occurs

with perceiving the infant as difficult to soothe, showing little enjoyment at being held in the arms of the adult, and having problems with maintaining alert states or attending to/interacting with people and objects for extended time.

There are studies that indicate early interventions focused on parental perception of the preterm infant's behaviors, as well as on sensitive caregiving, are effective in supporting parental assessment of a child's emotionality and soothability (Landsem et al., 2020). Offering early support to mothers who perceive their infants as temperamentally challenging, and whose rates of depressiveness are elevated, might prevent them from further mood problems.

We did not find a significant relationship between paternal depressiveness and child temperament assessment at 3 months CA. This is in contrast with studies in which paternal depression was related to child temperamental characteristics (Hanington et al., 2010). In research using Rothbart's approach to temperament, depression symptoms in fathers were found to be significantly related to the assessment of distress (Ramchandani et al., 2011) and negative affectivity (Sechi et al., 2020) in 3-month-old infants. Those studies, however, were conducted on the group of full-term infants' fathers. Far less is known about the links between depressive symptoms and infant temperament assessment in fathers of preterm infants. Due to the low internal consistency of EPDS for fathers, we could not verify our hypotheses referring to the links between paternal depressiveness at 3 and 6 months, and child temperamental assessment. This remains a direction for future studies. However, as we found similarities between maternal and paternal perceptions of a child's temperament and the temperamental assessment correlated with the severity of depressive symptoms in mothers, we hypothesize that interaction between parent-specific caregiving and child's temperamental characteristics may be related to the risk for postpartum depression. This hypothesis requires further investigation.

Future studies should also address a contribution of child gender to parental perceptions of preterm infants' temperament, which we haven't analyzed as this is outside of the scope of the present study. Research with full-term children points to an infant's gender as a significant predictor of parental assessment of their temperamental characteristics (Else-Quest et al., 2006; Sechi et al., 2020). Far less is known in this respect about preterm infants. In the study by Pesonen et al. (2006), infant perinatal status turned out to be significant for parental assessments of a child's temperament regardless of the birth term. The child's gender did not differentiate parental perceptions either. One might hypothesize that perinatal status, which has a strong impact on early infant and parent experiences, may have more impact on the maternal and paternal assessment of infant behavior and temperament than a child's gender *per se*. This hypothesis may be a direction for future studies.

Another promising direction for further research is the analysis of possible links between the severity and complications of prematurity, and maternal/paternal perceptions of infant temperament and parental mental health. This is especially relevant in light of recent findings on early programming of preterm infants' temperament, via gene methylation processes, due to neonatal exposure to pain and stress related to medical procedures and treatment in the Neonatal Intensive Care Unit (NICU) (Cassiano et al., 2016; Montirosso et al., 2016). Furthermore, interconnections between the severity of preterm infant medical conditions and parental mental health have already been established (Agostini et al., 2014; Carson et al., 2015; Neri et al., 2020). Neonatal data that we have collected and included in our sample characteristics clearly point to the numerous challenges that the infants under study were exposed to, not to mention an additional emotional burden for the parents. A question arises as to the possible role of infants' medical conditions in explaining the links between infant temperament and mothers' and fathers' depressiveness. Future studies should make an attempt at disentangling this important issue.

LIMITATIONS

Finally, several limitations of our study should be addressed. First of all, the size of our sample was rather small, with numerous implications for data analysis and the results. For example, with smaller samples the assumption of variables' distribution normality is often violated, preventing the use of more powerful statistical tests. In addition, a small sample size hinders the inclusion of more variables in the regression analysis, thus limiting the possibilities for testing different, more complex models of relationships among the variables. Furthermore, our sample was characterized by relatively high rates of parents with higher education and medium to high socio-economic status. Hence, the results cannot be generalized to samples with lower SES and education. Apart from that, the study design required the active participation of both parents, which is not a limitation in itself but does narrow the possibilities of extending our results to single-parent families or families with less involved fathers. Although this was outside of our study's scope, a lack of the inclusion of infants' medical conditions in the analyses can certainly be treated as a limitation in generalizing the results. Another limitation is the choice of EPDS as a measure of depressiveness in the case of fathers. As already mentioned, this screening tool, although widely used in other studies with fathers as participants, may not be well suited for discerning specific features of depressive symptoms that are characteristic for men, such as acting out, aggression, psychosomatic complaints, etc. This should be a focus of attention in future studies, with a possible choice of screenings specifically addressed to fathers (Baldoni and Giannotti, 2020), or the additional inclusion of other measures of depressive symptoms such as Center for Epidemiologic Studies Depression Scale (CES-D) or Patient Health Questionnaire-9 (PHQ-9). Furthermore, no information on the levels of depressiveness before childbirth was included in our study, not to mention the history of parental mental health in general. Last but not least, detailed information on the participants' current use of psychotherapy, parental support groups, and other sources of emotional support should have been included.

CONCLUSION AND IMPLICATIONS

Our study points to the importance of taking into account maternal mood along with perceptions of preterm infants' temperament as early as at the age of 3 months CA in the analysis of mothers' level of depressiveness later in the first year of the child's life. Complex, transactional relationships between an infant's temperament as assessed by the parents and parental mental health in the face of prematurity can be postulated and require further investigation. With bigger, multi-site cohorts of preterm infants and their parents and the newest statistical methods, longer-term trajectories of the interplay between the intensity of depressive symptoms and parental perceptions of child reactivity and self-regulation can and should be studied. Further studies should also assume a more fine-grained approach to temperament and, with bigger samples, assess more detailed temperamental profiles of preterm infants on all 14 lower-order dimensions, with closer attention to the severity of prematurity.

In terms of methodology, our results raise a concern regarding the use of the EPDS for measuring depressiveness in fathers of preterm infants. Thus, we add to the already existing call for more gender-sensitive screening tools for the risk of depression.

From a practical, clinical point of view, the associations we have found between infant temperament and maternal depressiveness may be of particular importance for designing assessment, prevention, and intervention measures specifically addressed to parents of prematurely born children. Considering the additional risks to child development and family well-being impinged by compromised parental mental health, psychological support for mothers and fathers of preterm infants should be offered far beyond an infant's stay in the NICU.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of the Faculty of Psychology, University of Warsaw. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GK, EK, and AN: study concept, design, data collection, data analysis, writing the manuscript, critical review, and approved the submitted version.

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Postpartum Depressive Symptoms and Their Selected Psychological Predictors in Breast-, Mixed and Formula-Feeding Mothers

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Background: Although breastfeeding is recommended by WHO and professionals as the most beneficial for newborn babies, many women find it challenging. Previous research yielded ambiguous results concerning the role of breastfeeding in the development of postpartum depression. The study aimed to identify the best predictors of depressive symptoms for each of these feeding method.

Methods: The participants were 151 women (mean age 29.4 yrs; SD = 4.5) who gave birth within the last 6 months and included 82 women classified as breastfeeding, 38 classified as mixed-feeding (breast and bottle), and 31 as formula-feeding. The study had a cross-sectional design using a web-based survey for data collection. The following measures were administered: The Edinburgh Postnatal Depression Scale; Sense of Stress Questionnaire; The Postpartum Bonding Questionnaire; Parenting Sense of Competence Scale; Infant Feeding Questionnaire.

Results: Women in study groups differed in stress, bonding difficulties, and beliefs related to feeding practices and infancy. There were no significant differences in the severity of depressive symptoms, but all mean EPDS scores were above 12. Maternal satisfaction, intrapsychic stress, and concerns about feeding on a schedule were the best predictors of EPDS scores for breastfeeding women. For mixed-feeding – emotional tension, concern about infant's hunger, overeating, and awareness of infant's hunger and satiety cues; while for the formula-feeding group, predictors included emotional tension, bonding difficulties, and such maternal feeding practices and beliefs as concern about undereating, awareness of infant's hunger and satiety cues, concerns about feeding on a schedule and social interaction with the infant during feeding.

Conclusion: Differences in predictors of postpartum depression for study groups suggest that breastfeeding itself may not be a risk for postpartum depression. However, the specificity of maternal experiences with the various types of feeding is related to difficulties promoting postpartum depression. Providing emotional and educational support appropriate for different types of feeding may be an essential protective factor for postnatal depression.

Keywords: postpartum depression, feeding methods, feeding beliefs, feeding behaviors, maternal competencies, stress, mother-child bonding disorders

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INTRODUCTION

Breastfeeding is strongly advised for at least the first 6 months of a child's life. It is advocated for its benefits for infants' health and emotional development (1). Breastfeeding is also considered the main maternal task, and women are expected to choose it and continue as long as possible. A variety of strategies used to promote breastfeeding include those concentrated on the benefits of such a feeding method and those focused on the risk of formula feeding (2). Initiation of breastfeeding usually takes place in postnatal wards. In this process, the support from medical staff plays an important role (3). Despite benefits for children, breastfeeding is also analyzed in the context of its effects for mothers, especially the risk of postpartum depression.

Postpartum depression (PPD) is considered a public health issue. It might affect as many as 9.6% of new mothers in high-income and 19.6% in low-income countries (4). Among factors associated with PPD, breastfeeding is often considered. However, its role either as a risk or as a protective factor is debated. Earlier studies indicated that exclusive breastfeeding increased the risk of PPD (5, 6) and that postpartum depression was more common among breastfeeding mothers (7). Such a view was not universal, as findings from other studies indicated the opposite – there were more cases of PPD among bottle-feeding mothers (8). More recent studies examining the effect of breastfeeding on PPD revealed a different pattern. According to Toledo et al. (9) and Gila-Diaz et al. (10), women who currently breastfed their infants or breastfed them for a more extended time expressed significantly lower PPD risk. In line with this finding are the results from the study by Islam et al. (11) that have pointed to the role of early cessation of exclusive breastfeeding for the increased risk of PPD. The mixed-feeding method might also be related to increased depression symptoms postpartum (12, 13). However, such results are not universal, as Fukui et al. (14) have found that breastfeeding did not affect PPD. The lack of clear breastfeeding – PPD link was also confirmed in the systematic review and meta-analysis conducted by Woldeyohannes et al. (15).

The relationship between breastfeeding and postpartum depression seems well documented, although the type of such association – whether breastfeeding decreases or increases the PPD risk – is still debated. The inclusion of additional factors might help in such a debate. One of such factors that might moderate the association of PPD and infant feeding is maternal breastfeeding self-efficacy. Its low level was associated with higher PPD scores in studies by Zubaran and Foresti (16) and Kossakowska (17). Another factor was maternal positive breastfeeding attitude associated with lower depressive symptoms at 6 months postpartum (18). Yet another factor was the satisfaction with breastfeeding – it was higher in women without PPD symptoms (19). Thus the relationship between breastfeeding and postpartum depression was analyzed in the context of various aspects of breastfeeding (i.e. duration, self-efficacy, positive/negative experiences, or attitudes toward breastfeeding) rather than in the context of the type of feeding itself. It is unclear whether the same factors are related to PPD symptoms for mothers who apply either of three feeding methods: breastfeeding, mixed, or formula feeding. Our study aimed to clarify whether mothers were at similar risk of postpartum depressive symptoms for each of these feeding methods. As the benefits of breastfeeding for maternal bonding were advocated for, we aimed to verify whether the mother-child bond developed differently in either of three feeding methods and whether PPD was similarly connected to maternal feeding beliefs, maternal self-esteem, and stress. Thus we aimed to identify the best predictors of depressive symptoms for each of these feeding methods.

MATERIALS AND METHODS

Study Design

This descriptive web-based cross-sectional study was conducted to identify predictors of postpartum depression for different feeding methods.

Ethical Consideration

The research procedure was performed in accordance with the Helsinki Declaration of Human Rights (20). The study was approved by the university advisory board. As the study was of an informative cross-sectional purely descriptive nature, no formal ethical approval was required under the country's legislation. Participants were informed of the purpose, risks, and benefits of the survey. They were told they could withdraw from the study at any time and for any reason and provided electronic informed consent. Such consent form was prepared following the Ethics Guidelines for Internet Mediated Research (21).

Inclusion Criteria

The following inclusion criteria were applied: at least 19 years of age at the time of admission to the study, giving birth to a healthy child within the last 6 months[1], no past or current clinical diagnosis of any psychiatric disease, including depression. As our study aimed to identify risk factors for postpartum depression depending on whether women are exclusively breastfeeding, mixed or formula milk only, the classification criteria for each of these groups were based on the WHO-recommended definitions. Exclusive breastfeeding was defined as infants being fed with breast milk only, without any additional food or drink, not even water (allowable exceptions were expressed breast milk, oral rehydration solutions, and drops or syrups of vitamins and minerals and medicines) (22). Mixed-feeding (MF) suggested that infants were fed breast milk with formula or complementary food. Formula-feeding (FF) was defined as infants being fed with any formula (23).

Procedure and Data Collection

The presented data were collected from July 2017 to March 2018. Women were recruited through social media (such as Facebook and Instagram) advertisements, information distributed at birth classes or pediatric clinics, and snowball sampling of participants' friends and relatives. Women interested in participating in the

[1]This criterion was set for the purpose of ensuring that mixed feeding or the formula feeding was not related to the introduction of complementary foods after 6 months. According to the WHO guidelines (1), up to the age of 6 months, the infant should be fed only with mother's milk.

study first contacted the researcher by e-mail (the e-mail address was given in the recruitment advertisement). They had to agree to participate by signing an electronic informed consent form. After that, they received a personalized link to the web-based survey.

Initially, a total of 187 mothers were interested in participating in the study. Of these, 31 were rejected at the recruitment stage due to failure to meet the inclusion criteria (i.e. more than 6 months from childbirth, younger than 19 years of age). Of the remaining 156 volunteers, five women did not fully complete questionnaires. Finally, results from 151 mothers (BF: $n = 82$; MF: $n = 38$; FF: $n = 31$) who met the eligibility criteria were included in the analyses.

Measures

Sociodemographic and Perinatal Questionnaire

Sociodemographic and perinatal characteristics included maternal age, level of education, financial status, relationship status, personal health history, number of weeks from childbirth, course of pregnancy, childbirth, and feeding experiences.

Postpartum Depression Symptoms

The Edinburgh Postnatal Depression Scale (EPDS) (24) assessed depressive symptoms among participants. EPDS is a well-validated 10-item self-report scale constructed to measure the intensity of depressive symptoms within the last seven days. Each item is rated on a 4-point scale ranging from 0 to 3. The higher scores indicate greater symptom severity (the Authors recommend a 12/13 cut-off point). Original research reports good internal consistency (24) – Cronbach's alpha = 0.87, which was confirmed in the validation study of the Polish version of EPDS (Cronbach's alpha = 0.91) (25). In the present sample, Cronbach's alpha was 0.83.

Stress Level

Sense of Stress Questionnaire (KPS – Kwestionariusz Postrzeganego Stresu) (26) measured the experienced stress. The questionnaire allows assessing total stress level and its three dimensions: emotional tension, external stress, and intrapsychic stress. KPS is a 27-items self-report measure. Each item is rated on a 5-point scale ranging from 1 (false) to 5 (true). The authors of the questionnaire reported high internal consistency for all scales, ranging from 0.70 to 0.81. In our sample, Cronbach's alpha value for total scores was 0.93.

Mother-Child Bond

The Postpartum Bonding Questionnaire (PBQ) (27) was used to assess the bond between mother and baby. The PBQ is a 25-item self-report instrument. In our study, we used the pre-validated Polish language version of the questionnaire (Bieleninik, unpublished materials). Each item of PBQ is rated on a 6-point scale ranging from 0 to 5. It consists of four subscales: impaired bonding (scale 1), rejection and anger (scale 2), anxiety about care (scale 3), and risk of abuse (scale 4). The total scores can also be calculated, and higher scores suggest poorer bonding. Reliability of PBQ in validation study was satisfactory - Cronbach's alpha for total scores was 0.80 (28, 29) and 0.92 in the current sample. In the present study, the risk of abuse scale results was not analyzed because it is a factor with only two items and the Cronbach's alpha was below the recommended value of 0.70.

Maternal Self-esteem

Parenting Sense of Competence Scale (PSOC) (30, 31) in Polish validated version (32) was used to examine maternal self-esteem on two dimensions – satisfaction and efficacy. PSOC is a self-report scale with 16 items assessed on a 6-point scale (ranging from 1 – strongly agree to 6 – strongly disagree). The satisfaction subscale refers to mothers' anxiety, motivation, and frustration, while the efficacy subscale assesses competence, problem-solving ability, and capability in the maternal role. Higher scores suggest higher competencies. The internal consistency of PSOC is satisfactory. The Cronbach's alpha coefficients for the total score were 0.79 in the original and 0.78 in the current study.

Maternal Feeding Behaviors and Beliefs

Infant Feeding Questionnaire (IFQ) (32) was used to identify maternal feeding practices and beliefs during infancy. IFQ is a 28-item self-report instrument. Items are rated on a 5-point scale, from 0 (never/disagree a lot) to 4 (always/agree a lot). In case of some statements (e.g. "I believed it was important for him to finish all of the formulae in his bottle,") "not applicable" response was added to make IFQ suitable for exclusively breastfeeding mothers. The questionnaire allows to assess maternal feeding behaviors/practices and beliefs on seven dimensions: concern about infant undereating or becoming underweight (factor 1), concern about infant's hunger (factor 2), awareness of infant's hunger and satiety cues (factor 3), concern about infant overeating or becoming overweight (factor 4), feeding infant on a schedule (factor 5), using food to calm infant's fussiness (factor 6), social interaction with the infant during feeding (factor 7). Original development and validation study revealed internal consistency for seven factors from 0.24 to 0.74 (32). Internal consistency on all seven scales in our sample was slightly higher than reported in the original validation study and ranged from 0.41 to 0.74. IFQ was designed to identify maternal feeding behaviors and beliefs during the first 12 months of their children's lives related to children becoming overweight in the second year of life. In the current study, the questionnaire was used to compare feeding attitudes in different feeding type mothers and to assess their predictive role for the occurrence of symptoms of postpartum depression.

Data Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 for Windows. Demographic characteristics were summarized as the mean (standard deviation, SD) for continuous variables and frequency counts (percentages) for categorical variables. The chi-square test was then used to estimate the significance of differences between mothers with different feeding practices. The Shapiro-Wilk test was used to check the normality of distributions for all analyzed variables. Due to the lack of normality of the distribution, the non-parametric Kruskal-Wallis test (with the Dunn's pairwise tests adjusted by the Bonferroni correction) was applied to compare more than two independent groups. Spearman's

correlation coefficient was used to assess a possible association between all continuous variables. Finally, the multivariate linear regression with a backward-elimination approach was used to estimate the predictors of postpartum depression for each type of feeding. For each regression model presented, the VIF (Variance Inflation Factor) value and its tolerance to detect multicollinearity in the regression analysis were determined. A VIF of 1 indicates no predictors of collinearity. The higher the value of VIF, the more significant the correlation of the outcome variable with other variables. According to the recommendation of Vittinghoff et al. (33), it was assumed that the VIF of 10 and more is regarded as very high, indicating strong collinearity of the predictors. In this case, the analyzed model should be corrected. Less liberal assumptions indicate that a VIF value> 5 means moderate multicollinearity (34), which is a cause for concern. The VIF values for the EBF and MF mothers regression models were not greater than 5 (from 1.014 to 1.020 for EBF and 1.014 to 1.246 for the MF group). In the FF group, the VIF value for impaired bonding was 6.858, indicating moderate collinearity based on more restrictive criteria. Therefore, the value of the tolerance coefficient for VIF was checked, which, according to Hair et al. (35), indicates a problem with multicollinearity when it is less than 0.2. In the current study, the tolerance for VIF in each regression model was more than 0.2. Therefore, the impaired bonding predictor was left in the regression model for the FF group. The level of statistical significance for the study was set at $p < 0.05$.

RESULTS

Study Sample Characteristics

One hundred and fifty-one women aged 19 to 41 years (M = 29.4; SD = 4.5) who gave birth within the last 6 months participated in this study. Infants aged between 2 and 24 weeks (M = 17.5; SD = 5.5). Eighty-two women were classified as exclusively breastfeeding (EBF group), 38 were classified as mixed-feeding (breast and bottle) (MF group), and 31 as fully formula-feeding (FF group). According to the Kruskal-Wallis test, there were no differences between feeding groups in terms of women's age ($H_{(2)} = 0.134$; p = 0.935) as well as infants' age ($H_{(2)} = 0.678$; p = 0.935). In the sample, most women were primiparous (59.6%), without previous miscarriages (76.2%), planned pregnancy (78.8%), without complication (74.8%). Most of the participants had skin-to-skin contact with their baby soon after delivery (78.1%), and most women planned to breastfeed before childbirth (90.7%). Chi-square tests indicated a significant difference between the feeding method groups only for the infant's gender (?22,151 = 8.533; $p < 0.05$). In the EBF group, male infants predominated (67.1%), while in the MF and FF group, there were more female infants (55.3 and 58.1%, respectively). Detailed demographical and obstetrics characteristic of the feeding sub-samples is presented in **Table 1**.

Postpartum Depression Symptoms

The mean EPDS scores were 13.4 (SD = 4.2), 12.6 (SD = 4.1), 14.6 (SD = 5.4) for EBF, MF, and FF groups, respectively. There were no significant differences in the severity of postpartum depression symptoms between groups ($H_{(2)} = 1.656$; p = 0.437), but all mean EPDS scores were above 12 cut-off points. The range of EPDS scores for each group is shown in **Figure 1**.

Stress Level, Parental Competencies, and Bonding

The scores for three groups of mothers calculated for the Sense of Stress Questionnaire (KPS), Postpartum Bonding Questionnaire (PBQ), Parenting Sense of Competence Scale (PSOC) as well as Infant Feeding Questionnaire (IFQ) are given in **Table 2**.

A Kruskal-Wallis test indicated differences between the mean ranks of Impaired bonding ($H_{(2)} = 9.272$; p = 0.010), rejection and anger ($H_{(2)} = 15.116$; p = 0.001) and total bonding difficulties scores ($H_{(2)} = 11.033$; p = 0.004) across the groups. Thus, Dunn's pairwise tests were carried out, and the evidence was found for differences between the EBF and FF groups on impaired bonding, rejection, and anger and on the total score ($p < 0.01$, $p < 0.001$, and $p < 0.01$, respectively; with the Bonferroni correction). The median of Impaired bonding scores for EBF mothers was 68.85 compared to 96.77 in the FF mothers. The median of rejection and anger scores for EBF mothers was 65.12 compared to 100.35 in the FF mothers. And the median of total bonding difficulties scores for EBF mothers was 67.72 compared to 98.32 in the FF mothers. There was no evidence for a difference between the other groups and Anxiety about care scores ($H_{(2)} = 5.265$; $p = 0.072$).

Similarly, the use of the Kruskal-Wallis test to compare the three dimensions of stress and overall stress level by feeding method showed that there is a difference between the mean ranks of the emotional tension ($H_{(2)} = 7.201$; $p = 0.027$), intrapsychic stress ($H_{(2)} = 7.063$; $p = 0.029$) and total level of stress across the study groups ($H_{(2)} = 6.963$; $p = 0.031$). According to Dunn's pairwise tests, this difference exists between the EBF and FF groups in emotional tension ($p < 0.05$), intrapsychic stress ($p < 0.05$) and total stress level ($p < 0.05$).

The median score of emotional tension for EBF mothers was 68.69 compared to 93.27 for FF mothers. The median score of intrapsychic stress for EBF mothers was 70.55 compared to 94.50 for FF mothers. Finally, the overall stress level median score for EBF mothers was 69.44 compared to 93.76 for FF mothers. There was no evidence for a difference between the other groups and External stress ($H_{(2)} = 3.407$; $p = 0.182$).

There were no differences in maternal efficacy ($H_{(2)} = 5.096$; $p = 0.078$), maternal satisfaction ($H_{(2)} = 5.658$; $p = 0.059$), and overall competences ($H_{(2)} = 5.048$; $p = 0.080$) measured by PSOC among the study groups.

Feeding Beliefs

According to data presented in **Table 2** women differed in their beliefs related to feeding practices at infancy, but only in case of concern about infant overeating ($H_{(2)} = 14.895$; $p < 0.01$) and feeding infant on a schedule ($H_{(2)} = 26.076$; $p < 0.001$).

For the concern about infant overeating, the differences were found according to Dunn's pairwise tests between EBF and MF groups ($p < 0.05$) and between FF and MF groups ($p < 0.001$). The median of concern about overeating for the MF mothers was the lowest (Mdn = 56.75) in comparison to EBF (Mdn =

TABLE 1 | Characteristic of the study sample by the type of feeding.

	EBF $n = 82$		MF $n = 38$		FF $n = 31$		χ^2 (df)	*p* value
	N	%	*N*	%	*N*	%		
Place of residence							6.900 (4)	0.141
City over 500,000 residents	51	62.2	20	52.6	25	80.6		
City below 500,000 residents	18	22.0	10	26.3	5	16.1		
Countryside	13	15.9	8	21.1	1	3.2		
Education							2.247 (2)	0.325
Higher education	64	78.0	29	76.3	20	64.5		
Marital status							0.281 (2)	0.869
Married	67	81.7	30	78.9	26	83.9		
Assessment of the financial situation							0.670 (2)	0.175
Good/very good	77	93.9	35	92.1	30	96.8		
The number of pregnancies							3.040 (4)	0.551
First	46	56.1	22	57.9	22	71.0		
Second	26	31.7	12	31.6	5	16.1		
Third and more	10	12.2	4	10.5	4	12.9		
Was the pregnancy planned							1.084 (2)	0.582
Yes	65	79.3	28	73.7	26	83.9		
Infant's gender							**8.533 (2)**	**0.014***
Male	55	67.1	17	44.7	13	41.9		
Previous miscarriages							1.048 (2)	0.592
No	65	79.3	27	71.1	23	74.2		
Complications in the last pregnancy							0.446 (2)	0.800
No	63	76.8	28	73.7	22	71.0		
Complications of the last childbirth							2.494 (2)	0.287
No	63	76.8	25	65.8	20	64.5		
Delivery mode							0.560 (2)	0.756
Natural childbirth	45	54.9	20	52.6	19	61.3		
Feeding plan planned before the baby was born							3.387 (4)	0.495
EBF	77	93.9	32	84.2	28	90.3		
MF	3	3.7	3	7.9	1	3.2		
FF	2	2.4	3	7.9	2	6.5		
Skin-to-skin contact immediately after delivery							2.588 (2)	0.274
Yes	67	81.7	30	78.9	21	67.7		

*EBF, exclusively breastfeeding; MF, mixed-feeding (both breast and bottle); FF, formula-feeding. *indicate $p < 0.05$.*

77.96) and FF mothers (Mdn = 99.68). There were no differences between breastfeeding and formula-feeding mothers.

For the Feeding infant on a schedule, Dunn's pairwise tests indicated the differences between FF and EBF ($p < 0.001$), as well as FF and MF groups ($p < 0.01$). The median of Feeding infant on a schedule for the FF mothers was the highest (Mdn = 106.47) in comparison to MF (Mdn = 72.91) and EBF mothers (Mdn = 65.91). There were no differences between breastfeeding and mixed-feeding mothers.

There were also no significant differences in other feeding beliefs such as concern about infant undereating or becoming underweight ($H_{(2)} = 2.563$; $p = 0.278$), concern about infant's hunger ($H_{(2)} = 2.645$; $p = 0.266$), awareness of infant's hunger and satiety cues ($H_{(2)} = 2.147$; $p = 0.342$), using feeding to calm infant's fussiness ($H_{(2)} = 4.949$; $p = 0.084$), and social interaction with the infant during feeding ($H_{(2)} = 1.919$; $p = 0.383$).

Predictors of Postpartum Depression Among EBF, MF, and FF Groups

The multiple linear regression analysis was used to determine predictors of postpartum depression for each infant feeding method group. Before it was performed, Spearman's correlation analyses were conducted in the total sample to determine the relations between the variables considered for inclusion in regression analysis. **Table 3** shows the relationships between the EPDS and the total scores and scores for each dimension of measured variables.

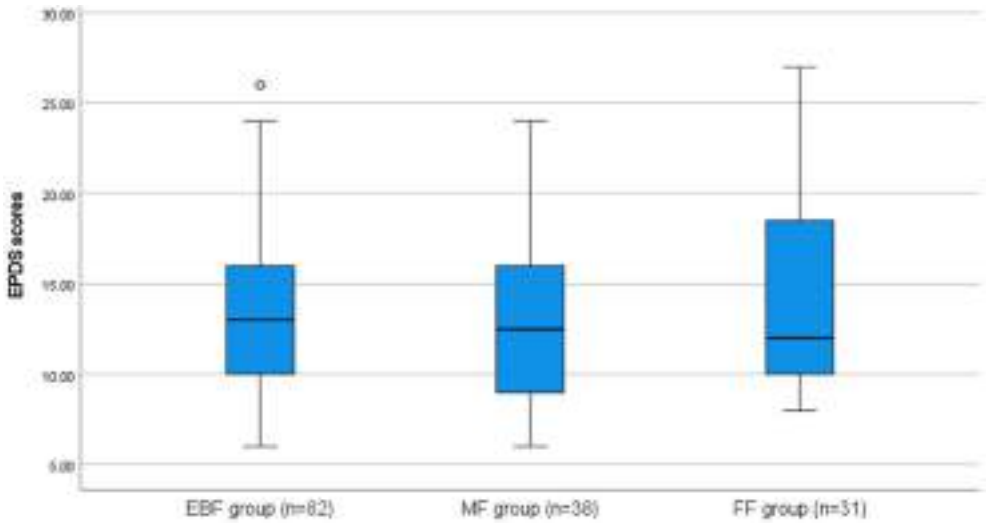

FIGURE 1 | Range, means, and SD of EPDS scores by the feeding method.

TABLE 2 | Descriptive statistics for psychological variables analyzed in the study according to the feeding method.

	EBF $n = 82$			MF $n = 38$			FF $n = 31$		
	M (SD)	Skewness	Kurtosis	M (SD)	Skewness	Kurtosis	M (SD)	Skewness	Kurtosis
Maternal Self-efficacy (PSOC)	33.3 (4.2)	−0.14	−0.82	35.3 (3.5)	−0.29	−0.29	33.6 (4.6)	−0.09	−0.86
Maternal satisfaction (PSOC)	30.5 (4.8)	−0.21	−0.43	30.4 (4.8)	0.15	0.15	28.4 (5.2)	0.28	1.04
Maternal competence (PSOC total)	63.9 (7.1)	−0.03	−0.06	65.8 (6.8)	0.08	0.08	62.0 (7.2)	0.71	−0.31
Emotional tension (KPS)	19.3 (6.8)	0.11	−0.73	20.8 (7.8)	0.06	−1.06	23.5 (8.1)	−0.57	−0.57
External stress (KPS	18.5 (5.1.)	0.39	−0.78	19.1 (6.0)	0.30	−1.08	20.7 (5.5)	0.14	−0.99
Intrapsychic stress (KPS)	15.4 (5.9)	0.69	−0.16	15.8 (6.6)	0.33	−1.32	19.6 (7.9)	0.41	−0.65
Stress level (KPS total)	53.2 (15.9)	0.37	−0.73	55.8 (19.4)	0.24	−1.21	63.9 (19.6)	−0.02	−0.74
Impaired bonding (PBQ)	10.8 (3.7)	0.35	−0.63	12.4 (6.6)	1.67	3.73	14.9 (7.9)	1.51	2.87
Rejection and anger (PBQ)	3.3 (2.6)	0.65	−0.32	5.1 (4.8)	1.27	1.57	7.7 (6.3)	1.19	1.00
Anxiety about care (PBQ)	6.3 (2.9)	1.17	2.12	6.3 (2.8)	0.78	0.60	7.0 (2.6)	0.71	1.15
Bonding difficulties (PBQ total)	29.9 (6.7)	0.35	−0.53	33.2 (12.4)	1.58	2.74	39.2 (14.9)	1.34	2.23
Concern about infant undereating (IFQ)	8.0 (2.4)	0.35	−0.79	8.1 (2.7)	0.23	−0.54	8.9 (2.9)	−0.36	−1.22
Concern about infant's hunger (IFQ)	5.4 (3.8)	1.55	0.98	4.7 (2.6)	1.51	1.56	5.3 (2.6)	1.29	1.25
Awareness of infant's hunger and satiety cues (IFQ)	6.3 (1.9)	0.43	−0.84	5.9 (1.7)	0.35	−1.29	6.7 (2.2)	0.34	−1.10
Concern about infant overeating (IFQ)	4.5 (1.7)	1.03	0.11	3.6 (1.1)	3.09	1.24	5.1 (1.7)	−0.05	−1.47
Feeding infant on a schedule (IFQ)	6.2 (0.9)	−0.04	4.35	6.5 (0.9)	2.27	5.03	7.3 (1.1)	−0.20	−0.86
Using food to calm infant's fussiness (IFQ)	5.5 (1.2)	−0.69	0.65	5.5 (1.2)	−0.11	0.26	4.8 (1.5)	−0.72	−1.01
Social interaction with the infant during feeding (IFQ)	7.9 (2.0)	−0.90	0.04	7.6 (2.0)	−0.35	−1.18	7.5 (1.8)	−0.85	1.35

EBF, exclusively breastfeeding; MF, mixed-feeding (both breast and bottle); FF, formula-feeding.

For the postpartum depression (EPDS scores), the strongest relationships were found between EPDS and maternal satisfaction ($rho = -0.50$; $p < 0.01$), and between EPDS and overall level of maternal competences ($rho = -0.48$; $p < 0.01$). As both correlation coefficients are negative, they indicate that a lower level of maternal satisfaction and overall level of maternal competencies are linked to higher intensity of postpartum depression symptoms.

EPDS scores were also positively but weakly correlated with all stress dimensions such as emotional tension ($rho = 0.35$; $p < 0.01$), external and intapsychic stress ($rho = 0.36$ and $rho = 0.25$, respectively; $p < 0.01$), and overall stress level ($rho = 0.36$; $p < 0.01$). That indicates that the higher stress is related to the higher intensity of postpartum depression symptoms.

A statistically significant but very weak positive correlation was also found between EPDS and impaired bonding ($rho = 0.26$;

TABLE 3 | Correlation of EPDS and other psychological variables scores ($N = 151$).

Variable	Maternal self-efficacy (PSOC)	Maternal satisfaction (PSOC)	Maternal competence (PSOC total)	Emotional tension (KPS)	External stress (KPS)	Intrapsychic stress (KPS)	Stress level (KPS total)	Impaired bonding (PBQ)	Rejection and anger (PBQ)	Anxiety about care (PBQ)	Bonding difficulties (PBQ total)	Concern about infant undereating (IFQ)	Concern about infant's hunger (IFQ)	Awareness of infant's hunger and satiety cues (IFQ)	Concern about infant overeating (IFQ)	Feeding infant on a schedule (IFQ)	Using food to calm infant's fussiness (IFQ)	Social interaction with the infant during feeding (IFQ)
Postpartum Depression (EPDS)	−0.28*	−0.50*	−0.48*	0.35*	0.36*	0.25*	0.36*	0.26*	0.28*	0.24*	0.29*	0.11	0.18*	0.22*	0.07	0.09	0.03	−0.04

*$p < 0.05$.

$p < 0.01$), rejection and anger ($rho = 0.28$; $p < 0.01$), anxiety about care ($rho = 0.24$; $p < 0.01$), and total bonding difficulties ($rho = 0.29$; $p < 0.01$), indicating that bonding difficulties were accompanied by higher intensity of postpartum depression symptoms. Among the behaviors and beliefs about infant feeding, only two were significantly related to EPDS scores: concern about infant's hunger ($rho = 0.18$; $p < 0.05$), and awareness of infant's hunger and satiety cues ($rho = 0.22$; $p < 0.01$). The results indicate that the more mothers were concerned about infant undereating and hunger and were aware of infant's hunger and satiety cues, the higher was the intensity of postpartum depression symptoms. However, these coefficients indicated a very weak correlation.

Multiple linear regression optimized by the backward-elimination method was conducted separately for each group of mothers to assess the predictors of postpartum depression (outcome variable). In all analyses, explanatory variables introduced into the regression equation included: maternal satisfaction, self-efficacy and overall level of maternal competencies, emotional tenses, external and intrapsychic stress and general stress level, impaired bonding, rejection, and anger, anxiety about care, and maternal feeding behaviors and beliefs such as concern about infant undereating or becoming underweight, concern about infant's hunger, awareness of infant's hunger and satiety cues, concern about infant overeating or becoming overweight, feeding infant on a schedule, using food to calm infant's fussiness, and social interaction with the infant during feeding, represented by the relevant scores from administered measures.

Based on regression analysis results, it was found that the model proposed to predict postpartum depression in the EBF group was proven significant ($F_{(3,81)} = 10.347$; $p < 0{,}001$). Three variables: maternal satisfaction, intrapsychic stress, and belief in feeding infants on a schedule, were significant in this model (adjusted $R^2 = 0.257$, $p < 0.01$), and they simultaneously can explain 25.7% of the variance. The results of regression analysis are presented in **Table 4**.

The significant regression analysis model proposed to predict postpartum depression in the MF group (**Table 5**) included such variables as emotional tension, mothers' concerns about infants' hunger, awareness of infant's hunger and satiety cues, and concern about infant overeating ($F_{(4,37)} = 28.259$; $p < 0{,}001$). All these variables simultaneously explain 74.7% of variance of postpartum depression (adjusted $R^2 = 0.747$, $p < 0.01$).

In the regression analysis for the last group – FF mothers, it was found that the model proposed to predict postpartum depression was proven significant ($F_{(7,30)} = 18.391$; $p < 0{,}001$). The model (**Table 6**) included seven variables that altogether explain 80.3 % of variance of postpartum depression (adjusted $R^2 = 0.803$, $p < 0.001$). Thus, the predictors of postpartum depression in the FF group were maternal emotional tension, impaired bonding and anxiety of infant care, concern about infant undereating, awareness of infant's hunger and satiety cues, feeding infant on a schedule, and social interaction with the infant during feeding.

The predictive values of the β coefficient for Emotional tension ($\beta = -0.551$) and Impaired bonding ($\beta = -0.924$) are negative,

TABLE 4 | The multiple regression analysis for variables predicting postpartum depression among exclusively breastfed mothers (EBF group).

Variable in the equation	*B*	*SE B*	*β*	*t*	*p-value* [LL; HL 95% CI]	*VIF*
Maternal satisfaction (PSOC)	−0.353	0.098	−0.349	−3.608	0.001 [−0.549; −0.158]	1.018
Intrapsychic stress (KPS)	0.179	0.069	0.249	2.570	0.012 [0.040; 0.317]	1.020
Feeding infant on a schedule (IFQ)	−1.338	0.540	−0.239	−2.479	0.015 [−2.413; −0.263]	1.014

B, non-standardized regression coefficients; SE B, non-standardized regression coefficients error; β, standardized regression coefficient.

TABLE 5 | The multiple regression analysis for variables predicting postpartum depression among mix-fed mothers (MF group).

Variable in the equation	*B*	*SE B*	*β*	*t*	*p-value* [LL; HL 95% CI]	*VIF*
Emotional tension (KPS)	0.355	0.044	0.678	8.131	<0.001 [0.266; 0.444]	1.014
Concern about infant's hunger (IFQ)	0.692	0.134	0.435	5.159	<0.001 [0.419; 0.964]	1.037
Awareness of infant's hunger and satiety cues (IFQ)	0.542	0.227	0.220	2.386	0.023 [0.080; 1.004]	1.246
Concern about infant overeating (IFQ)	−0.859	0.327	−0.241	−2.623	0.013 [−1.525; −0.193]	1.238

B, non-standardized regression coefficients; SE B, non-standardized regression coefficients error; β, standardized regression coefficient.

TABLE 6 | The multiple regression analysis for variables predicting postpartum depression among formula-fed mothers (FF group).

Variable in the equation	*B*	*SE B*	*β*	*t*	*p-value* [LL; HL 95% CI]	*VIF*
Emotional tension (KPS)	−0.551	0.098	−0.820	−5.628	0.001 [−0.753; −0.348]	3.220
Impaired bonding (PBQ)	−0.924	0.117	−1.675	−7.879	<0.001 [−1.166; −0.681]	6.858
Anxiety about care (PBQ)	1.125	0.224	0.682	5.022	<0.001 [0.662; 1.588]	2.795
Concern about infant undereating (IFQ)	1.639	0.219	0.893	7.467	<0.001 [1.158; 2.093]	2.171
Awareness of infant's hunger and satiety cues (IFQ)	1.743	0.264	0.700	6.603	<0.001 [1.927; 2.289]	1.707
Feeding infant on a schedule (IFQ)	1.980	0.441	0.389	4.491	<0.001 [1.068; 2.893]	1.136
Social interaction with the infant during feeding (IFQ)	−4.327	0.543	−1.441	−7.965	<0.001 [−5.451; −3.203]	4.967

B, non-standardized regression coefficients; SE B, non-standardized regression coefficients error; β, standardized regression coefficient; VIF, value of variance inflation factor.

which indicates that the occurrence of postpartum depression symptoms is explained by the low level of emotional tension and the lack of difficulties in building a mother-infant bond. We refer to this result in the Discussion section.

DISCUSSION

The first aim of our study was to clarify whether, for each of the analyzed feeding methods, mothers were at similar risk of postpartum depressive symptoms. Our findings indicate that there were no significant differences in the severity of such symptoms. These results seem to differ from some of those published so far, which indicate that the infant feeding method may be related to a maternal mood where breastfeeding mothers are less depressed (9, 10) or formula feeding women have higher rates of depression than women who breastfeed (36). Islam et al. (11) analysis show that non-exclusively breastfeeding mothers were more likely to experience depressive symptoms than exclusively breastfeeding mothers. Similarly, in the study

conducted by Takashori (37), there was a significant difference in the prevalence of alleviated EPDS scores between breastfeeding and non-breastfeeding mothers (2.5 and 19.4%, respectively). Our results contradict those findings and indicate that maternal depressive symptoms are not related to the feeding method. However, it should be noted that the relationship between postpartum depressive symptoms and breastfeeding (including exclusive breastfeeding) is ambiguous and might be considered reciprocal – as the experience of depressive symptoms might affect breastfeeding initiation and its duration adversely.

Moreover, the relationship between depressive symptoms and feeding methods is more profound when additional variables are taken into account, such as breastfeeding self-efficacy (17) or breastfeeding intention (38). The study by Bora et al. (38) also indicates a link between breastfeeding and maternal depression, that is mediated by feeding intention, i.e. mothers who planned to breastfeed and went on to do so were around 50% less likely to become depressed than mothers who had planned to, and did not breastfeed. In our study, the mean EPDS scores in all feeding-type groups were above 12, the cut-off point indicating the depression risk. Therefore, they seem to confirm that the causes of depressive symptoms in the postpartum period are more complex and should be searched for among other factors, than the type of feeding.

The previous study has shown that prolactin and oxytocin production during breastfeeding is associated with lower maternal stress levels and enhanced mother-infant bonding (39). Our results indicate that formula-feeding mothers also experience greater emotional tension and higher intrapsychic and general stress than women who breastfeed exclusively. Also, the most increased bonding difficulties (reflected in higher scores on impaired bonding and rejection and anger) occurred in the formula-feeding group, while the lowest was among exclusively breastfeeding women. However, without considering the other factors that may mediate or moderate between feeding patterns and bonding with the baby, our findings should be interpreted with care and caution. Such an approach is supported by Hairston et al. (40) study, indicating that mother-infant bonding is not associated with feeding type. It suggests that if the mother has no other difficulties or mental disorders, breastfeeding is neither a threat to developing a bond with the child nor a protective factor for this bond.

The maternal feeding behaviors and beliefs were only partially connected to how the infant was fed. In the formula-feeding group, concerns related to providing feeding on a schedule were the highest compared to the other groups, while they were the lowest in the exclusive breastfeeding group. However, what seems important is that there were no differences between the exclusively breastfeeding and mix-feeding groups. These results seem to suggest that breastfeeding might be a factor preventing excessive worrying about whether the baby is being fed regularly, and it seems understandable, as breastfeeding should be on-demand. Thus, if the baby signals their hunger and the baby's weight and height increase in line with developmental norms, the mother does not have to additionally control the feeding hours, which reduces the number of concerns about caring for the baby. Perhaps this is one of the factors related to breastfeeding that minimizes the risk of postpartum depressive symptoms in breastfeeding women. Another difference between the groups is maternal concern about infant overeating or becoming overweight. The weakest concerns about overeating occurred in the group of mix-feeding mothers, while the strongest fears were typical for formula-feeding mothers. Similarly, as above, there were no differences between the exclusively breastfeeding and mix-feeding groups. Assuming that the fear of overeating in formula-feeding mothers may be accompanied, on the one hand, by the desire to strictly "stick to the feeding schedule" to ensure the child's proper physical development, and on the other hand, doubts as to whether the feeding times set by the schedule correspond to the baby's hunger, this may also be an explanation of the higher severity of depression among women who feed their children with formula milk.

Our findings concerning identifying the best predictors of depressive symptoms for each feeding method clearly indicate that there are differences in each group of mothers.

A lack of maternal satisfaction emerged as the most crucial predictor of mothers' EPDS scores in regression analysis for exclusively breastfeeding mothers. Although included in the regression equation, maternal satisfaction was previously not differentiated by the type of feeding. Previous studies have indicated a negative correlation between maternal satisfaction and postpartum depression (31, 41, 42). Similarly, in our study negative correlation between those variables was found as well. It may indicate that satisfaction or dissatisfaction associated with maternal role is primarily related to breastfeeding. Possible feeding failures may lower maternal satisfaction and thus increase the risk of depressive symptoms.

Moreover, the recent findings by Avilla et al. (19) indicate a positive association between maternal satisfaction with breastfeeding and PPD symptoms. In the current study, maternal satisfaction in general meaning was measured. However, since its association with postpartum depression did not appear anywhere except in the regression equation for the EBF group, mothers in this group likely assessed their satisfaction through the prism of breastfeeding. Two other predictors of depressive symptoms in this group are intrapsychic stress and concerns about feeding on a schedule. It should be clarified here that intrapsychic stress refers to the result of a woman's confrontation with herself as a mother. Thus, a high level of intrapsychic stress describes experiencing fears, worries, and a sense of losing meaning in life resulting from difficulties in overcoming the challenges of everyday life and achieving goals, tasks, and plans. Adaptation to motherhood, especially in its initial period, is often accompanied by difficulties in implementing tasks resulting from the new role, which may contribute to the occurrence of depressive symptoms. In addition, breastfeeding mothers who experience potential failure (e.g., due to inexperience in breastfeeding or difficulty in latching on to the breast) may be worried about their baby being provided with enough milk, which fosters depression.

In the group of mixed breastfeeding mothers, emotional tension was found among the predictors of postpartum depression. Further factors are related only to maternal concerns and behaviors associated with the course of feedings, such as concern about infant's hunger, awareness of infant's hunger and

satiety cues, and concern about infant overeating. It appears that combining breastfeeding with formula milk may be associated with psychological benefits for mothers. On the one hand, while breastfeeding, they do not experience a feeling of failure as a mother, as they fulfill the social expectation for breastfeeding. Additionally, they share the special closeness that comes from physical contact with the baby during latching on to the breast, even if - as mentioned above - the influence of breastfeeding on the formation of the mother-infant bond is not as strong as it was supposed (40). On the other hand, formula milk gives a certain sense of security when feeding difficulties arise, or the mother gives up breastfeeding for personal reasons. At the same time, it should be noted that in this group - apart from emotional tension - the predictors of postpartum depression were factors related to the physiological aspects of a child's nutrition.

The highest number of predictive factors were found for formula-feeding mothers. Additionally, the direction of the indicated relationships is surprising. In univariate analysis, emotional tension and impaired bonding were positively correlated with maternal postpartum depression. Both emerged as the most important predictors of formula-feeding mothers' EPDS scores in regression analysis, and were negatively related to postpartum depression symptoms. It seems to us that the reasons for such results may be twofold. Firstly, univariate correlation analysis was carried out on the entire group, including all women participating in the study, regardless of the feeding method. Secondly, the role of fear of being judged by the environment should be considered. After having a baby, many women experience social pressure to breastfeed their babies. We assume that mothers nursing formula milk might fear ostracism and stigma when not breastfeeding. Thus, the disclosure of emotional tension and impaired bonding risks is being assessed even more negatively. This explanation seems to confirm the congruent direction of the relationship for another predictor of bonding disorders - anxiety about care. In this case, a higher level of anxiety predicts the onset of symptoms of postpartum depression. It can be assumed that concerning experiencing anxiety about care, there is no need to hide from the environment because caring for a child, also in social perception, is associated with numerous difficulties and challenges, so feeling uncertainty usually does not cause a negative assessment.

The other predictors, as in the MF group of mothers, refer to issues related to the child's feeding and include concern about infant undereating, awareness of infant's hunger and satiety cues, feeding infant on a schedule, and social interactions with the infant during feeding. The relationship between the first three and PPD is positive. It indicates that the greater the anxiety associated with various aspects of formula-feeding, the greater the risk of developing postpartum depression symptoms. It is worth noting that concern about infant undereating appeared in the regression model only in this group (FF group). Such results seem to complement the studies by Anato et al. (43), which indicate that maternal postpartum depression strongly correlates with inappropriate complementary feeding practices of infants and is a strong predictor of infants' undernutrition measured as stunting and underweight. The last predictor of postpartum depression in this group is poor interactions with the baby during feeding. This relationship, although noted in the current study, should, in our opinion, be interpreted with caution in order not to stigmatize formula-feeding mothers as having difficulties in establishing social interactions with the baby and further developing a mother-infant bond. The reason for this may be the presence of other factors that were not controlled in our study. At the same time, if the mother experiences difficulties in interacting with the baby during breastfeeding and sees the reasons for them in the fact that she feeds with bottles and formula milk, and the baby has no physical contact with the breast and breast milk, this may be a factor increasing the feeling of guilt over being an insufficiently good mother and thus aggravating the symptoms of PPD.

Study Limitations and Implications for Further Research

Despite the high importance of identifying predictors of postpartum depression in terms of how the baby is fed in the first 6 months of life, our study has certain limitations that should be considered. First, the cross-sectional nature of the study precludes drawing causal conclusions. Thus, prospective longitudinal studies are needed to explore the association between postpartum depression symptoms and its potential risk among women in groups that differ in the feeding pattern. In addition, these studies should consider the relationship between breastfeeding intention and initiation when controlling for other PPD risk factors. Secondly, as participants were volunteers and the study sample was relatively small, especially when divided into different feeding types groups, and may not represent the total population. Thirdly, the limitations of the online survey as a data collection method (despite our various recruitment strategies) should also be mentioned, particularly sample bias. Those who, for various reasons, do not have access to the Internet, are not users of social media, or are unable to use information technology fluently cannot take part (44). Indeed, in our study, most women were well-educated, married, with satisfying economic situations, and living in large urban areas. This could call into question the generalizability of the findings. On the other hand, as Callegaro et al. (45) recommend, the possibility to complete the set of questionnaires in a safe Internet environment without any pressure may protect from social desirability bias. An additional limitation that should be taken into account is the low value of Cronbach's alpha coefficient for the IFQ factor describing the social interactions of the mother with the baby during feeding. A low value ($\alpha < 0.50$) means low internal consistency, and thus may affect the reliability of the results obtained in the measurement for this factor. In spite of it, we included the obtained results because this factor appeared as a predictor only in the MF mothers group. However, we are aware of this limitation and its consequences. In further studies using IFQ, we recommend checking the factor structure of the questionnaire and, if necessary, determining factors with acceptable reliability for the tested sample. It should be noted as well that in most research EPDS is used usually by the 4^{th} month postpartum. Some women in our study filled in the EPDS at a later time, as our inclusion criteria considered

delivery within the last 6 months. As EPDS Manual (46) presents evidence of the administration of the scale in the additional context (including women in the antenatal period and men) we decided to administer EPDS in our study even if more than usual time might have passed since delivery. As the scale was used as the indicator of depressive symptoms and not as the criterion for depression diagnosis the later time of its administration should not compromise its role as the screening tool. Finally, our study was not based on direct observation of mother-infant dyads during feeding episodes. Thus it relies on maternal self-reports related to feeding concerns and practices. Direct observation of maternal behavior in real feeding interactions might provide additional data on such concerns and possibly on predictors of depression. It is quite likely as a previous study (47) provided evidence on the difference in maternal-infant interactions between breastfeeding and bottle-feeding mothers.

Nevertheless, the study results indicate several vital relationships between postpartum depression symptoms among new mothers depending on how they feed their infants, which should be further investigated in prospective research.

CONCLUSIONS

The differences in predictors of postpartum depression between three various types of infant feeding suggest that breastfeeding itself may not be a risk for postpartum depression. The specificity of maternal experiences with the various type of feeding is related to difficulties that can – in different ways – promote postpartum depression. Thus, providing emotional and educational support appropriate for different types of feeding may be an essential protective factor for postnatal depression. Participation in support groups for new mothers may facilitate the exchange of experiences and concerns and show women the similarity of their problems, while techniques adapted from cognitive-behavioral therapy (CBT) may help to manage maternal distress, what was already advocated for (48). Future investigation should focus not only on whether a woman breastfeeds but also on the importance of feeding methods for an individual and experiences related to feeding.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the university advisory board. As the study was of an informative cross-sectional purely descriptive nature, no formal ethical approval was required under the countries' legislations. Participants were informed of the purpose, risks, and benefits of the survey. They were told they could withdraw from the study at any time and for any reason and provided electronic informed consent. Electronic informed consent was obtained from all subjects involved in the study in accordance with the Ethics Guidelines for Internet-mediated Research by British Psychological Society.

AUTHOR CONTRIBUTIONS

KK and EB-B: conceptualization, resources, data curation, writing—original draft preparation, writing—review and editing, and supervision. KK: methodology, formal analysis, investigation, and project administration. All authors have read and agreed to the published version of the manuscript.

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Physical and Psychological Childbirth Experiences and Early Infant Temperament

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Objective: To examine how physical and psychological childbirth experiences affect maternal perceptions and experiences of early infant behavioural style (temperament).

Background: Unnecessary interventions may disturb the normal progression of physiological childbirth and instinctive neonatal behaviours that facilitate mother–infant bonding and breastfeeding. While little is known about how a medicalised birth may influence developing infant temperament, high impact interventions which affect neonatal crying and cortisol levels could have longer term consequences for infant behaviour and functioning.

Methods: A retrospective Internet survey was designed to fully explore maternal experiences of childbirth and her postnatal perceptions of infant behaviour. Data collected from 999 mother–infant dyads were analysed using Pearson's correlations and multiple analyses of covariance, employing the Bonferroni method of correction to establish initially significant variables. Multiple linear regressions were conducted to determine major perinatal contributors to perceived early infant temperament.

Results: Multiple regression analyses on each of the eight Mother and Baby Scales outcome variables indicated that early infant behavioural style (0–6 months) was largely predicted by subjective maternal states during and post-childbirth, postnatal depression scores, maternal personality traits and infant age. For example, infant age (Beta = 0.440, $p = 0.000$) was the most significant predictor of Alert-Responsive infant behaviour, followed by maternal Postnatal Positive experience (Beta = 0.181, $p = 0.000$). In contrast, depression (EPDS) scores (Beta = 0.370, $p = 0.000$) were the most significant predictor of Unsettled-Irregular infant behaviour, followed by Anxious-Afraid Birth Emotions (Beta = 0.171, $p = 0.000$) and infant age (Beta = –0.196, $p = 0.000$). Mothers also perceived their infants as more Alert-Responsive (Beta = 0.080, $p = 0.010$) and Easier overall (Beta = 0.085, $p = 0.008$) after a Supported birth experience.

Conclusion: Maternal and infant outcomes were influenced by multiple physical and psychological perinatal variables. The mother's subjective experience appeared to be of equal significance to more objective factors (e.g. birthplace/mode). Social support

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enhanced the mother's childbirth experience, benefitting her perceptions of her baby's early temperament. These findings provide further support for current World Health Organisation intrapartum guidelines (2018) on the importance of making childbirth a '*positive experience*' for women.

Keywords: childbirth experience, infant temperament and behaviour, mother-infant bonding and attachment, postnatal anxiety and depression, post-traumatic stress disorder

INTRODUCTION

Rising levels of childbirth interventions have become a major concern in recent years (Dahlen, 2014; NHS England National Maternity Review, 2016; WHO, 2018). The term 'childbirth/obstetric intervention' is used here to refer to any medical interference with the spontaneous physiological progression of 'normal' labour and birth, whether due to medical indication, complications or maternal request. While interventions, such as induction and Caesarean section (C-section), were designed to preserve the life and wellbeing of mother and infant, unnecessary interventions may disturb the progression of normal physiological labour and birth, leading to an increased risk of further interventions and complications (Uvnäs-Moberg et al., 2019). This may impede instinctive neonatal behaviours that facilitate mother–infant bonding and breastfeeding post-birth (Widström et al., 2019). Moreover, obstetric interventions increase the risk of the mother developing postpartum depression (PPD) or childbirth-related post-traumatic stress disorder (CB-PTSD; Ayers et al., 2016; Horsch and Garthus-Niegel, 2019).

Therefore, we know that a negative birth experience can have an impact on postnatal maternal mood. Postnatal depression in turn may lead to emotional and behavioural problems in the infant and young child (Murray et al., 2014, 2018). Although infants whose mothers still manage to engage despite their diagnosis can develop well, children are at an increased risk of having behavioural problems aged 3.5 years and cognitive and psychological problems in adolescence if postnatal depression persists (Netsi et al., 2018). Similarly, evidence shows that CB-PTSD may have negative impacts on mother–infant interactions and maternal sensitivity toward her baby (Figueiredo et al., 2008; Parfitt and Ayers, 2009). As well as being very distressing for women suffering from such perinatal psychological disorders, CB-PTSD in the longer term may have negative consequences for the infant's social–emotional and cognitive development (Garthus-Niegel et al., 2017). Thus, it appears that there could be an indirect pathway between childbirth and infant behaviour *via* postnatal maternal mood.

It is also possible that there are direct links through the inter-connected maternal–infant neurohormonal systems during childbirth (Buckley, 2015; Buckley and Uvnäs-Moberg, 2019). Furthermore, and contrary to previous beliefs (Anand, 2001), we know that the foetus and newborn infant can feel physiological pain and pain-related distress (Anand and Hickey, 1987; Grunau and Craig, 1987; Craig et al., 1993). Certain obstetric interventions, such as assisted birth, have been directly associated with increased levels of neonatal cortisol and crying (Taylor et al., 2000; Gitau et al., 2001). However, comparatively little attention has been given to the possible impacts of childbirth on longer term infant behavioural style, otherwise known as temperament (Thomas and Chess, 1977; Carey and McDevitt, 2016).

Temperament has been defined as '*a quality that varies among individuals, is moderately stable over time and situation, is under some genetic influence, and appears early in life—a coherent profile of behavior, affect (emotional state), and physiology (neurochemistry of the brain)*' (Kagan, 2018, p. 38). It is also '*the behavioral style of the individual, the characteristic pattern of experiencing and reacting to the external and internal environment*'. (Carey and McDevitt, 2016, p. 26). These ideas, which together describe temperament as an interaction between genes and the environment, have become widely accepted. Thus, temperament appears to be based on a combination of biological and psychological or experiential substrates.

Assessing infant temperament independently is an intensive activity and therefore research often relies on maternal self-report, although the mother's mental health post-birth might affect actual or perceived infant temperament. The potential disruptive impact of maternal PPD on normal mother–infant interactions (Murray et al., 2014, 2018; Matthies et al., 2017) may disturb the development of an enduring positive relationship (Feldman, 2017) and subsequent infant behaviour (Feldman et al., 2009). Conceivably, an unsettled infant might exacerbate any maternal mental health issues (Britton, 2011), further affecting mother–infant relationships and longer term infant behaviour.

As well as the finding that newborn infants up to 8 weeks are more likely to be unsettled after an assisted birth (using forceps or ventouse extraction) or emergency C-section (Taylor et al., 2000; Gitau et al., 2001), some authors (Dahlen et al., 2013; Douglas and Hill, 2013) have further suggested that birth complications could affect longer term infant temperament due to the subsequent increase in maternal and foetal cortisol levels (Gitau et al., 1998). This 'stress response' may over-stimulate the neonatal hypothalamic–pituitary–adrenal (HPA) axis, with potentially long-term emotional and behavioural consequences for the infant (Dahlen et al., 2013; Douglas and Hill, 2013).

Nevertheless, research exploring how childbirth may (directly or indirectly) affect early infant behaviour and developing temperament is sparse. Our previous qualitative research explored maternity care providers' perceptions of how this might occur (Power et al., 2019). Our findings highlighted that, while infants may react directly to physical birth events, such as induction, they could also be responding to their mother's subjective birth experience. Infants who experienced obstetric complications or interventions were perceived as more challenging to care for

after birth and often required more comforting. Furthermore, newborns whose mother was distressed or overwhelmed by the birth were also more likely to be unsettled, reflecting her emotional state. This was a possibility originally suggested by Taylor et al. (2000) who argued that a mother's psychological reaction to the birth could potentially mediate her infant's crying and stress response to inoculations at 8 weeks after an assisted birth.

This suggestion led to the current study, which aimed to examine whether mothers' physical and psychological experiences of pregnancy, childbirth and the early postnatal period are associated with perceptions of their infants' behavioural style, while also considering broader maternal demographic factors, personality and postnatal mood.

MATERIALS AND METHODS

Design

A retrospective online survey examining physical and psychological experiences of childbirth, maternal mental health and infant behaviour.

Participants

Mothers were eligible to participate if they were over 18 years of age, had an infant aged 0–30 weeks from a singleton pregnancy, resided in the United Kingdom and had no major health problems. Exclusion criteria were: any major health problems in mother or infant; premature birth (<37 weeks); multiple birth (>1 infant) or low birthweight (<5.5 lb) (WHO, 2022).

Measures

Participants completed an anonymous online survey about their physical and psychological experiences of pregnancy, childbirth and the early postnatal period, alongside a validated measure of perceived infant behavioural style. The survey included items examining the following criteria.

Maternal and Infant Demographic Factors

Maternal age, ethnicity, education, postcode, monthly household income and relationship status were reported by mothers, as well as parity (number of children), infant age, gender, gestational age and birthweight (if known).

Physical Perinatal Factors

Birthplace (hospital, midwife led unit, home), how labour commenced (e.g. induction or spontaneous) and progressed (e.g. acceleration), timings for each labour stage (hours/minutes), birth interventions (e.g. foetal scalp electrode), birth mode (normal, assisted, planned or emergency C-section), pain ratings, pain relief methods (e.g. 'gas and air', pethidine, epidural, water and hypnobirthing) and pre/postnatal complications (e.g., infection, urinary retention) (Stephansson et al., 2016). Items also examined complications, such as foetal distress, meconium in the waters or resuscitation, alongside whether their baby's head was born gently, whether they had immediate skin-to-skin contact and how they first fed and currently feed their baby (breast, expressed or formula).

Psychological Perinatal Factors

Mothers reported how they felt physically and emotionally during pregnancy, childbirth and the postpartum period (e.g. how happy, fearful, energetic or vulnerable they felt). Responses were captured *via* five-point Likert scales (1 = strongly disagree to 5 = strongly agree). Many validated psychological tools, such as the Edinburgh Postnatal Depression Scale (Cox et al., 1987) and the State and Trait Anxiety Inventory (Spielberger et al., 1970), use four-point Likert scales. Thus, the Likert scale is a typical response scale in similar questionnaires that allows for variation between responses to be fully explored.

The subjective measures of pregnancy, birth and postnatal experiences were based on the literature around women's psychological responses to childbirth and the perinatal period. To the best of our knowledge, at the time of designing this survey, there was no single validated tool that could measure the mother's actual experience and emotional responses to her experience throughout the perinatal period. Indeed, although there are some validated tools relating to maternal interpretations of the birth experience, such as the Birth Satisfaction Scale (Martins and Fleming, 2011), which examines the mother's satisfaction with the birth and her care, and a tool by Siassakos et al. (2009) which looks at women's perceptions of their *operative* birth experience, no one tool covered the period with the breadth required. Furthermore, while maternal satisfaction with the birth, including operative birth experiences and the care she receives, are very important, we were specifically interested in the wider potential impacts of the mother's *physical* and *psychological* responses to her pregnancy, birth and postnatal experiences on her baby. Consequently, we developed our own questions with a focus on how the mother felt during each stage of her journey, which we could then compare with her perceptions of her baby's early behavioural style.

Infant Behaviour

Infant behaviour was measured using the Mother and Baby Scales (MABS; Wolke and James-Roberts, 1987). This 63-item questionnaire assesses maternal confidence and self-efficacy alongside the mother's perceptions of specified infant behaviours over the past 7 days. Participants respond *via* six-point Likert scales (0 = not at all to 5 = often/very much) to items, such as '*My baby has settled quickly and easily*' and '*During feeds my baby has tended to fuss and cry*'. The scale contains eight sub-scales: Alert-Responsive (A-R); Unsettled-Irregular (U-I); Easiness (E); Alertness during Feeds (ADF); Irritable during Feeds (IDF); Lack of Confidence in Caretaking (LCC) and Breastfeeding (LCBF); and Global Confidence (GC) (see **Table 1** for definitions and distribution of MABS scores).

The MABS have high levels of reliability and validity (Wolke, 1995) and have also demonstrated validity in relation to newer self-report infant temperament questionnaires (Oates et al., 2018). While originally designed for newborn infants, research has employed the MABS with infants aged 0–6 months (Oates et al., 2018), as well as older infants (Field et al., 2002), and in research exploring relationships between infant behaviour, maternal confidence, postpartum depression and low-self-esteem (Denis et al., 2012).

TABLE 1 | Mother and baby scales (MABS) and distribution of scores.

MABS area of interest *(abbreviations)*	Description of measure	Mean	SD	Range (min-max)
General	**General categories**			
Alert-responsive (A-R)	Infant alertness, attentiveness and communicativeness with caregivers	39.27	5.13	30.00 (16–46)
Unsettled-irregular (U-I)	Crying/fussing + regularity of eating, sleeping and elimination routines	49.63	12.79	69.00 (19–88)
Lack of confidence in caretaking (LCC)	How capable the mother feels when caring for her baby	32.40	9.12	60.00 (10–70)
Overall impressions	**Maternal perceptions of her baby's behaviour and her own confidence**			
Easiness (easy)	How calm, alert and settled the infant appears overall	24.28	2.30	12.00 (16–28)
Global confidence (GC)	How confident the mother feels about coping; general anxiety level	17.74	1.88	8.00 (13–21)
Feeding	**Infant behaviour during feeding**			
Alert during feeds (ADF)	Alertness during feeds	17.09	4.46	23.00 (6–29)
Irritable during feeds (IDF)	Whether the infant feeds reluctantly or with difficulty or irritability	19.18	7.05	39.00 (7–46)
Lack of confidence in breastfeeding (LCBF)	If breastfeeding, whether experienced as problematic (e.g. tension, conflicting advice, technique and birth impacts)	16.49	6.27	38.00 (7–45)

N = 999 for all MABS items except lack of confidence in breastfeeding where it is 855.

Maternal Personality and Postnatal Wellbeing

Heritability factors are known to play an important role in personality development and subsequent behaviour (McAdams and Olson, 2010), and postnatal maternal mood is known to affect infant behaviour (Glover et al., 2018). Therefore, three measures of maternal trait, state and postnatal mood were collected:

a. Maternal personality was measured using the Ten Item Personality Inventory (TIPI). The TIPI (Gosling et al., 2003) is a short version of Goldberg's original hundred-item Big Five Inventory (1992) that self-assesses the personality traits of Extroversion, Conscientiousness, Openness (to new experiences), Agreeableness and Emotional Stability *via* seven-point Likert scales (1 = 'disagree strongly'; 7 = 'agree strongly'). Gosling et al. (2003) established the TIPI's construct validity and test–retest reliability, and it has been widely used in public health research (e.g. Johnston and Brown, 2013).
b. Maternal mental health was measured using the 10-item Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) which assesses symptoms of maternal postnatal mood disorder over the previous 7 days. The EPDS presents 10 multiple choice statements (e.g. '*I have been able to laugh and see the funny side of things*'), with check box answers on a four-point Likert scale (1 = As much as I ever could/did; 4 = No never/hardly at all). Mothers with scores of 13 or above are considered high risk. The sensitivity, internal consistency, validity and reliability of the EPDS as an effective screening instrument for postnatal depression are well established, and it is widely used in both research and clinical practice in the United Kingdom and elsewhere (e.g., Shrestha et al., 2016).
c. Current maternal anxiety state may have affected the mother's interpretation of childbirth and her baby's behaviour. Therefore the six-item short form of the 'State' scale of Spielberger's State and Trait Anxiety Inventory (STAI; Spielberger et al., 1970) was included to measure mothers' current anxiety levels (Marteau and Bekker, 1992). This short version of the STAI State includes six short statements regarding emotional state (e.g. '*I feel calm/tense/content/upset*') on a four-point Likert scale (1 = not at all; 4 = very much). Positive items are reverse scored and therefore higher scores are indicative of higher anxiety levels. This tool is considered a reliable and valid measure of anxiety states (Marteau and Bekker, 1992).

Procedure

This study was designed and implemented in accordance with the ethical standards of the Declaration of Helsinki, developed by the World Medical Association (2018). A University Department of Psychology Research Ethics Committee granted ethical approval for the study.

Participants were recruited between June 2014 and March 2017 *via* advertisements on United Kingdom mother–infant sites (e.g. bounty.com) and social media (e.g. Facebook and Twitter). The study took place on SurveyMonkey®. On accessing the anonymous online survey, participants were presented with an information page outlining the purpose of the study and eligibility criteria, as well as data protection and confidentiality arrangements. Following electronic consent, participants were asked to complete standard demographic information before beginning the survey. Participation took approximately 15–30 min. Afterwards, participants were thanked and presented with a debrief page outlining where to seek further information and professional support if needed.

Data Analysis

Raw data were imported from SurveyMonkey™ into SPSS version 26 (SPSS United Kingdom Ltd). Each of the four questionnaires incorporated in the survey was first scored according to their individual instructions. Multiple statements concerning pregnancy or postnatal complications were summed and included as continuous scores rather than individual items. Continuous, nominal and ordinal data could then be quantified and interpreted *via* the associated tools for analysis: correlations and ANOVAs to establish similarities, differences and interactions of infant behaviour in relation to the birth experience and surrounding factors. Finally, multiple linear regressions were used to establish predictors. Our analysis plan is further detailed below.

To begin, factor analyses were carried out on participant-rated statements concerning their subjective perceptions of the perinatal experience. This technique was applied where multiple statements rated on a five-point Likert scale had the potential for reduction to fewer items: subjective maternal physical and psychological experiences of pregnancy, childbirth and the early postnatal period and overall maternal perceptions of the birth experience (e.g. positive/supported/directed). Mothers had responded to questions and a list of potential answers concerning their personal perceptions of the perinatal period (e.g. '*How did you feel during pregnancy/your birth*'). Principal components analyses (PCA) were conducted using Direct Oblimin rotation methods, as recommended by Field (2009) for inter-correlated socio- or psychological data. Factors with an eigenvalue over one were used; computed factors were saved as regression scores, named and used in subsequent data analyses.

To determine which confounding variables required controlling for, Pearson's bivariate correlations (with two-tailed hypotheses) and Multivariate Analyses of Variance (MANOVAs) were first performed on the sociodemographic and infant characteristics data. Thus, infant characteristics (current infant age, gender, gestational age at birth and birth weight) and sociodemographic variables (maternal age, education, ethnicity, household income, relationship status and number of children) were considered. Significantly associated maternal and infant factors were subsequently controlled for in all further statistical analyses.

Dummy coded variables (yes = 1, no = 0) were created in SPSS where required. Pearson's partial correlations, controlling for covariates and excluding cases listwise, were conducted where independent variables reflected either ratio or interval data. MANCOVAs were carried out for categorical independent variable data, using the *a priori* Bonferroni correction method of analysis, with all means comparisons chosen in advance (Howell, 2012, 2016). This method of planned comparisons produces equal or slightly more conservative results to planned *post-hoc* tests, while having the advantage of allowing covariates to remain in the equation. An alpha level of <0.05 was used to assess the results of all correlations and MANOVAs.

Monthly household income was categorised using the five income brackets taken from the Office for National Statistics (ONS) division of quintiles from 2014 to 2016, corresponding with the survey design and data collection period (Office for National Statistics, 2017). For multiple linear regression analyses, household incomes were further divided into dichotomous variables: < or >£2,700/month, corresponding to the approximate median gross household income of £2,700/month in the same period (Office for National Statistics, 2019).

Certain factors had the potential to be bi-directional in causality. However, placing perceived infant behaviour and maternal confidence as the speculated outcome variables was integral to the overall study aims: to explore how physical (objective) birth events, psychological variables and the subjective maternal experience of childbirth may influence mother-reported infant behaviour. A predictive form of analysis was chosen to establish the strongest independent variables and to indicate which factors might explain the greatest proportion of the total variance in infant behavioural scores and maternal confidence when all other factors were held constant. Multiple linear regression was used with the forced entry method, excluding cases pairwise to maximise data retention.

Finally, therefore, multiple linear regressions were performed for each of the eight MABS items. In line with Field (2009), multicollinearity was managed in a second regression run for each outcome variable to reduce the inherent inter-correlations often found in psychological data (Field, 2009). Given the large sample size, outliers were only removed if they had an exceptionally large residual (over 30), a leverage value greater than three times the average, or were considered to significantly influence the regression line. Cook's distance was then employed as a measure of outlier influence and interpreted as satisfactory when <1 in all remaining cases. The Durbin–Watson test was used to establish independence of residuals (Field, 2009). The adjusted R^2 is reported throughout.

RESULTS

Initially, 1,152 mothers completed the survey although 153 did not meet the inclusion criteria, leaving 999 in the analysis. Mean maternal age on completion of the survey was 32 years ($SD = 4.2$; range 19–44 years); mean infant age was 15.31 weeks ($SD = 7.48$; range 0–30 weeks). **Table 2** presents further demographic information.

Infant Behaviour

For inclusion in analyses, participants must have completed the Mother and Baby Scales (MABS)—999 mothers who met all the inclusion criteria completed the scale, although only 855 completed the breastfeeding section, corresponding to the breastfeeding data. The MABS data were analysed and coded according to instructions (Brazelton and Nugent, 1995).

Associations between the MABS scores, infant characteristics and maternal demographic background were explored. Infant Age, Infant Gender, Gestational Age, Birth Weight, Maternal Age, Maternal Education and Number of Children were significantly associated with MABS scores and therefore controlled for in all further analyses.

Physical Perinatal Factors, Perceived Infant Behaviour and Maternal Confidence

Pregnancy and Postnatal Complications

The number of complications experienced by mothers during pregnancy and postnatally were computed. Altogether, 37% experienced at least one pregnancy complication (mean 0.51; SD 0.78; range 0–5) and 50.3% at least one postnatal complication (mean 0.91; SD 1.20; range 0–7). Partial Pearson's correlations identified significant positive associations between the number of pregnancy complications and Unsettled-Irregular infant behaviour as well as Lack of Confidence in Caretaking and Breastfeeding. Similarly, Number of Postnatal Complications had significant positive relationships with Unsettled-Irregular and Irritable during Feeds and negative associations with maternal confidence measures (**Table 3**). Therefore, where more

TABLE 2 | Maternal demographic background.

Indicator	Group	*N*	%
Age	19–24	48	4.8
	25–29	217	21.7
	30–34	454	45.4
	35–39	243	24.3
	40–44	32	3.2
Ethnicity	White (British/Irish/Other)	948	94.9
	Mixed/Multiple ethnic group	20	2.0
	Asian/Asian British	13	1.3
	Black African/Black Caribbean	11	1.1
	Other ethnic group	4	0.4
Education (highest level)	No formal qualifications	2	0.2
	GCSE or equivalent	32	3.2
	A level or equivalent	108	10.8
	Degree or equivalent	450	45.0
	Vocational qualification	45	4.5
	Postgraduate or equivalent	361	36.1
Relationship status	Single	19	1.9
	Partner (not living with)	6	0.6
	Cohabiting	261	26.1
	Married	712	71.3
Number of children	1	544	54.5
	2	346	34.6
	3	81	8.1
	4	21	2.1
	5+	4	0.4
Household income*	Less than £1,000/month	25	2.5
	£1,000–£1700/month	103	10.3
	£1701–£2,700/month	229	22.9
	£2,701–£4,200/month	335	33.5
	£4,201 or more/month	206	20.6
United Kingdom area of residence	England	735	73.6
	Wales	130	13.0
	Scotland	67	6.7
	Northern Ireland	27	2.7

Gross household income brackets before tax and after benefits or savings (Office for National Statistics, 2017). Actual percentages (%) are reported for each demographic variable. Where percentages do not total 100, the discrepancy is due to missing data.

perinatal complications were experienced, infant behaviour was reported as more Unsettled, Irregular and Irritable and the mother felt less confident.

Birthplace

Mothers were asked where they had given birth [hospital, midwife led unit (MLU) or home]. A MANCOVA was conducted to highlight any significant differences between birth settings. Bonferroni tests highlighted that infants were rated as less Alert and Responsive after a hospital birth compared to a MLU or home birth: Hospital $M = 39.07$, $SD = 5.26$; MLU $M = 39.70$, $SD = 4.70$; Home $M = 39.83$, $SD = 4.75$ [F (2, 799) = 3.258, $p = 0.039$]. Additionally, infants were rated as more Unsettled and Irregular after a hospital or MLU birth than after a homebirth: Hospital $M = 50.58$, $SD = 12.57$; MLU $M = 50.60$, $SD = 12.56$; Home $M = 45.06$, $SD = 10.13$ [F (2, 799) = 6.788, $p = 0.001$]. Finally, mothers reported lower Lack of Confidence in Breastfeeding after homebirths rather than hospital or MLU births: Hospital $M = 17.06$, $SD = 6.61$; MLU $M = 16.43$, $SD = 5.66$; Home $M = 13.58$, $SD = 4.09$ [F (2, 799) = 6.753, $p = 0.001$].

Start of Labour

A series of MANCOVAs were conducted for each start of labour method in relation to MABS. Notably, infants were significantly less Unsettled-Irregular after Spontaneous Labour ($N = 489$) than by any means of induction: Yes Spontaneous Labour $M = 49.43$, $SD = 12.67$; No Spontaneous Labour $M = 50.67$, $SD = 11.99$ [F (1, 812) = 3.79, $p = 0.05$]. Infants were also less Alert-Responsive after a Sweep ($N = 179$) than after No Sweep: Yes Sweep $M = 38.64$, $SD = 5.50$; No Sweep $M = 39.43$, $SD = 5.00$ [F (1, 812) = 5.77, $p = 0.016$].

Mothers reported *lower* Lack of Confidence in Breastfeeding after Spontaneous Labour: Yes Spontaneous Labour $M = 15.74$, $SD = 6.01$; No Spontaneous Labour $M = 17.68$, $SD = 6.49$ [F (1, 812) = 16.87, $p = 0.000$]. Equally, mothers reported *greater* Lack of Confidence in Breastfeeding after a Membrane Sweep: Yes Membrane Sweep $M = 17.98$, $SD = 7.00$; No Membrane Sweep $M = 16.13$, $SD = 6.01$ [F (1, 812) = 5.99, $p = 0.015$]. Similarly, they reported greater Lack of Confidence in Breastfeeding when Induced by Pessary and Drip ($N = 60$): Yes Pessary and Drip $M = 19.45$, $SD = 8.01$; No Pessary and Drip $M = 16.30$, $SD = 6.07$ [F (1, 812) = 11.26, $p = 0.001$].

Duration of Stages of Labour

Pearson's partial correlations were conducted to assess associations between the length of each labour stage (latent, active and 2nd stage) and MABS scores. Length of Latent Stage was inversely associated with Alert-Responsive infant behaviour, while lengths of Active Stage and Second Stage were positively associated with Unsettled-Irregular infant behaviour and Lack of Confidence in Caretaking and Breastfeeding. Overall, infants were generally less alert, more unsettled and mothers less confident, after a longer labour (see **Table 3**).

Labour Interventions

Mothers responded to a series of questions about interventions that may have occurred during labour. These included whether they had experienced Artificial Rupture of Membranes (ARM), (continuous) Electronic Foetal Monitoring (EFM), Foetal Scalp Electrode (FSE) or a Foetal Blood Sample (FBS). **Table 4** highlights significant differences in MABS outcomes between mothers who reported the presence or absence of these interventions. ARM, acceleration of labour, continuous EFM and FSE were linked to an increase in perceived Unsettled-Irregular infant behaviours, while mothers who experienced ARM also reported their infants as being more Irritable during Feeds. In addition, mothers had greater Lack of Confidence in Caretaking and Breastfeeding after ARM, acceleration of labour, continuous EFM and FSM.

Birth Mode

A series of MANCOVAs assessed differences in perceived infant behaviour and maternal confidence according to Birth Mode. Infants were most likely to be Unsettled-Irregular after Assisted Birth (see **Table 5**). In addition, mothers felt a greater Lack of Confidence in Caretaking after Assisted Birth or Emergency Caesarean Section and greater Lack of Confidence in Breastfeeding after Assisted Birth.

TABLE 3 | Pregnancy and postnatal complications, stages of labour and MABS.

Factor	Pregnancy complications	Postnatal complications	Stages of labour		
			Latent stage (h) $n = 687$	Active stage (h) $n = 714$	2nd stage (min) $n = 750$
Alert-responsive	−0.016, $p = 0.613$	0.032, $p = 0.322$	−0.101, $p = 0.009^{**}$	0.022, $p = 0.565$	0.029, $p = 0.438$
Unsettled-irregular	0.103, $p = 0.001^{**}$	0.066, $p = 0.041^{*}$	0.045, $p = 0.240$	0.113, $p = 0.003^{**}$	0.099, $p = 0.007^{**}$
Lack of confidence in caretaking	0.140, $p = 0.000^{***}$	0.082, $p = 0.011^{*}$	0.022, $p = 0.561$	0.127, $p = 0.001^{**}$	0.104, $p = 0.005^{**}$
Easiness	−0.070, $p = 0.030^{*}$	−0.009, $p = 0.789$	−0.017, $p = 0.662$	−0.053, $p = 0.162$	−0.049, $p = 0.188$
Global confidence	−0.074, $p = 0.021^{*}$	−0.086, $p = 0.008^{**}$	−0.044, $p = 0.255$	−0.032, $p = 0.392$	−0.068, $p = 0.066$
Alert during feeds	0.010, $p = 0.762$	−0.009, $p = 0.774$	0.033, $p = 0.396$	0.018, $p = 0.630$	−0.019, $p = 0.609$
Irritable during feeds	0.105, $p = 0.001^{**}$	0.086, $p = 0.008^{**}$	0.049, $p = 0.205$	0.022, $p = 0.562$	−0.013, $p = 0.717$
Lack of confidence in breastfeeding	0.088, $p = 0.011^{*}$	0.140, $p = 0.000^{***}$	−0.007, $p = 0.872$	0.095, $p = 0.019^{*}$	0.114, $p = 0.004^{**}$

*Pearson's r: $p < 0.05$.
**Pearson's r: $p < 0.01$.
***Pearson's r: $p < 0.001$.

Pain Ratings and Pain Relief During Labour

Pearson's partial correlations found that Pain Ratings during labour were positively associated with Unsettled-Irregular infant behaviour and inversely associated with overall infant Easiness. Pain Ratings were also associated with lower maternal confidence ratings—both globally and in relation to caretaking (**Table 6**).

In terms of pain relief, nitrous oxide (Entonox) was positively associated with Unsettled-Irregular infant behaviour and Lack of Confidence in Breastfeeding; Pethidine was positively associated with Irritable during Feeds and Lack of Confidence in Caretaking and inversely associated with Global Confidence; Spinal Block was associated with Lack of Confidence in Breastfeeding; while Epidural was associated with less perceived infant Easiness, more Unsettled-Irregular behaviour and lower maternal Confidence in Caretaking and Breastfeeding (**Table 6**).

Natural Methods of Pain Relief During Labour and Birth

Partial correlations highlighted significant associations between certain natural methods of pain control and infant behaviour. Hypnobirthing was inversely associated with Unsettled-Irregular, $r\ (234) = -0.068$, $p = 0.033$. Reflexology during labour was positively associated with perceived infant Easiness [$r\ (9) = 0.071$, $p = 0.026$] and Acupuncture during labour was inversely associated with Alert during Feeds [$r\ (6) = -0.071$, $p = 0.026$]. Thus, infants were reported as 'easier' after Reflexology and as more 'relaxed during feeds' after Acupuncture. However, both Acupuncture ($n = 8$, 0.8%) and Reflexology ($n = 11$, 1.1%) had small sample sizes, undermining the reliability of these findings. Therefore, Reflexology and Acupuncture were excluded from further analyses.

Tearing and Episiotomy

A MANCOVA employing the Bonferroni correction explored differences between mothers who had or had not experienced a 'Tear or Episiotomy'. Notably, Episiotomy was too small a group to include as a stand-alone item ($n = 4$, 0.4%). Although there were no significant differences in perceived infant behaviour, differences in maternal Global Confidence were seen between 'No Tear' ($n = 187$) and 'Tear or Episiotomy' ($n = 812$): No Tear $M = 18.20$, $SD = 1.76$; Tear or Episiotomy $M = 17.63$, $SD = 1.86$ [$F\ (1,\ 815) = 10.351$, $p = 0.001$].

Foetal and Neonatal Distress

MANCOVAs were conducted between MABS and foetal or neonatal distress signals. Significant increases were seen for Unsettled-Irregular and Irritable during Feeds after Foetal Distress (**Table 7**). Maternal confidence scores were also lower after Foetal Distress. No significant differences were seen for any MABS infant behaviour items after Meconium in Waters, although Confidence in Caretaking and Breastfeeding scores were significantly lower. Global Confidence was less after Resuscitation.

Gentle Birth of Head

Mothers were asked to recall how gently their baby's head had been born on a five-point Likert scale (1 = strongly disagree; 5 = strongly agree). This factor was then transformed into a dichotomous variable: 'Gentle Birth of Head' or 'Other' (a non-gentle birth of the head). Infants were perceived as more Alert-Responsive, less Unsettled-Irregular and Easier overall after a Gentle Birth. In addition, Gentle Birth of Head led to an increase in Global Confidence scores alongside a decrease in Lack of Confidence in Breastfeeding scores (**Table 7**).

Skin-to-Skin Care

MANCOVAs were conducted to differentiate between infants who did or did not have immediate skin-to-skin contact with their mother post-birth. Infants who experienced immediate 'Skin-to-Skin' contact were reported as less Unsettled-Irregular: Yes Skin to Skin $M = 49.63$, $SD = 12.39$; No Skin to Skin $M = 54.30$, $SD = 11.88$ [$F\ (1,\ 812) = 11.826$, $p = 0.001$]. Infants were also reported as Easier overall: Yes Skin to Skin $M = 24.25$, $SD = 2.29$; No Skin to Skin $M = 23.55$, $SD = 2.21$ [$F\ (1, 812) = 6.491$, $p = 0.011$].

Overall, mothers reported less Lack of Confidence in Caretaking if they had experienced immediate skin-to-skin contact with their baby post-birth: Yes Skin to Skin $M = 31.96$, $SD = 8.55$; No Skin to Skin $M = 34.96$, $SD = 7.72$ [$F\ (1, 812) = 4.773$, $p = 0.029$]. They also reported less Lack of Confidence in

TABLE 4 | Labour interventions and MABS.

Factor MABS	Labour intervention—M (SD) and significance														
	ARM *n* = 209			Acceleration *n* = 191			EFM *n* = 363			FSE *n* = 159			FBS *n* = 46		
	Yes	No	*Sig.*	Yes	No	*Sig.*	Yes	No	*Sig.*	Yes	No	*Sig.*	Yes	No	*Sig.*
A-R	38.66 (5.66)	39.47 (4.92)	*F* (1,779) = 3.11, $p = 0.078$	39.08 (5.29)	39.32 (5.10)	*F* (1, 790) = 0.38, $p = 0.537$	39.23 (5.06)	39.30 (5.22)	*F* (1,788) = 0.67, $p = 0.413$	39.30 (5.13)	39.30 (5.16)	*F* (1,740) = 0.34, $p = 0.562$	38.80 (4.89)	39.38 (5.07)	*F* (1,728) = 0.14, $p = 0.708$
U-I	51.42 (12.90)	49.29 (12.16)	*F* (1,779) = 4.59, $p = 0.032^{*}$	51.62 (12.67)	49.35 (12.32)	*F* (1, 790) = 4.73, $p = 0.030^{*}$	51.66 (12.43)	48.67 (12.34)	*F* (1,788) = 11.93, $p = 0.001^{**}$	52.01 (11.79)	49.45 (12.71)	*F* (1,740) = 4.74, $p = 0.030^{*}$	53.26 (12.87)	49.67 (12.47)	*F* (1,728) = 2.40, $p = 0.122$
LCC	33.49 (9.36)	31.73 (8.30)	*F* (1,779) = 4.67, $p = 0.031^{*}$	34.14 (8.50)	31.56 (8.52)	*F* (1, 790) = 5.06, $p = 0.025^{*}$	33.67 (8.77)	31.04 (8.22)	*F* (1,788) = 10.16, $p = 0.001^{**}$	33.58 (8.79)	31.83 (8.48)	*F* (1,740) = 1.13, $p = 0.287$	35.46 (8.18)	31.90 (8.51)	*F* (1,728) = 4.23, $p = 0.040^{*}$
Easy	24.28 (2.33)	24.17 (2.28)	*F* (1,779) = 0.40, $p = 0.532$	24.16 (2.25)	24.20 (2.31)	*F* (1, 790) = 0.09, $p = 0.761$	24.15 (2.17)	24.23 (2.40)	*F* (1,788) = 0.50, $p = 0.481$	24.22 (2.36)	24.20 (2.30)	*F* (1,740) = 0.03, $p = 0.872$	24.09 (2.15)	24.18 (2.30)	*F* (1,728) = 0.01, $p = 0.927$
GC	17.71 (1.85)	17.74 (1.88)	*F* (1,779) = 0.00, $p = 0.952$	17.54 (1.91)	17.80 (1.84)	*F* (1, 790) = 1.09, $p = 0.297$	17.66 (1.88)	17.81 (1.86)	*F* (1,788) = 0.46, $p = 0.496$	17.75 (1.79)	17.78 (1.88)	*F* (1,740) = 0.20, $p = 0.655$	17.22 (2.04)	17.78 (1.87)	*F* (1,728) = 2.39, $p = 0.122$
ADF	16.64 (4.26)	16.90 (4.51)	*F* (1,779) = 0.25, $p = 0.618$	16.86 (4.23)	16.77 (4.50)	*F* (1, 790) = 0.17, $p = 0.680$	17.02 (4.36)	16.59 (4.48)	*F* (1,788) = 1.48, $p = 0.225$	16.80 (4.17)	16.86 (4.47)	*F* (1,740) = 0.17, $p = 0.679$	17.09 (4.49)	16.84 (4.42)	*F* (1,728) = 0.273, $p = 0.601$
IDF	20.07 (7.25)	18.92 (6.62)	*F* (1,779) = 4.09, $p = 0.044^{*}$	19.09 (6.80)	19.25 (6.82)	*F* (1, 790) = 0.48, $p = 0.490$	19.43 (7.04)	19.07 (6.70)	*F* (1,788) = 0.10, $p = 0.750$	19.87 (6.82)	19.10 (6.84)	*F* (1,740) = 1.06, $p = 0.304$	20.19 (6.50)	19.15 (6.83)	*F* (1,728) = 0.19, $p = 0.661$
LCBF	18.07 (7.00)	15.87 (5.85)	*F* (1,779) = 12.95, $p = 0.000^{***}$	18.43 (6.62)	15.84 (6.02)	*F* (1, 790) = 12.62, $p = 0.000^{***}$	17.86 (7.01)	15.43 (5.34)	*F* (1,788) = 19.11, $p = 0.000^{***}$	17.35 (7.06)	16.15 (5.97)	*F* (1,740) = 1.90, $p = 0.169$	19.00 (7.17)	16.30 (6.17)	*F* (1,728) = 4.83, $p = 0.028^{*}$

*MABS factors are defined in **Table 1**.*

**Multivariate analysis of covariance F ratios: $p < 0.05$.*

***Multivariate analysis of covariance F ratios: $p < 0.01$.*

****Multivariate analysis of covariance F ratios: $p < 0.001$.*

TABLE 5 | Birth mode and MABS.

Factor	Mode of birth—mean (SD)				
	Normal ***n*** **= 646**	**Assisted** ***n*** **= 147**	**Planned C-section** ***n*** **= 66**	**Emergency C-section** ***n*** **= 136**	**Significance**
A-R	39. 21 (5.19)	39.68 (4.43)	38.90 (5.55)	39.18 (5.35)	F (3, 802) = 0.69, p = 0.559
U-I	49.01 (12.14)	52.52 (13.25)	51.43 (12.07)	51.47 (12.61)	F (3, 802) = 3.20, p = 0.023*
LCC	31.18 (8.34)	34.96 (8.69)	31.75 (8.78)	34.57 (8.29)	F (3, 802) = 4.352, p = 0.005**
Easy	24.21 (2.31)	24.42 (2.37)	23.79 (2.20)	24.03 (2.09)	F (3, 802) = 1.28, p = 0.279
GC	17.85 (1.79)	17.42 (2.07)	17.51 (1.98)	17.51 (1.87)	F (3, 802) = 1.56, p = 0.196
ADF	16.56 (4.37)	17.56 (4.34)	17.90 (4.95)	16.67 (4.33)	F (3, 802) = 2.74, p = 0.042*
IDF	19.01 (6.45)	20.06 (7.72)	19.53 (7.56)	19.32 (7.48)	F (3, 802) = 0.31, p = 0.817
LCBF	15.8 (5.7)	19.2 (8.3)	17.0 (5.9)	17.5 (6.1)	F (3, 802) = 7.07, p = 0.000***

MABS items are defined in ***Table 1****.*
**Multivariate analysis of covariance F ratios: p < 0.05.*
***Multivariate analysis of covariance F ratios: p < 0.01.*
****Multivariate analysis of covariance F ratios: p < 0.001.*

TABLE 6 | Pain ratings, pain relief and MABS.

Factor	Pain ratings and pain relief						
	Pain level ***n*** **= 955**	**No meds.** ***n*** **= 79**	**G and A** ***n*** **= 696**	**Pethidine** ***n*** **= 141**	**Spinal** ***n*** **= 112**	**Epidural** ***n*** **= 224**	**General anaesthetic** ***n*** **= 12**
A-R	−0.049, p = 0.131	0.021, p = 0.506	−0.056, p = 0.081	−0.037, p = 0.256	−0.018, p = 0.572	−0.029, p = 0.375	−0.001, p = 0.972
U-I	0.142, p = 0.000***	−0.025, p = 0.430	0.073, p = 0.022*	0.056, p = 0.083	0.029, p = 0.375	0.109, p = 0.001**	0.038, p = 0.238
LCC	0.085, p = 0.009**	−0.035, p = 0.271	0.047, p = 0.141	0.090, p = 0.005**	0.043, p = 0.185	0.156, p = 0.000***	0.057, p = 0.075
Easy	−0.070, p = 0.032*	0.044, p = 0.167	−0.049, p = 0.126	0.008, p = 0.808	0.034, p = 0.292	−0.075, p = 0.020*	−0.008, p = 0.801
GC	−0.073, p = 0.026*	0.003, p = 0.930	−0.033, p = 0.299	−0.072, p = 0.024*	−0.058, p = 0.070	−0.037, p = 0.249	0.046, p = 0.151
ADF	−0.013, p = 0.683	0.031, p = 0.328	−0.041, p = 0.197	0.014, p = 0.660	0.012, p = 0.710	−0.003, p = 0.923	0.034, p = 0.294
IDF	0.055, p = 0.092	−0.048, p = 0.135	0.021, p = 0.505	0.068, p = 0.034*	0.021, p = 0.521	0.039, p = 0.223	0.029, p = 0.374
LCBF	0.016, p = 0.657	−0.012, p = 0.546	0.073, p = 0.035*	−0.020, p = 0.559	0.072, p = 0.038*	0.148, p = 0.000***	0.034, p = 0.326

MABS items are defined in ***Table 1****; No meds., no pain relief and G and A, gas and air.*
**Pearson's r: p < 0.05.*
***Pearson's r: p < 0.01.*
****Pearson's r: p < 0.001.*

Breastfeeding after immediate skin-to-skin contact with their baby: Yes Skin to Skin M = 16.37, SD = 6.16; No Skin to Skin M = 18.90, SD = 7.43 [F (1, 812) = 8.493, p = 0.004].

Feeding Method: First Feed

The sample consisted of 882 (88.3%) mothers who initiated breastfeeding and 117 (11.7%) who began feeding by any other method, such as syringe fed, formula or expressed bottle fed. Therefore, to facilitate further analyses, First Feed was dichotomised into two groups: Breastfed ('breastfed') and Other ('expressed', 'formula' or 'other'). In a MANCOVA for First Feed and MABS, perceptions of Unsettled-Irregular infant behaviours increased if the First Feed was 'Other': First Feed Breastfed M = 49.56, SD = 12.27; Other M = 54.06, SD = 13.26 [F (1, 811) = 5.436, p = 0.020].

Current Feeding Method

Current Feed responses were likewise dichotomised: 'Currently Breastfed' and 'Other'. The sample consisted of 850 participants (85.1%) who were currently breastfeeding, while 146 (14.6%) were feeding by another method (e.g. formula). A MANCOVA was conducted for Current Feeding Method and MABS. Infants were less Alert during Feeds if currently breastfeeding: Currently Breastfed M = 16.73, SD = 4.36; Other M = 20.05, SD = 5.37 [F (1, 812) = 5.339, p = 0.021]. Mothers also understandably had *lower* Lack of Confidence in Breastfeeding if they were currently breastfeeding their baby: Currently Breastfed M = 16.45, SD = 6.20; Other M = 20.33, SD = 8.64 [F (1, 812) = 3.901, p = 0.049].

Subjective and Psychological Factors, Infant Behaviour and Maternal Confidence

As outlined in the Data Analysis section, PCA with Direct Oblimin rotation methods were used to analyse multiple subjective statements regarding mothers' personal experiences of pregnancy, childbirth and the postnatal period, as well as her overall perceptions of the birth experience.

As there was no one validated scale that covered individual maternal responses to the whole perinatal period, subjective

TABLE 7 | Foetal distress signals, gentle birth of head and MABS.

Factor M (SD)	Foetal distress Yes *n* = 194 M(SD)			Meconium in waters Yes *n* = 173 M(SD)			Resuscitation Yes *n* = 57 M(SD)			Gentle birth of head Yes *n* = 369 other *n* = 630 M(SD)		
	Yes	No	Sig.	Yes	No	Sig.	Yes	No	Sig.	Yes	Other	Sig.
A-R	39.56 (4.84)	39.19 (5.18)	F (1, 812) = 0.835, p = 0.361	39.39 (4.71)	39.23 (5.20)	F (1, 812) = 0.041, p = 0.839	39.32 (5.13)	39.26 (5.12)	F (1, 812) = 0.027, p = 0.870	39.71 (4.91)	38.98 (5.23)	F (1, 811) = 4.747, p = 0.030*
U-I	54.41 (13.22)	48.97 (12.02)	F (1, 812) = 21.168, p = 0.000***	51.21 (13.39)	49.68 (12.20)	F (1, 812) = 2.612, p = 0.106	52.94 (12.35)	49.75 (12.39)	F (1, 812) = 3.811, p = 0.051	47.51 (11.77)	51.44 (12.56)	F (1, 811) = 16.636, p = 0.000***
LCC	34.83 (8.90)	31.58 (8.35)	F (1, 812) = 12.018, p = 0.001**	34.23 (8.35)	31.74 (8.51)	F (1, 812) = 4.959, p = 0.026*	32.77 (6.88)	32.12 (8.62)	F (1, 812) = 0.647, p = 0.421	30.80 (8.03)	32.99 (8.73)	F (1, 811) = 5.551, p = 0.019*
Easy	24.08 (2.32)	24.22 (2.28)	F (1, 812) = 0.348, p = 0.555	23.96 (2.19)	24.25 (2.31)	F (1, 812) = 2.903, p = 0.089	23.55 (2.51)	24.24 (2.27)	F (1, 812) = 4.245, p = 0.040	24.47 (2.29)	24.03 (2.27)	F (1, 811) = 6.110, p = 0.014*
GC	17.19 (1.97)	17.86 (1.81)	F (1, 812) = 13.928, p = 0.000***	17.59 (1.89)	17.77 (1.85)	F (1, 812) = 0.849, p = 0.357	17.19 (2.18)	17.77 (1.83)	F (1, 812) = 4.903, p = 0.027*	18.08 (1.71)	17.53 (1.91)	F (1, 811) = 11.706, p = 0.001**
ADF	16.53 (4.22)	16.85 (4.45)	F (1, 812) = 0.667, p = 0.414	16.25 (4.32)	16.90 (4.42)	F (1, 812) = 2.888, p = 0.090	16.00 (4.03)	16.84 (4.43)	F (1, 812) = 1.362, p = 0.243	16.75 (4.44)	16.82 (4.40)	F (1, 811) = 0.068, p = 0.794
IDF	20.74 (8.02)	18.91 (6.51)	F (1, 812) = 6.911, p = 0.009**	19.72 (7.15)	19.13 (6.77)	F (1, 812) = 0.898, p = 0.344	19.85 (6.29)	19.19 (6.86)	F (1, 812) = 0.909, p = 0.341	18.52 (6.01)	19.67 (7.27)	F (1, 811) = 3.033, p = 0.082
LCBF	19.38 (8.14)	15.92 (5.63)	F (1, 812) = 14.704, p = 0.000***	18.65 (7.39)	16.11 (5.95)	F (1, 812) = 11.937, p = 0.001**	17.00 (6.54)	16.50 (6.27)	F (1, 812) = 0.451, p = 0.502	15.18 (5.22)	17.37 (6.72)	F (1, 811) = 13.307, p = 0.000***

*MABS items are defined in **Table 1**.*

**Multivariate analysis of covariance F ratios: $p < 0.05$.*

***Multivariate analysis of covariance F ratios: $p < 0.01$.*

****Multivariate analysis of covariance F ratios: $p < 0.001$.*

statements around the mother's sense of her own physical and psychological wellbeing during the three major stages (pregnancy, childbirth and the postnatal period) were derived from the literature. Questions relating to women's subjective birth and perinatal experiences were analysed using principal components analysis (PCA) and explained 62%–68% of the variance for each period, as well as for maternal overall perceptions of her birth experience. This compares well to Foley et al. (2014) validation of the Birth Memories and Recall Questionnaire (The Birth MARQ), which examines the relationship between childbirth memories and postpartum mood disorders, explaining 64% of the variance. It also compares favourably to the Childbirth Questionnaire (Dencker et al., 2010) which accounted for 54% of the total variance, with a focus on maternal satisfaction with the birth rather than on her emotional responses to birth and perinatal experiences. Our results showed good internal consistency and reliability between factors stemming from the PCA (Field, 2009) and were therefore considered fit for use in subsequent analyses in relation to infant behaviour.

Subjective pregnancy states included 'felt happy and excited/anxious and fearful about the birth' (labelled Positive Pregnancy Emotions) and 'had plenty of energy/felt tired and drained' (labelled Positive Physical Pregnancy). In both cases, a higher score indicated a more positive subjective experience. Subjective birth states included: Positive ('strong, happy, energised and focused'); Neglected ('abandoned' or 'ignored'); Aware-Alert ('aware' and 'alert'); and Anxious-Afraid ('anxious, afraid, vulnerable and overwhelmed') Birth Emotions.

These subjective pregnancy and childbirth factors in relation to MABS are presented in **Table 8**. Pearson's partial correlations identified numerous significant associations between subjective experiences of pregnancy, childbirth and the postnatal period and reported infant behaviour. Positive maternal experiences were associated with easier infant behaviour, while negative experiences were associated with more challenging infant behaviour (**Table 8**).

Next, Pearson's partial correlations were conducted between subjective maternal postnatal states, the mother's overall perceptions of her birth experience and her baby's temperament. Feeling physically and mentally positive post-birth and having an overall positive, supported experience were associated with maternal perceptions of easier and more settled infant behaviour. Equally, feeing distressed postnatally and having a more directed birth experience overall were associated with more difficult, unsettled infant behaviour (see **Table 8**). Notably, the factor Maternal Postnatal Distress comprised nine items describing negative emotions, such as anger, guilt, confusion and distress. Conversely, Postnatal Positive comprised eight items describing positive postnatal emotions, such as euphoria, exhilaration, relief and pride.

Personality, Postnatal Mood and Current State

Maternal personality (TIPI), postnatal mood (EPDS) and current state (STAI State) were significantly associated with MABS items. For example, a more positive mood, feeling calm and traits, such as Openness to new experiences and Emotional Stability, were associated with easier infant behavioural style (see **Table 9**).

Perinatal Predictors of Infant Behaviour and Maternal Confidence

As described above, multiple physical and psychological factors were associated with MABS. The next section examines the factors that best predicted infant behaviour and maternal confidence when all other significant variables were held constant. STAI State was highly correlated with EPDS (>0.7). Given that STAI State probably reflected the mother's current (postnatal) mood, it was decided that EPDS would remain. Consequently, STAI State was removed in the following analyses to reduce multicollinearity.

Regression Analyses for MABS

As multiple physical and psychological factors were associated with MABS, the next section examines the factors that best predicted perceived infant behaviour and maternal confidence. Multiple linear regression analyses were conducted for each MABS item to predict maternal reports of infant behaviour and her own self-reported confidence. Significant perinatal factors for infant behaviour and maternal confidence—as highlighted by the Pearson's correlations and MANCOVAs described above—were entered into the final regression models.

MABS items were split into infant behaviours (**Table 10**) and maternal confidence (**Table 11**). Infant behaviour was predicted by a combination of (current) infant age, maternal demographic background, subjective physical and psychological experiences of childbirth and the postnatal period (e.g. Anxious-Afraid Birth Emotions or Postnatal Physical Wellbeing) and psychological factors (e.g. EPDS scores), while more objective physical factors, such as Number of Postnatal Complications, did not remain significant in the final regression model. For example, Alert-Responsive infant behaviour was predicted by higher infant age, maternal openness, lack of maternal higher education, having a supported experience and feeling positive post-birth (**Table 10**). Therefore, infants generally grew more settled, alert and responsive with increased age, regardless of their birth experience, although infant 'easiness' or how unsettled they were perceived as was still affected by maternal mood (EPDS scores) and personality, as can be seen in the regression table for infant behaviour (**Table 10**).

The predominant predictors of maternal confidence were whether she had given birth before, known as parity (Number of Children), her subjective perinatal experience (e.g. Postnatal Positive) and psychological factors, such as EPDS and Emotional Stability (**Table 11**).

In summary, **Figure 1** highlights the main factors identified as having the strongest associations and predictive values for infant behavioural outcomes. It emphasises the equal importance of physical and psychological factors at all stages of the perinatal journey and the ability of appropriate levels of social and professional support to shield and protect mother and infant from the immediate and potentially long-lasting impacts of a negative birth experience.

DISCUSSION

The aim of this study was to examine how maternal physical and psychological experiences of pregnancy, childbirth and the early postnatal period may be associated with the mother's

TABLE 8 | Subjective pregnancy states, birth emotions, postnatal states, overall birth experience and MABS.

Factor	Pregnancy states $n = 981$		Birthing emotions $n = 944$				Postnatal states $n = 945$			Overall birth experience $n = 908$		
	Positive emotions	Positive physical	Positive	Neglected	Aware-alert	Anxious-afraid	Postnatal distress	Postnatal positive	Postnatal physical wellbeing	Positive	Supported	Directed
A-R	0.085, $p = 0.009^{**}$	0.067, $p = 0.039^{*}$	0.189, $p = 0.000^{***}$	−0.126, $p = 0.000^{***}$	0.064, $p = 0.052$	−0.078, $p = 0.018$	−0.121, $p = 0.000^{***}$	0.243, $p = 0.000^{***}$	0.058, $p = 0.079$	0.123, $p = 0.000^{***}$	0.165, $p = 0.000^{***}$	−0.075, $p = 0.026^{*}$
U-I	−0.241, $p = 0.000^{***}$	−0.202, $p = 0.000^{***}$	−0.197, $p = 0.000^{***}$	0.148, $p = 0.000^{***}$	−0.094, $p = 0.004^{**}$	0.297, $p = 0.000^{***}$	0.259, $p = 0.000^{***}$	−0.208, $p = 0.000^{***}$	−0.256, $p = 0.000^{***}$	−0.207, $p = 0.000^{***}$	−0.112, $p = 0.001^{**}$	0.138, $p = 0.000^{***}$
LCC	−0.128, $p = 0.000^{***}$	−0.111, $p = 0.001^{**}$	−0.100, $p = 0.002^{**}$	0.136, $p = 0.000^{***}$	−0.120, $p = 0.000^{***}$	0.196, $p = 0.000^{***}$	0.221, $p = 0.000^{***}$	−0.110, $p = 0.001^{**}$	−0.149, $p = 0.000^{***}$	−0.178, $p = 0.000^{***}$	−0.104, $p = 0.002^{**}$	0.126, $p = 0.000^{***}$
Easy	0.156, $p = 0.000^{***}$	0.091, $p = 0.005^{**}$	0.148, $p = 0.000^{***}$	−0.088, $p = 0.008^{**}$	0.028, $p = 0.392$	−0.160, $p = 0.000^{***}$	−0.164, $p = 0.000^{***}$	0.193, $p = 0.000^{***}$	0.119, $p = 0.000^{***}$	0.143, $p = 0.000^{***}$	0.081, $p = 0.015^{*}$	−0.044, $p = 0.192$
GC	0.229, $p = 0.000^{***}$	0.171, $p = 0.000^{***}$	0.187, $p = 0.000^{***}$	−0.079, $p = 0.016^{*}$	0.093, $p = 0.005^{**}$	−0.205, $p = 0.000^{***}$	−0.188, $p = 0.000^{***}$	0.213, $p = 0.000^{***}$	0.211, $p = 0.000^{***}$	0.176, $p = 0.000^{***}$	0.089, $p = 0.008^{**}$	−0.049, $p = 0.143$
ADF	0.030, $p = 0.354$	0.071, $p = 0.027^{*}$	0.068, $p = 0.037^{*}$	−0.049, $p = 0.137$	0.019, $p = 0.558$	−0.040, $p = 0.224$	−0.041, $p = 0.210$	0.074, $p = 0.024^{*}$	0.058, $p = 0.076$	0.041, $p = 0.217$	0.051, $p = 0.132$	0.015, $p = 0.658$
IDF	−0.172, $p = 0.000^{***}$	−0.180, $p = 0.000^{***}$	−0.110, $p = 0.001^{**}$	0.056, $p = 0.091$	−0.095, $p = 0.004^{**}$	0.134, $p = 0.000^{***}$	0.136, $p = 0.000^{***}$	−0.137, $p = 0.000^{***}$	−0.172, $p = 0.000^{***}$	−0.092, $p = 0.006^{**}$	−0.047, $p = 0.160$	0.034, $p = 0.318$
LCBF	−0.136, $p = 0.000^{***}$	−0.048, $p = 0.163$	−0.056, $p = 0.110$	0.165, $p = 0.000^{***}$	−0.100, $p = 0.004^{**}$	0.200, $p = 0.000^{***}$	0.178, $p = 0.000^{***}$	−0.070, $p = 0.048^{*}$	−0.206, $p = 0.000^{***}$	−0.179, $p = 0.000^{***}$	−0.072, $p = 0.045^{*}$	0.155, $p = 0.000^{***}$

*MABS items are defined in **Table 1**.*

**Pearson's r: $p < 0.05$.*

***Pearson's r: $p < 0.01$.*

****Pearson's r: $p < 0.001$.*

TABLE 9 | Maternal personality (TIPI), postnatal mood (EPDS), current state (STAI State) and MABS.

Measure	Factor	Big 5 personality traits (TIPI) *N* = 953					EPDS total *N* = 922	State anxiety *N* = 947
		Extroversion	Agreeable	Conscientious	Emotional stability	Openness		
MABS	Alert-responsive	0.075, $p = 0.023^{*}$	0.095, $p = 0.004^{**}$	0.043, $p = 0.190$	0.065, $p = 0.047^{*}$	0.129, $p = 0.000^{***}$	–0.123, $p = 0.000^{***}$	–0.158, $p = 0.000^{***}$
	Unsettled-irregular	–0.122, $p = 0.000^{***}$	–0.134, $p = 0.000^{***}$	–0.162, $p = 0.000^{***}$	–0.291, $p = 0.000^{***}$	–0.150, $p = 0.000^{***}$	0.412, $p = 0.000^{***}$	0.396, $p = 0.000^{***}$
	Lack of confidence in caretaking	–0.084, $p = 0.010^{*}$	–0.050, $p = 0.128$	–0.102, $p = 0.002^{**}$	–0.240, $p = 0.000^{***}$	–0.008, $p = 0.814$	0.380, $p = 0.000^{***}$	0.315, $p = 0.000^{***}$
	Easiness	0.082, $p = 0.012^{*}$	0.105, $p = 0.001^{**}$	0.068, $p = 0.037^{*}$	0.165, $p = 0.000^{***}$	0.170, $p = 0.000^{***}$	–0.172, $p = 0.000^{***}$	–0.221, $p = 0.000^{***}$
	Global confidence	0.133, $p = 0.000^{***}$	0.116, $p = 0.000^{***}$	0.149, $p = 0.000^{***}$	0.303, $p = 0.000^{***}$	0.141, $p = 0.000^{***}$	–0.350, $p = 0.000^{***}$	–0.335, $p = 0.000^{***}$
	Alert during feeds	0.084, $p = 0.010^{*}$	0.004, $p = 0.895$	0.138, $p = 0.000^{***}$	0.070, $p = 0.033^{*}$	0.079, $p = 0.016^{*}$	–0.088, $p = 0.008^{**}$	–0.072, $p = 0.028^{*}$
	Irritable during feeds	–0.091, $p = 0.005^{**}$	–0.104, $p = 0.001^{**}$	–0.082, $p = 0.012^{*}$	–0.209, $p = 0.000^{***}$	–0.117, $p = 0.000^{***}$	0.310, $p = 0.000^{***}$	0.286, $p = 0.000^{***}$
	Lack of confidence in breastfeeding	–0.093, $p = 0.008^{**}$	–0.052, $p = 0.142$	–0.027, $p = 0.448$	–0.145, $p = 0.000^{***}$	–0.013, $p = 0.716$	0.227, $p = 0.000^{***}$	0.181, $p = 0.000^{***}$

**Pearson's r: p < 0.05.*
***Pearson's r: p < 0.01.*
****Pearson's r: p < 0.001.*

TABLE 10 | Predictors of infant behaviour (0–6 months).

MABS	Variables	Unstandardised coefficients		Standardised coefficients	*t*	*p*
		B	*SEB*	*β*		
Alert-responsive	Constant	33.941	0.825		41.165	0.000
	Infant age	0.302	0.020	0.440	14.884	0.000
	Higher education	–1.198	0.432	–0.082	–2.772	0.006
	Postnatal positive	0.929	0.161	0.181	5.784	0.000
	Experience supported	0.409	0.159	0.080	2.565	0.010
	Maternal openness	0.348	0.132	0.079	2.642	0.008
Unsettled-irregular	Constant	48.555	1.040		46.695	0.000
	Infant age	–0.331	0.051	–0.196	–6.653	0.000
	Anxious-afraid BE	2.180	0.419	0.171	5.204	0.000
	Number of PN complications	–0.323	0.330	–0.031	–0.981	0.327
	EPDS total	0.902	0.079	0.370	11.400	0.000
Easiness	Constant	22.958	0.434		52.900	0.000
	Infant age	0.054	0.010	0.176	5.476	0.000
	Higher education	–0.547	0.213	–0.083	–2.576	0.010
	Postnatal positive	0.306	0.078	0.133	3.923	0.000
	Birth partner and birth companion	0.551	0.208	0.085	2.645	0.008
	Maternal openness	0.244	0.065	0.124	3.754	0.000
	EPDS total	–0.046	0.015	–0.104	–3.054	0.002
Alert during feeds	Constant	14.785	0.836		17.692	0.000
	Infant age	0.139	0.018	0.234	7.566	0.000
	Higher education	–1.000	0.401	–0.078	–2.494	0.013
	Breastfed currently	–1.904	0.396	–0.151	–4.810	0.000
	Conscientiousness	0.498	0.119	0.129	4.183	0.000
Irritable during feeds	Constant	24.086	1.603		15.026	0.000
	Infant age	–0.179	0.030	–0.190	–6.035	0.000
	Birth weight	–1.363	0.419	–0.102	–3.254	0.001
	PN physical wellbeing	–0.697	0.233	–0.099	–2.991	0.003
	EPDS total	0.380	0.045	0.279	8.443	0.000

B, unstandardised coefficient; SEB, standard error of unstandardised coefficient; β, standardised beta; BE, birth emotions; PN, postnatal; and EPDS, Edinburgh postnatal depression scale (total scores).

perceptions of her infant's behaviour, taking into account broader maternal demographic factors, postnatal mood and personality. The study had several notable findings, and numerous aspects of childbirth and the perinatal period were associated with perceived early infant behaviour. Although certain childbirth interventions, complications, birth mode and types of pain

TABLE 11 | Predictors of maternal confidence and self-efficacy (MABS).

MABS	Variables	Unstandardised coefficients		Standardised coefficients	*t*	*p*
		B	*SEB*	*β*		
Global confidence	Constant	17.481	0.313		55.887	0.000
	Postnatal positive	0.215	0.063	0.114	3.445	0.001
	PN physical wellbeing	0.200	0.063	0.106	3.179	0.002
	Emotional stability	0.172	0.050	0.133	3.427	0.001
	EPDS total	−0.075	0.015	−0.206	−5.116	0.000
Lack of confidence in caretaking	Constant	30.836	0.770		40.052	0.000
	Number of children	−1.987	0.361	−0.166	−5.503	0.000
	EPDS total	0.650	0.053	0.369	12.253	0.000
Lack of confidence in breastfeeding	Constant	30.293	0.775		39.103	0.000
	Number of children	−1.824	0.359	−0.153	−5.081	0.000
	Meconium in waters	2.579	0.726	0.107	3.554	0.000
	EPDS total	0.624	0.053	0.357	11.828	0.000

B, unstandardised coefficient; SEB, standard error of unstandardised coefficient; and β, standardised beta.

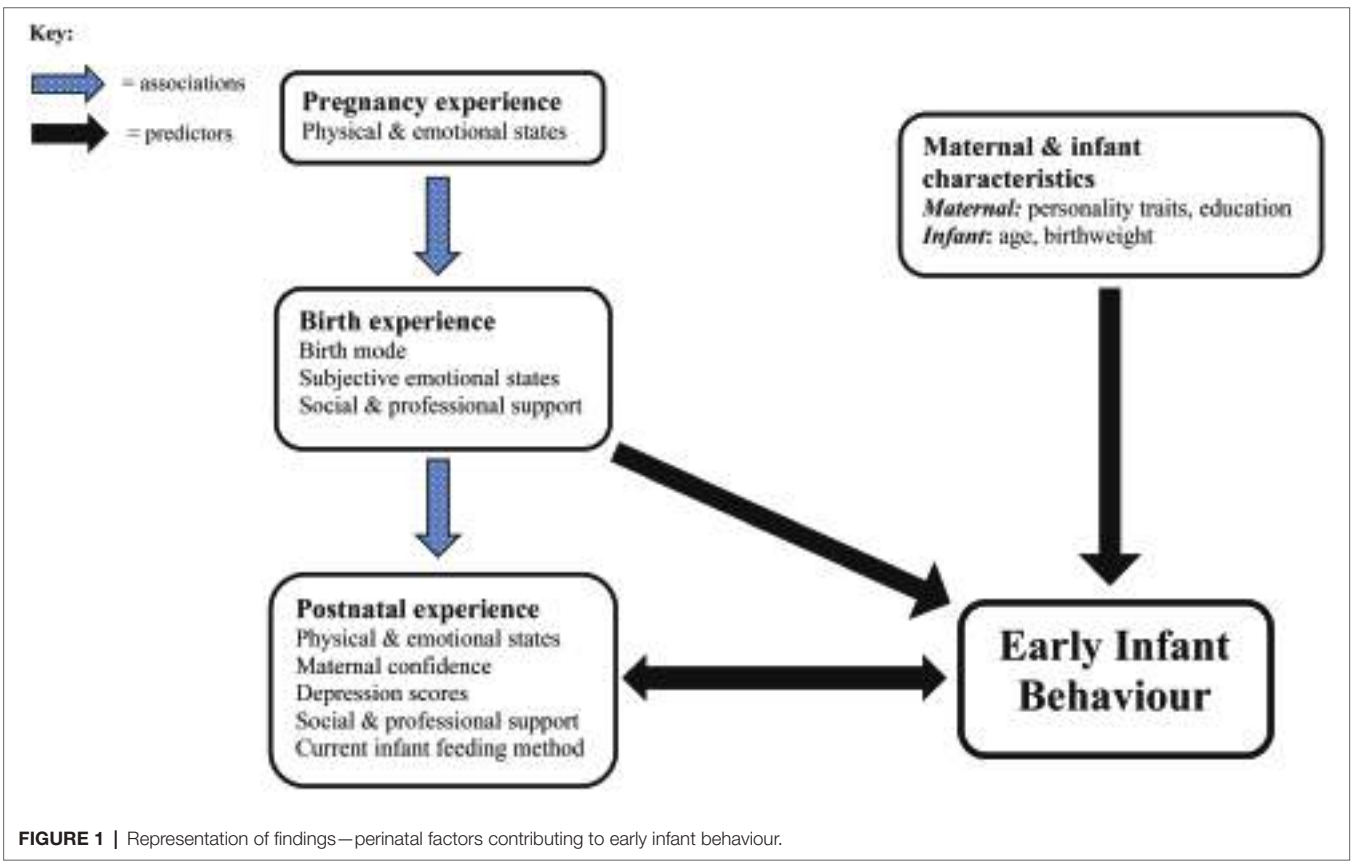

FIGURE 1 | Representation of findings—perinatal factors contributing to early infant behaviour.

relief were associated with less settled infant behaviour (0–6 months), regression analyses highlighted that subjective and psychological factors, alongside maternal personality traits, largely predicted perceived infant behavioural style and maternal confidence outcomes.

In addition, the mother's sense of wellbeing during and post-birth was reflected in higher levels of reported confidence and self-efficacy alongside her perceptions of easier infant behaviour. The predictability of birth events could play a key role in situations where the mother's sense of agency and control is increased or diminished, as research shows that agency in relation to free choice is particularly important for unpredicted negative events (Tanaka and Kawabata, 2019). More specifically, a Dutch study found that women were less happy with the care they received if they had experienced an instrumental vaginal (assisted) birth, an emergency C-section, less control during the active (dilation) stage or a more directed second (pushing) stage (Baas et al., 2017). This may help to explain the differences in maternal and infant responses between planned or unplanned C-sections in the present study. An

elective C-section should involve at least an element of predictability, choice and a chance to prepare.

These findings support the concept that subjective maternal perceptions of childbirth may contribute to early infant temperament development or to maternal perceptions of her baby's behavioural style. This could have important implications for maternity and midwifery practice, particularly for more vulnerable mother–infant pairs, or those who experience a challenging birth. The main findings are further discussed under the following headings.

Physical Perinatal Factors

Although many of the more objective factors, such as interventions, birthplace, birth mode and gentle birth of the infant's head, were associated with infant and maternal outcomes, breastfeeding was the only physiological perinatal factor that retained significance in the regression models for perceived infant behaviour. Specifically, 'currently breastfeeding' was associated with less Unsettled-Irregular behaviour over the first 6 months. Furthermore, infants were reported as less Alert during Feeds if they were currently breastfeeding, indicating that breastfeeding could be less stimulating and more relaxing for the infant. Breastfeeding is an instinctive newborn behaviour, highly sensitive to external stimuli from emotions, such as anxiety and fear (Moore et al., 2016). Its initiation and continuation could therefore be affected by the mother's physical and emotional response to her birth and her new baby, including whether mother and newborn infant were able to have immediate skin-to-skin contact. Moreover, a mother feeling able to breastfeed her baby could signify that she had a more physiological birth with less pain relief (Widström et al., 2011; Brown and Jordan, 2013). Indeed, a systematic review by Uvnäs-Moberg et al. (2019) highlights the associations of spontaneous physiological birth experience with increased hormonal and physiological wellbeing of mother and infant post-birth, which is likely to make initiating and continuing breastfeeding easier.

This finding may also be connected to the close skin-to-skin contact that naturally occurs during breastfeeding, regulating hormonal systems after a challenging birth, enhancing oxytocin and lowering cortisol levels, reducing the negative impacts of pain and stress on neonatal and maternal HPA axes and benefitting mother–infant neurobiological wellbeing and synchrony post-birth (Carter, 2014; Feldman, 2015; Mooney-Leber and Brummelte, 2017).

The Psychological Birth Experience

Consistent with a meta-analysis highting how maternal perceptions of a traumatic birth may contribute more to symptoms of CB-PTSD than objective physical factors, such as birth mode (Ayers et al., 2016), we found that self-reported infant behaviour was largely predicted by psychological and subjective maternal factors. However, this finding could also indicate that strong psychological variables, such as postnatal depression, may override other contributory factors (Leigh and Milgrom, 2008). Indeed, EPDS scores were the strongest predictor of several infant and maternal outcome variables including unsettled, irritable and irregular infant behaviour alongside lower general maternal confidence as well as confidence in caretaking and breastfeeding. These findings could mean that depressed mothers perceive their infant as more difficult (McGrath et al., 2008). Furthermore, they may indicate that the mother's personal feelings of birth trauma, represented here by negative birth and postnatal emotional states, such as Anxious-Afraid, Neglected and Postnatal Distress, contribute equally to PPD and CB-PTSD, with an adverse impact on mother–infant bonding (Stuijfzand et al., 2020), in turn affecting infant temperament. Alternatively, a challenging birth experience could lead directly to increased unsettled infant behaviour *via* physiological pathways, as discussed. This may result in lower maternal confidence combined with more negative thoughts and feelings. Thus, the relationship between mother and infant states of wellbeing or otherwise is likely to be bi-directional (see **Figure 1** above).

Also consistent with Ayers et al. (2016), correlational analyses here showed that certain subjective factors, such as Anxious-Afraid, Postnatal Distress and EPDS scores, were directly related to more interventionist birth modes. Therefore, these findings provide further support for a pathway between obstetric interventions, lack of control, negative birth emotions and postpartum mood disturbances (Blom et al., 2010; Ayers et al., 2016; Field, 2017). In turn, negative postnatal maternal mood may adversely impact on mother–infant interactions and subsequent infant behaviour and development (Murray et al., 2018). Our results show that maternal interpretations of the birth could be equally important to more objective measures, such as birth mode and obstetric complications and interventions.

How Maternal Wellbeing Might Be Associated With Infant Behaviour

There are several potential pathways for how the mother's birth experience, maternal wellbeing and infant behaviour could be interacting with one another.

Maternal Psychological Experience of Birth

Mothers who experienced a difficult birth were more likely to report feeling Anxious-Afraid or Neglected ('ignored' or 'abandoned') during childbirth and distressed postnatally, and these negative emotional states were associated with maternal reports of Unsettled-Irregular infants. As speculated by prior research (Douglas and Hill, 2013), this may be connected to the interacting hormonal systems of mother and infant. Higher cortisol levels can dysregulate the HPA axis, potentially causing long-term changes to the infant microbiome and epigenome (Dahlen et al., 2013, 2014; Almgren et al., 2014), with consequences for future behaviour and development (Gitau et al., 2001; Wolke et al., 2009; Schmid et al., 2010; Prokasky et al., 2017).

In contrast, having a more 'supported' experience and feeling positive post-birth predicted higher scores for Alert-Responsive infant behaviour and overall perceived infant Easiness. These mothers rated their midwife as helpful and informative and felt 'emotionally supported' throughout, reflecting evidence that

mothers experience less anxiety post-childbirth if they feel well cared for during the birth (Field, 2017). This pathway could occur physiologically *via* an easier birth and maternal recovery, with the mother's wellbeing during and post-birth encouraging neonatal wellbeing *via* their inter-connected hormonal systems (Buckley, 2015; Buckley and Uvnäs-Moberg, 2019). Alternatively, a mother who experiences positive birth emotions and therefore increased levels of oxytocin and beta-endorphins, may simply *perceive* her newborn infant more positively. Subjective maternal response to childbirth may therefore be a factor in the mother's own postnatal wellbeing (Ayers et al., 2016) and her subsequent perceptions of and interactions with her baby (Murray et al., 2014, 2018) as well as affecting the infant's behavioural response (Taylor et al., 2000).

Postnatal Mood

Higher maternal postnatal depression (EPDS) scores predicted perceptions of unsettled, irregular and irritable infant behavioural style, supporting previous research identifying a link between postnatal depression and perceptions of more 'difficult' infant behaviour (Gonidakis et al., 2008; Britton, 2011). This relationship is likely to be bi-directional: a crying, irritable infant may affect maternal mood, exacerbated by sleep deprivation (Eastwood et al., 2012), and an infant may become unsettled in response to negative maternal mood (Martini et al., 2017).

EPDS postnatal depression scores were associated with maternal Postnatal Distress, which in turn was associated with both the physical and emotional birth experience, aligning with evidence that negative birth experiences and postnatal psychological states contribute to postpartum depression (Bell and Andersson, 2016). Moreover, a difficult or interventionist birth might lead directly to increased unsettled infant behaviour; and excessive infant crying predicts later EPDS scores, particularly if the mother feels unable to console her baby (Radesky et al., 2013).

Oxytocin promotes bonding and attachment (Feldman, 2017; Uvnäs-Moberg et al., 2019). Conversely, depressed mothers with lower oxytocin levels are more likely to ignore their infant's cues (Mah et al., 2017). Consequently, postnatal depression and maternal withdrawal are associated with interactional difficulties, affecting mother–infant bonding and infant outcomes even after maternal mood improves (Murray et al., 2014, 2018; Oyetunji and Chandra, 2020).

Maternal Personality

As expected, heritable maternal character traits predicted self-reported infant behavioural style and maternal confidence ratings. The mother's personality influences outcomes on three levels: how she feels, the way she responds to her newborn baby and the postnatal environment she creates (Carey and McDevitt, 2016). Therefore, the impact of maternal personality on infant behaviour occurs through a combination of genetic and environmental influences. Although the personality trait 'Emotional Stability' was not retained as a predictor variable for perceived infant behaviour, it predicted Global Confidence and was inversely related to EPDS scores which came through as a strong predictor of Unsettled-Irregular infant behaviour over the first 6 months. Thus, maternal mood, personality and infant temperament were reciprocally associated.

Birth Companions

A less anticipated finding was that the presence of an extra birth companion alongside the birth partner positively predicted maternal perceptions of infant Easiness. Potentially, having two continuously supportive figures in the birthing room contributes more effectively to a positive birth experience with positive outcomes, including enhanced maternal perceptions of her baby. Furthermore, we know that continuous emotional support from a female companion, such as a doula, may lessen maternal stress levels, boost oxytocin (Buckley, 2015) and encourage a shorter labour and a normal birth, with lower use of analgesia and higher infant Apgar scores (Bohren et al., 2017). Decades of research illustrate the positive psychological impacts of doula support (Sosa et al., 1980; Kennell et al., 1991; Bohren et al., 2017). For instance, mothers accompanied in labour by a doula are known to have increased confidence in caretaking, lower levels of depression and to think more positively of their infants (Klaus and Kennell, 1997).

Sociodemographic Status and Maternal Expectations of Motherhood

Finally, sociodemographic variables were associated with certain types of infant behaviour. Mothers who did not attend higher education perceived their infants as more alert, responsive and easier overall. These findings might be explained through examining previous research which shows that mothers with higher education in established careers can find the transition to motherhood more challenging and have lower life satisfaction after having a baby (Harwood et al., 2007). This general negative mood could in turn affect the mother's perceptions of her baby's behaviour (McGrath et al., 2008). Furthermore, parents of higher social classes may have higher expectations of their children's future (Lareau, 2011; Irwin and Elley, 2013). Unrealistic expectations of their baby could result in disappointment and contribute to depressive symptoms (Martin et al., 2013), in turn negatively impacting on maternal confidence and ability to bond with her infant.

Strengths and Limitations

This study provided an in-depth exploration of a concept previously only alluded to in the research literature on childbirth and infant behaviour: that potentially long-term physiological impacts of childbirth on the infant's behavioural style and stress response system (Douglas and Hill, 2013) could possibly be mediated by the mother's subjective response to the birth (Taylor et al., 2000). Indeed, our findings showed that the mother's subjective response to the birth affected her perceptions of her baby's behaviour more than the objective physical experience. However, care needs to be taken between statistical and clinical significance, particularly where effect sizes are small. Quantitative psychological data often has this issue, in part due to the common inter-correlation of psychological

variables (Field, 2009), the difficulty in separating out such variables and thus the small individual contribution that each one finally makes to the overall picture. Nevertheless, as a whole and often supplemented by qualitative data (e.g. Power et al., 2019), the summative effect of multiple small statistical differences for different though inter-related physical and psychological variables (such as birth mode and postnatal psychological wellbeing/distress) might make an actual difference to real life experiences. Therefore, they become meaningful to maternity and perinatal care in the context of the other research evidence in this area.

Nevertheless, this research is not without limitations. First, while the online nature of the study allowed for a nationwide data collection strategy, this increasingly popular research method may contain drawbacks, especially in equity of recruitment. For instance, non-native English speakers or those without a good level of written English may have felt intimidated by the length of the survey as well as the language contained within the survey. To encourage maximum inclusivity, questions were made as straightforward and self-explanatory as possible with the majority of responses (except for, e.g. birth weight) recorded *via* check boxes. However, ethnic minority use of the Internet is slightly below average (Gov.uk, 2019). This may have contributed to a mostly white Caucasian sample population, which was also skewed toward breastfeeding, older mothers who were living with a partner. Despite this, and although an online survey did not cater for women without Internet access due to factors such as socio-economic deprivation, reportedly most women of childbearing age in the United Kingdom have access to the Internet (Gov.uk, 2019). There was a wide variation in participants' socio-economic status and women from a diverse range of socio-economic groups took part in the survey.

There are drawbacks to employing a self-report retrospective survey linked to the issue of subsequent validity of findings in regard to accurate recall of autobiographical memories (Belli, 1998). However, having had a period of reflection since an emotive or anxious birth situation might in fact aid more accurate recall. Retrospective questionnaires have become a popular, cost-effective and acceptable method of collecting pregnancy and childbirth data (Intong et al., 2017). Moreover, questionnaires about childbirth have been found to have excellent validity during the first few months post-birth (Bat-Erdene et al., 2013).

Retrospective reports of infant behaviour could be affected by biased memories of events and current behaviours during periods involving growth spurts, teething or weaning, all of which may alter the infant's normal behavioural patterns. They could also be influenced by maternal mood, although this effect is considered small (McGrath et al., 2008). Maternal ratings of infant behavioural scores are significantly associated with trained observer ratings (Rothbart et al., 2001; Henderson and Wachs, 2007; Zentner and Bates, 2008). Thus, an infant behaviour questionnaire was chosen that focused on specific everyday infant behaviours over the past 7 days (MABS), and the survey was completed within 6 months of the birth.

As this was a cross-sectional study, a future prospective longitudinal study could measure the same sample of women and infants at various time points throughout their perinatal experience. Importantly, the sample population was self-selecting. This undoubtedly affected the type of participant who completed the online questionnaire, rendering the recruitment strategy less inclusive. Potentially, however, a more homogeneous sample could help clarify findings in terms of specific impacts of childbirth experience on perceived infant behaviour.

Given that these findings provide support for those of a previous qualitative study, with health professional data collected over a similar period (Power et al., 2019), a future study should include a measure of perceived birth trauma and CB-PTSD symptoms as well as a scale for mother–infant interactions and bonding–attachment behaviours. This may provide a more complete picture, such as that suggested by **Figure 2**. The 'hypothetical contributors' shown in **Figure 2** represent items for future testing based on the findings in this study, the aforementioned health professional data and the wider research literature.

Difficulties in bonding and attachment processes could be a key point in this connection between the mother's response to childbirth (e.g. Postnatal Positive/Distress) and interpretations of her baby's behaviour. Stuijfzand et al. (2020) study showed that maternal distress at 1 month postpartum—which was associated with a traumatic birth experience—adversely impacts mother–infant bonding at 3 months postpartum. These authors also highlighted antenatal support in the pathway to a positive or negative birth experience and CB-PTSD. Similarly, Davies et al. (2008) found associations between CB-PTSD symptoms post-childbirth and more negative maternal perceptions of her infant alongside lower attachment; and a large Internet survey of mothers giving birth during the COVID-19 pandemic found that acute stress during childbirth had adverse impacts on mother–infant bonding and breastfeeding (Mayopoulos et al., 2021).

Despite their possible contribution to infant behavioural outcomes, no direct measures were used here to assess symptoms of CB-PTSD or bonding and attachment behaviours between the mother and her baby. Nevertheless, the suggested pathway in this study between maternal birth experience and perceived infant behavioural style—*via* the influences of postpartum maternal mood on mother–infant bonding and attachment—warrants further investigation. To include measures of CB-PTSD symptomology alongside early mother–infant interactions and bonding would therefore add to a more complete theoretical model for future testing (see **Figure 2**). In line with Stuijfzand et al. (2020) findings, professional and social support during pregnancy have been added to this model. Thus, **Figure 2** aims to provide a broader picture of the potential mechanisms behind the associations found in this study between maternal childbirth experience and infant behavioural style. The 'Potential pathway' box illustrates how a negative birth experience may be part of a pathway involving (maternal) Postnatal Distress, symptoms of CB-PTSD, bonding and attachment issues and maternal perceptions of more difficult, unsettled infant behaviour.

Our results add to a large body of research illustrating the complexity of childbirth and its potential outcomes for mother and infant. They highlight how infant and maternal outcomes of childbirth appear to be mutually influenced by one another's response to birth and by multiple physiological and psychological perinatal variables, such as feeling anxious and afraid or neglected

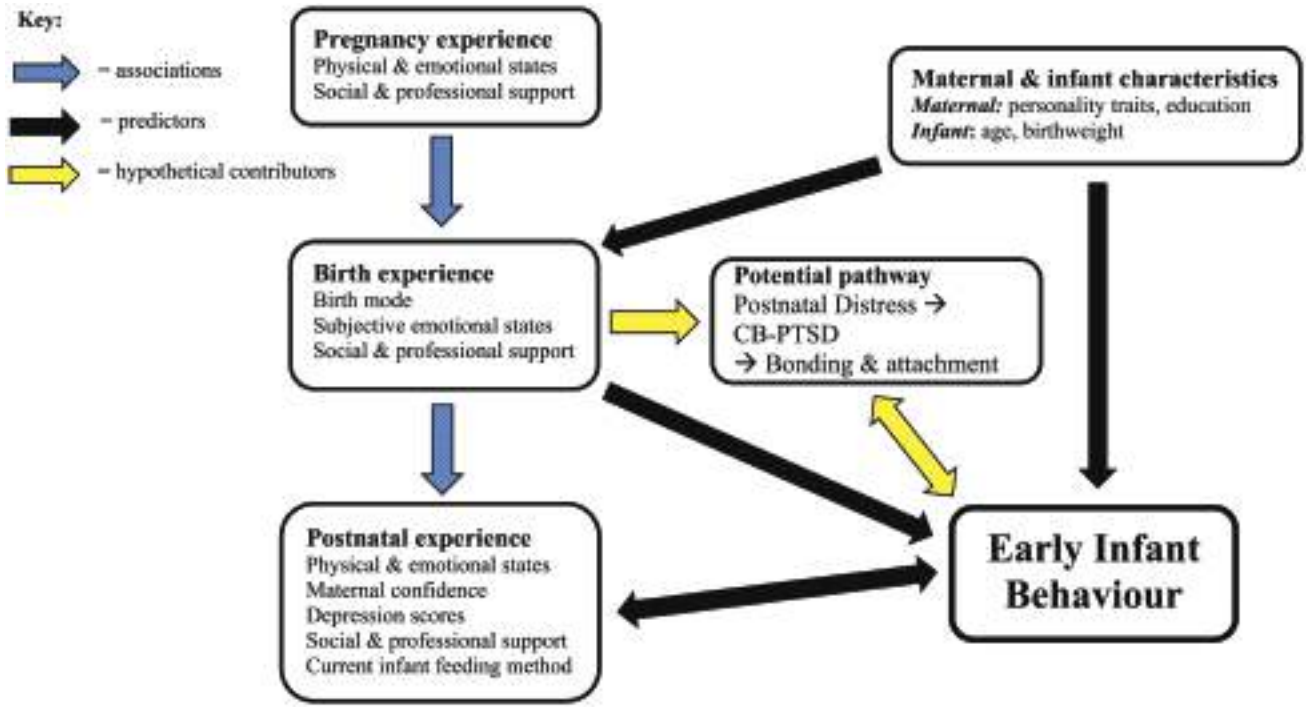

FIGURE 2 | A theoretical model of perinatal factors contributing to early infant behaviour.

during childbirth. Social and professional support the mother receives during the perinatal period may positively enhance her response to childbirth, in turn benefitting her infant's behavioural style. This finding is particularly pertinent in light of United Kingdom maternity policies involving restrictions on home births, water births and partner accompaniment in early labour during the COVID-19 pandemic. In some areas, this led to an increase in women opting for 'free-births' without any professional care—often to keep their partner with them throughout labour and birth and, for others, to avoid catching COVID (Feeley et al., 2021). Restrictions on partner accompaniment during early labour also led to more women accidentally giving birth alone in hospital settings if there happened to be staff shortages and labour was unexpectedly quick (Feeley et al., 2021).

Our findings therefore provide further support for the current United Kingdom maternity and midwifery services' objective to increase staffing numbers, reduce risk and promote a model of safe, consistent, continuous and emotionally supportive care for all expectant mothers (NHS England National Maternity Review, 2016; Scottish Government, 2017; The Regulation and Quality Improvement Authority, Northern Ireland, 2017; Healthcare Inspectorate Wales, 2020). Overall, these United Kingdom-wide reviews emphasise that health care should be both individualised and family centred with a focus on equity of care and informed choice.

The most recent of these maternity reviews—namely the Welsh review (Healthcare Inspectorate Wales, 2020)—although notably its investigations were carried out *pre*-March 2020, observed that maternity services have been very stretched during the COVID-19 pandemic. These problems arising in maternity care across the United Kingdom are intensifying previous issues of staff shortages and a lack of emotionally supportive care and are leading to increased reports of psychological distress in new mothers (Alcindor, 2021). Considering the impacts of the sudden reduction in face-to-face support for mothers and their babies during the early pandemic (Silverio et al., 2021), which is still occurring in some areas of maternity and perinatal care, it is vital that these services are made a priority in the government's plans to 'build back better'. Following the MBRACE report (MBRACE-UK, 2020), an urgent emphasis must especially be placed on equity of care. Thus, both physical and psychological wellbeing during and after childbirth need to become the objective for all mothers and their infants.

Maternity research collaboratives, including The Lancet Midwifery Series (ten Hoope-Bender et al., 2014) and the European Cooperation in Science and Technology (COST, 2020), have highlighted the importance of promoting and valuing high-quality and compassionate midwifery and newborn care for this all-important mother–infant health and wellbeing. This notion of 'quality' midwifery care was set out by ten Hoope-Bender et al. (2014) to include providing preventative, respectful and supportive care to women and their infants, swift medical treatment where required and using medical interventions only when clinically indicated. Consistent with our findings, research evidence around the importance of facilitating optimal neurohormonal states during physiological labour and birth emphasises the interconnectedness of psychosocial and physiological factors for positive birth outcomes (Downe et al., 2020; Olza et al., 2020). Aligning with prior evidence around the significance of mother–infant

neurobiological wellbeing and synchrony post-birth (Carter, 2014; Feldman, 2015; Mooney-Leber and Brummelte, 2017), our findings show how a positive birth experience enhances postnatal maternal mood and the mother's perceptions and experiences of her baby's early temperament, encouraging a happier and more fulfilling long-term relationship for both.

CONCLUSION

As recommended by the WHO (2018, p. 1) in their intrapartum guidelines supporting women's right to a '*positive birth experience*', this should include '*giving birth to a healthy baby in a clinically and psychologically safe environment with continuity of care and emotional support*'. Promoting maternal emotional wellbeing alongside physical safety during and after childbirth is of paramount importance. High-quality one-to-one midwifery care during childbirth may benefit the mother's physiological and psychological states (Olza et al., 2020) and consequently enhance her perceptions and experiences of her baby's behaviour. Conceivably, protecting the mother's neurohormonal state during childbirth and postnatally could also help to protect her against postpartum mood disorders and in this way promote more sensitive parenting and increase mother–infant bonding behaviours, with a positive impact on infant socio-emotional and cognitive development (Murray et al., 2014, 2018; Field, 2017; Tichelman et al., 2019). This could benefit not only the mothers and infants themselves but also their families and the wider society in which they live.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Swansea University Department of Psychology Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CP: design, conceptualisation, methodology, data collection, formal analysis, writing—original draft, writing—review and editing, and project administration. CW and AB: design, conceptualisation, methodology, data analysis support, writing—review and editing, and supervision. All authors gave approval for submission, contributed significantly to the article, and are responsible for its contents.

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Do Maternal Self-Criticism and Symptoms of Postpartum Depression and Anxiety Mediate the Effect of History of Depression and Anxiety Symptoms on Mother-Infant Bonding? Parallel–Serial Mediation Models

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Introduction: History of depression symptoms, including before and during pregnancy, has been identified as an important risk factor for postpartum depression (PPD) symptoms. This condition has also been associated with diverse implications, namely, on the quality of mother–infant bonding. Moreover, the role of self-criticism on PPD has been recently found in several studies. However, the link between these factors has not been explored yet. Furthermore, anxiety symptoms in postpartum has been less studied.

Methods: This study analyzed whether the history of depression symptoms predicted mother–infant bonding, *via* self-criticism and PPD symptoms. The same model was repeated with a history of anxiety and postpartum anxiety symptoms. A total of 550 mothers of infants <24 months old participated in this cross-sectional study and answered an online survey.

Results: Through a parallel–serial mediation model, the results show that in a first step, self-criticism dimensions of inadequate-self, hated-self, and reassuring-self, and in a second step, PPD symptoms, mediate the relationship between the history of depression symptoms and mother–infant bonding. However, the relationship between the history of anxiety symptoms and bonding is not mediated by all the considered chain of mediators, being only mediated by one of the self-criticism dimensions, inadequate self.

Conclusions: The current study confirmed the association of history of both depression and anxiety with mother–infant bonding. While in the case of history of anxiety symptoms, the relation was only mediated by inadequate self-dimension of self-criticism, in the case of history of depression symptoms, the relation was mediated by self-criticism and postpartum depressive symptoms. The buffering effect of reassuring-self on bonding and

negative affect was also evidenced. Psychological and preventive interventions should address this evidence to target interventions for mother–infant bonding problems in accordance with previous and actual current maternal risk factors.

Keywords: bonding, depression, anxiety, self-criticism, mothers, postpartum

INTRODUCTION

With the pregnancy and the birth of a child, mothers face important physiological, psychological, and social challenges and, for some, these periods may entail substantial emotional pain and distress (Staneva et al., 2015). Depression affects 7–25% of women during the antenatal period (Gavin et al., 2005; Field et al., 2006; Dubber et al., 2015; Staneva et al., 2015), and 11–20% of women during the postpartum period, making postpartum depression (PPD) the most prevalent clinical condition after childbirth and an important public health problem (de Tychey et al., 2005). Also, it is estimated that 30–50% of cases will last 6 months or more and 25% of mothers will continue to be depressed 1 year later (National Institute for Health and Care Excellence, 2003). Recent studies had even highlighted the stable and chronic trajectory of these symptoms until at least 24 months after childbirth (Kiviruusu et al., 2020). The PPD is a relatively common postpartum complication with a global pooled prevalence of 17.7% with significant heterogeneity across different nations (Hahn-Holbrook et al., 2018). The PPD is characterized by disabling symptoms such as persistent sadness, low self-esteem, anxiety, irritability and sleep/appetite alterations, dysphoria, loneliness, emotional lability, insomnia, confusion, guilt, and suicidal ideation (Letourneau et al., 2011). The previous psychopathology, specifically the history of prior depression, has been highlighted as one of the most important PPD risk factors (Robertson et al., 2004). More importantly, PPD may not only impact a mother's self-care but also the ability to cope with the care of the child.

In addition to the postpartum depressive symptoms, the symptoms of anxiety symptomatology are also common in postpartum and during pregnancy. Although it remains less studied than PPD and is largely underdiagnosed (Sawers and Wong, 2018), the two conditions are mostly comorbid (Hofmeijer-Sevink et al., 2012; Kubota et al., 2014; Takehara et al., 2018). Anxiety symptoms overlap with PPD, but they are distinct diagnostic entities; therefore, screening for the postpartum mental difficulties should include not only depression but also anxiety (Nakić Radoš et al., 2018). In addition, despite the inconsistency of the studies concerning the prevalence of anxiety during the postpartum period, some studies suggest that 20–25% of women have anxiety disorders during pregnancy, and 15–20% in the postpartum period. When anxiety symptoms in general are explored (trait anxiety), these rates increase to 25–33% during pregnancy, 17–22% in the postpartum period, and 15–33% in the late postpartum period (e.g., Grant et al., 2008; Dennis et al., 2013), highlighting the long-term duration of anxious symptoms. Despite the high prevalence of anxiety problems in the postpartum period, there is a lack of studies of this condition (Matthey et al., 2003; Wenzel et al., 2003; Tietz et al., 2014). The previous psychopathology, particularly the history of anxiety, might be highlighted as one of the most important postpartum anxiety risk factors, characterized by autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect (Lovibond and Lovibond, 1995). Matthey et al. (2003) found that a previous history of anxiety disorder posed a major risk factor for anxiety at 6 weeks postpartum.

Bonding is a complex phenomenon that represents numerous stages in the development of the relationship between mother and baby (Hill and Flanagan, 2020). Maternal bonding, which is believed to develop during pregnancy or immediately after childbirth as a dynamic construct (Bicking Kinsey and Hupcey, 2013) and continues to improve in the first months of the infant's life (Muzik et al., 2013), is defined as "an affective state of the mother," and corresponds to emotions and cognitions of a mother toward her baby (Billings, 1995; Klaus et al., 1995; Bicking Kinsey and Hupcey, 2013). A maternal bonding refers to the emotional messages and actions a mother displays to her baby, while attachment refers to the caregiver's closeness and commitment that enables a baby to form a positive connection with them (Goulet et al., 1997; Redshaw and Martin, 2013). Impaired mother–infant bonding includes delays in mothers' emotional responses toward their infant, anger, hostility, indifference, and rejection (Brockington et al., 2001, 2006). The mother–infant bond attracts a lot of attention, not only having an important role in the baby's wellbeing but also in the child's cognitive and emotional development (e.g., Tamis-LeMonda et al., 2001; Cirulli et al., 2003).

Considering the studies examining the relationship between mother–infant bonding problems and PPD and postpartum anxiety, it can be said that a poor parental mental health is one of the main risk factors for impaired parent–infant interactions that may lead to adverse effects on bonding (Reck et al., 2004; Parfitt and Ayers, 2009). Although disorders of mother–infant bonding are seen even in healthy postpartum mothers (Vengadavaradan et al., 2019), research on potential risk factors related to mother–infant bonding has focused on postpartum maternal mental health, in particular on PPD (Handelzalts et al., 2021). Research to date provides substantial evidence that both antenatal depressive symptoms (Kolk et al., 2021) and PPD measured early after childbirth could predict bonding difficulties until 1 year after childbirth (Brockington et al., 2006; Moehler et al., 2006; Muzik et al., 2013; Nonnenmacher et al., 2016; Tsuchida et al., 2019; Kasamatsu et al., 2020; Handelzalts et al., 2021). Depression in pregnancy and after birth could have an adverse impact on women, their children, and their relationships (World Health Organization, 2008). Other studies demonstrated that not only PPD but also depressive symptoms are related to impaired mother–infant bonding (Moehler et al., 2006; Edhborg et al., 2011; Hairston et al., 2011; Tietz et al.,

2014; Dubber et al., 2015; Garcia-Esteve et al., 2016; Kasamatsu et al., 2020; Nakić Radoš et al., 2020). According to some studies addressing multiple risk factors, both the history of depression (Nonnenmacher et al., 2016; Badr et al., 2018) and depression in pregnancy (Ohoka et al., 2014; Daglar and Nur, 2018) along with PPD, have been associated with impaired mother–infant bonding. Similarly, in one study, clinically defined maternal depressive disorder during pregnancy is shown to negatively impact maternal–fetal bonding (McFarland et al., 2011), suggesting that the basis for poor mother–infant bonding in PPD may have roots in pregnancy (Lefkovics et al., 2014). On the other hand, another study showed that the maternal depression during pregnancy was not significantly associated with mother–infant bonding (Brassel et al., 2020).

In addition to the symptoms of depression, anxiety-related problems also have effects on bonding. Several research projects have investigated the link between postpartum anxiety and mother–infant bonding (e.g., Edhborg et al., 2011; Tietz et al., 2014). Tietz et al. (2014) found that mothers with postpartum anxiety disorder reported significantly lower bonding than healthy mothers. Further analysis showed that it was not a diagnosis of anxiety disorder itself but concurrent subclinical depressive symptoms together with avoidance of anxiety-related situations, that predicted lower mother–infant bonding. Similarly, in rural Bangladesh, maternal anxiety symptoms were positively associated with mother's emotional bonding (Edhborg et al., 2011). In another study, the higher levels of postpartum-specific anxiety were related to impaired overall bonding scores, subscales of impaired general bond, rejection and anger, and infant-focused anxiety across the first 6-months of life (Fallon et al., 2021). Feldman et al. (1997) stated that an increased anxiety during prenatal and postnatal periods seem to interfere with the mother's ability to bond and interact sensitively with the child. In addition, several studies indicate the significance of maternal anxiety on mother–infant bonding behaviors, the mother–infant relationship, and mother–infant interaction (e.g., Manassis et al., 1994; Nicol-Harper et al., 2007; Feldman et al., 2009; Kaitz et al., 2010).

Self-criticism was also considered as a mediator in this study. Despite the increasing attention in literature, self-criticism has been scarcely studied in the context of adaptation and transition to motherhood but represents a promising mechanism to comprehend postpartum distress. Self-criticism refers to a persistent and intense form of internal dialogue that involves self-scrutiny and expression of hostility and contempt toward the self (Whelton and Greenberg, 2005; Kannan and Levitt, 2013). There are two different forms of self-criticism, known as the "hated-self" and the "inadequate self." The first one focuses on harsh self-loathing and the desire to remove unwanted aspects of the self with the function of self-persecution. The second one focuses on shortcomings or failures, with the function of self-correction (Gilbert et al., 2004). Referring to the relationship between self-criticism and history of depression and anxiety, both forms of self-criticism, but especially hated-self, have been consistently associated with psychopathology (Castilho et al., 2017; Kotera et al., 2021). For example, some studies showed that the high levels of self-criticism have been consistently shown to be a risk factor for the development of depression (e.g., Ehret et al., 2015; Zhang et al., 2019). Other research on female adolescents demonstrates that self-criticism successfully predicted the first onset of nearly all depressive and anxiety disorders (Kopala-Sibley et al., 2017). However, in their study on student samples, McIntyre et al. (2018) did not find that self-criticism predicted future levels of anxiety. On the other hand, self-reassurance (i.e., the ability to focus on one's positive aspects and be compassionate toward the self when things go wrong) functions as a buffer against self-criticism and therefore appears to be a protective factor against the development of psychopathology (Gilbert et al., 2004; Werner et al., 2019).

In the postpartum period, women seem to be particularly prone to self-criticism (Brassel et al., 2020), given the changes in maternal identity and the lack of control and autonomy accompanying motherhood (Priel and Besser, 1999; Brassel et al., 2020). Concerning the association between self-criticism and PPD and postpartum anxiety, such thinking style and emotions may heighten women's vulnerability to postpartum depression and anxiety symptoms. Although research on the effects of self-criticism on postpartum depression symptoms is still limited, existing studies have shown that postpartum depressed women presented higher levels of self-criticism compared to non-depressed women, and both depressed and non-depressed mothers' self-criticism was related to state anxiety (Vliegen and Luyten, 2009). In addition, self-criticism was strongly and positively associated with postpartum depressive symptoms (Vliegen et al., 2006; Besser et al., 2007). However, it is important to consider that self-criticism is described as a transdiagnostic factor, rather than a specific cognitive appraisal from depression, given that it seems prevalent in other psychological disorders (Luyten et al., 2007), such as anxiety disorders (Vliegen and Luyten, 2009; Castilho et al., 2014), stress (Luyten et al., 2011; Mandel et al., 2015), and social anxiety (Shahar et al., 2015; Lazarus and Shahar, 2018).

Self-criticism may also be associated with difficulties in mother–infant bonding. Beebe et al. (2007) found that at 4 months, self-critical mothers displayed less gaze and facial coordination with their infant and poorer infant attachment security at 20 months. Mothers may interpret infant signals and behavior as a reflection of their self-inadequacy and may therefore interact less with the child (Kaminer et al., 2007) or reduce their involvement in caregiving (Reizer and Mikulincer, 2007). In addition, self-critical mothers may project onto the infant feelings of resentment due to the loss of control and autonomy imposed by motherhood (Priel and Besser, 1999; Casalin et al., 2014; Brassel et al., 2020).

In summary, although there is evidence of the maternal history of depression and other forms of psychopathology as predictors of PPD and the quality of mother–infant bonding, studies have rarely included self-criticism as a mechanism explaining this link. Furthermore, although many studies have studied categorical diagnoses of PPD and anxiety disorders, they have not been able to capture the vast range of severity and intensity of depressive and anxious symptoms across the diverse stages of the postpartum period (Gorham, 2020). Furthermore, the history of maternal anxiety symptoms has been poorly

studied in the literature on postpartum (in)adaptation. As such, this study aimed to analyze the association between maternal history of depression and anxiety symptoms, and mother–infant bonding, through self-criticism and levels of depressive and anxiety symptoms. According to previous studies, we first hypothesized that having a history of depression symptoms would predict less mother–infant bonding through higher levels of self-criticism and higher PPD. Although anxiety has been less explored in literature, given its high prevalence in the postpartum period and its relation to self-criticism, we also hypothesized that the history of anxiety symptoms affects bonding, *via* self-criticism and postpartum anxiety.

MATERIALS AND METHODS

Participants

The sample included 550 Portuguese mothers, aged 18–48 years ($M = 32.76$, $SD = 5.06$). Most mothers had completed a university degree, were married/living with their partner, and were not currently on maternity leave. Concerning delivery mode, 63.7% reported giving birth vaginally and 36.3% giving birth through cesarean (programmed or emergency). The percentage of mothers who reported a chirurgical mode of delivery (planned or emergency cesarean section) is in line with the average of Portuguese national statistics for cesarean, that is, 36% (INE, 2021). Infants were aged between 2 weeks and 24 months ($M = 8.57$ months, $SD = 6.51$). The participants' demographic characteristics are shown in **Table 1**.

The inclusion criteria were as listed in the following: (a) To be a biological mother of one baby <24 months old, excluding twins; (b) to have conceived the baby in a context of a heterosexual relationship; (c) to have adequate knowledge of the Portuguese language to be able to complete questionnaires; and (d) to be 18 years and over. Mothers completed an online survey. Informed consent was obtained from all the women before they answered the protocol. Among the 556 mothers who participated, six questionnaires were excluded because one or more measures left more than 20% of the questions incomplete. In sum, 550 mothers were included in this study. Based on the cut-off points used by Lovibond and Lovibond (1995), mean scores indicated normal levels of depression and anxiety among participants.

TABLE 1 | Sociodemographic characteristics of the sample.

	***M* (*SD*)/*n* (%)**
Mothers' age (years)[a]	32.76 (5.06)
Mothers' education	
Basic/secondary education	206 (37.5%)
University degree	342 (62.1%)
Other	2 (0.4%)
Mothers' marital status	
Single	33 (6.0%)
Partnered without living together	12 (2.2%)
Married/partnered and living together	499 (90.7%)
Divorced/separated	6 (1.10%)
Household monthly income	
Less than €1583	283 (51.5%)
1€583 or above	267 (48.5%)
Gestational complications	
Yes (e.g., high-risk pregnancy, maternal health problems, fetus'/baby's health complications)	313 (56.9%)
No	237 (43.1%)
Mode of delivery	
Vaginal delivery	245 (44.5%)
Instrumental vaginal delivery	106 (19.2%)
Planned cesarean section	96 (17.5%)
Emergency cesarean section	103 (18.8%)
Gestational age	
Preterm childbirth (<37 weeks)	33 (6.0%)
Post-term childbirth (37 weeks or more)	517 (94.0%)
Currently in maternity leave	
Yes	237 (43.1%)
No	312 (56.9%)
Infants' age (months)[b]	8.57 (6.51)
Number of children	
1	349 (63.5%)
2	163 (29.6%)
3 or more	33 (6.4%)
Missings	3 (0.5%)

[a] *One participant did not report her age.*
[b] *Eight participants did not report the age of their infants.*

Measures

Sociodemographic and Clinical Background Questionnaire

Sociodemographic and clinical background questionnaire was applied to obtain information about the sociodemographic characteristics (e.g., age, relational status, academic degree, professional situation, cohabitation, number/ages of children, and type of delivery), pregnancy, breastfeeding, problems during and postpartum of the participants. This questionnaire also included several questions related to risk factors for PPD symptoms and (in)adaptation, such as maternal psychopathology; medical support during pregnancy, childbirth, and postpartum; childbirth experience; baby's temperament; distress during pregnancy; partner's distress during pregnancy/in the present; and body image. For this study, four items assessed the history of depression and anxiety symptoms, respectively ("Before pregnancy, did you feel sad or depressed often?" and "During pregnancy, did you feel sad or depressed often?" "Before pregnancy, did you feel anxious, nervous and/or tense often?" and "During pregnancy, did you feel anxious, nervous and/or tense often?"). The two items assessing the history of depression symptoms were aggregated and entered in the analyses as independent variables. The same procedure was repeated to obtain the score from history of anxiety symptoms. Each of these items were measured on a 5-point Likert scale, ranging from 1 ("I strongly disagree") to 5 ("I strongly agree"). The use of this scale was to capture a dimensional continuum rather than a simplistic and dichotomic answer (yes or no). Good correlations were found between the items that measured the history of

depression symptoms ($r = 0.60$, $p < 0.001$) and the history of anxiety symptoms ($r = 0.57$, $p < 0.001$).

Forms of Self-Criticizing and Self-Reassuring Scale

The Portuguese version of the forms of self-criticizing and self-reassuring scale (FSCSRS) (Gilbert et al., 2004; Castilho et al., 2015) consisted of 21 items to assess how critical/attacking or how supportive and reassuring participants are when things go wrong. The scale has three subscales. The subscale of "Inadequate-self" (10 items) assesses the feeling of inadequacy of the self in the face of failures, obstacles, and mistakes ("I think I deserve my self-criticism"). The subscale of "Hated-self" (three items) evaluates a more destructive response, based on self-loathing, anger, and aversion to failure situations, characterized by a disliked relationship with the self and by a desire to hurt, chase, and assault the self ("I get so angry with myself that I want to hurt myself or harm myself"). The subscale of "Reassuring-self" (8 items) assesses a positive, warm, comforting, and compassionate attitude toward the self ("I still like who I am"). The FSCSRS starts with a first probe statement: "When things go wrong for me (…)." The participants respond on a 5-point scale (ranging from 0 = "not at all like me" to 4 = "extremely like me") on a series of questions (e.g., "I think I deserve my self-criticism," "There is a part of me that puts me down," and "I find it easy to forgive myself"). The statements of the FSCSRS were derived from clinical work with depressed people where Pinto–Gouveia had noted some typical thoughts depressed patients offered about their self-criticism and ability to self-reassure (Castilho et al., 2015). Higher mean scores reflect a greater sense of inadequacy, hated-self, and self-reassurance (scores 0–5). The internal reliability of "Inadequate-self" was $\alpha = 0.92$, of "Hated-self" was $\alpha = 0.74$, and of "Reassuring-self" was $\alpha = 0.92$.

Depression Anxiety Stress Scale

Depression, anxiety, and stress levels of participants were measured using the Portuguese version of depression anxiety stress scale (DASS-21) (Lovibond and Lovibond, 1995; Pais-Ribeiro et al., 2004). The DASS-21 is a self-report scale with 21 items, seven for each subscale (e.g., "I felt that life was meaningless," "I felt I was close to panic," and "I found it difficult to relax"). The "Depression scale" measures symptoms of dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The "Anxiety scale" measures autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. Finally, the "Stress scale" assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient. The participants rate the extent to which they have experienced each symptom over the past week, on a 4-point scale (0 = "did not apply to me at all" to 3 = "applied to me very much, or most of the time"). The sum scores for DASS dimensions were computed and, for comparison with the original DASS, scores were multiplied by two. Higher scores indicate more frequent anxiety, depression, and stress symptoms (scores 0–42). It must be highlighted that we intentionally used a dimensional score of depressive and anxious symptoms to capture symptoms in a continuum of severity, rather than a clinical diagnosis of PPD or anxiety disorders associated with postpartum. The structure of the Portuguese version of DASS-21 was identical to the original version, with the same items on the same scale. Good internal reliability was obtained for all subscales [depression ($\alpha = 0.87$), anxiety ($\alpha = 0.82$), and stress ($\alpha = 0.90$)].

Postpartum Bonding Questionnaire

Mother–infant bonding was assessed by the Portuguese short version of the postpartum bonding questionnaire (PBQ) (Brockington et al., 2001; Nazaré et al., 2012). The PBQ is a self-report, 12-item scale that assesses the mother's feelings or attitudes toward her baby (e.g., "I feel distant from my baby" and "I love to cuddle my baby"). The participants were asked to rate how often they agreed with these statements reflecting their experience on a 6-point scale ranging from 0 (always) to 5 (never), with reverse coding of positive statements. Higher mean scores indicate greater problems of mother–infant bonding. Through confirmatory factorial analysis the authors in the Portuguese version of the scale analyzed six models, which were based on previous PBQ studies (Nazaré et al., 2012). A 12-item structure that corresponded to the first factor of the original structure of the scale, named impaired mother–infant bonding (Brockington et al., 2001), was identified as having the best fit to their data, with good levels of internal as well as temporal consistency, along with adequate values of convergent and discriminant validity. In this study, a good internal reliability was obtained for the postpartum bonding scale ($\alpha = 0.75$).

Procedure

This study is part of a larger research project dedicated to risk and protective factors for (un)adjustment to motherhood. The study was previously approved by the Ethics and Deontology Committee of the School of Psychology and Life Sciences from University Lusofona. The data collection occurred between February and March of 2020. A non-probabilistic sampling was delivered based on a snow-ball method. The study comprised an online survey made in Typeform and was advertised in internet forums of mothers and on Facebook groups dedicated to maternal topics.

Statistical Analysis

Data analyses were performed using IBM SPSS (v. 28). Descriptive analyses were conducted for sociodemographic and study variables. Zero-order correlations between the study variables were computed. Effect sizes of correlations were based on Cohen's guidelines (1988; small: Pearson's $r = 0.10$; medium: $r = 0.30$; and strong: $r = 0.50$).

To test our hypotheses and examine whether the main effects of history of depression symptoms and anxiety symptoms on mother–infant bonding are mediated by self-criticism (inadequate, hated, and reassuring self), as well as postpartum negative affect (depression and anxiety symptoms), we tested two parallel and serial mediation models using PROCESS version 4.0 for IBM SPSS Statistics (Model 80; Hayes, 2018). In the models performed, history of depression and anxiety

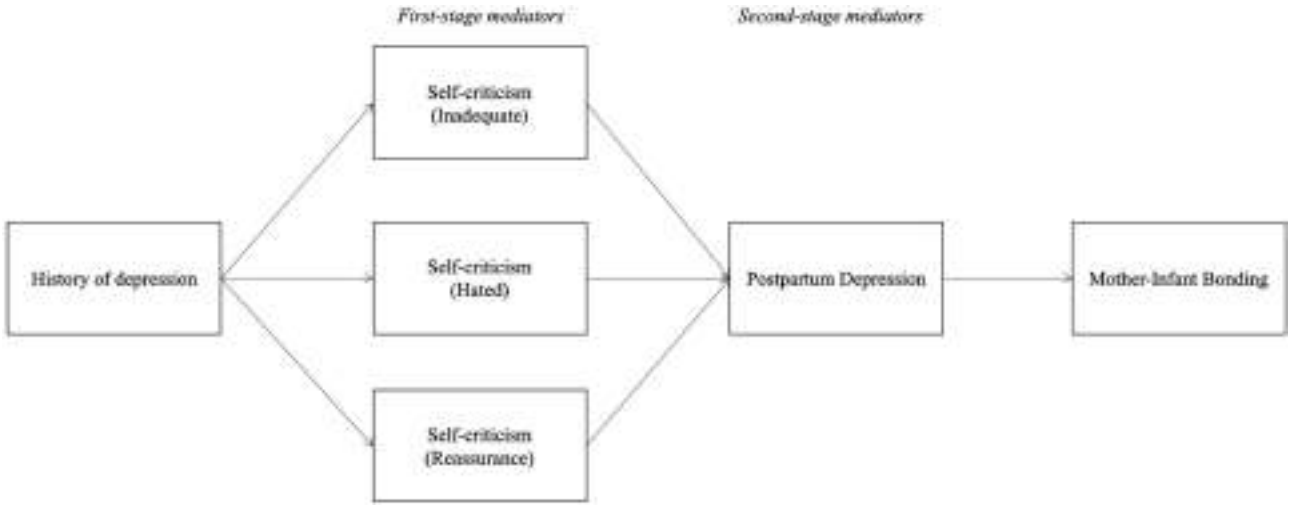

FIGURE 1 | Conceptual mediation model for the presumed influence of history of depression symptoms on mother–infant bonding, through self-criticism and PPD symptoms.

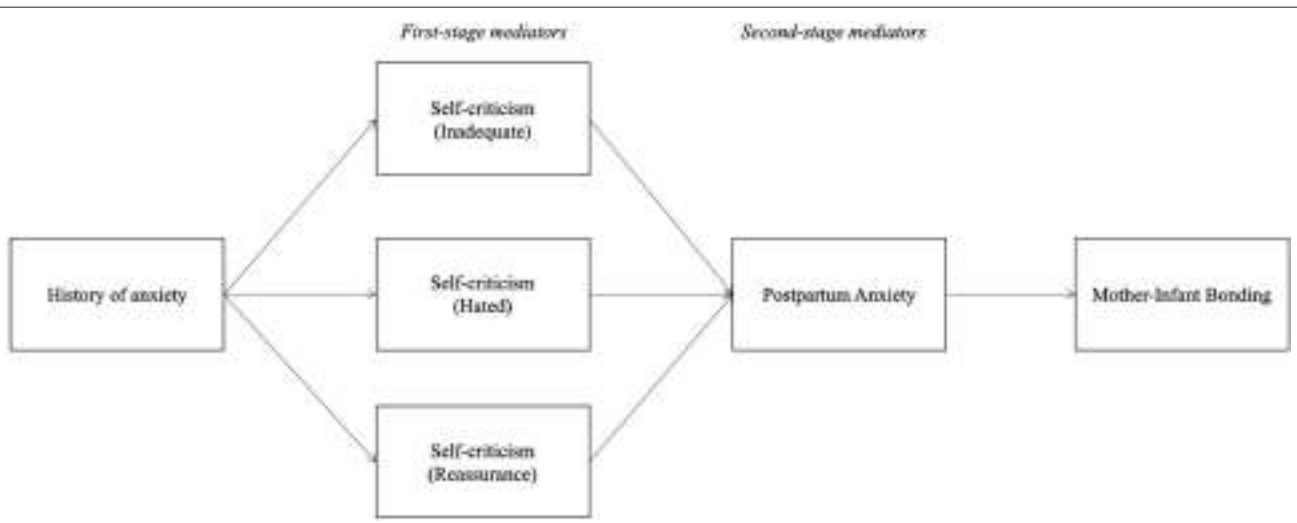

FIGURE 2 | Conceptual mediation model for the presumed influence of history of anxiety symptoms on mother–infant bonding, through self-criticism and postpartum anxiety symptoms.

symptoms were entered as independent variables (each tested independently), self-criticism dimensions were the parallel first step mediators, postpartum negative affect (depression or anxiety) was the serial second step mediator and bonding the dependent variable. Accordingly, the first tested model evaluated the indirect effect of the history of depression symptoms (before and during pregnancy) on mother–infant bonding through the three dimensions of self-criticism (as first step mediators), and PPD symptoms (as a second step mediator; see **Figure 1**). The second tested model checked the indirect effect of the history of anxiety symptoms (before and during pregnancy) on mother–infant bonding through the three dimensions of self-criticism (as first step mediators) and postpartum anxiety symptoms (as second step mediator; see **Figure 2**). Given that comorbidity between depression and anxiety is common (Kalin, 2020), to control for these overlapping symptoms and consider the variability caused by the history of depression and anxiety symptoms before and during pregnancy, we included these variables as covariates in the analysis. As such, in Model 1, we controlled for the effect of history of anxiety symptoms and in Model 2, we controlled for the effect of history of depression symptoms. Additionally, we controlled for the effect of infants' age, mothers' age, income, and gestational complications. Indirect effects were tested through a bootstrapping procedure, including 5,000 bootstrap and 95% bias-corrected, and accelerated confidence intervals. Indirect effects were considered significant when zero was not included in the bootstrap 95% Confidence Interval.

TABLE 2 | Correlations and descriptive statistics of history of depression and anxiety symptoms, self-criticism, postpartum negative affect, and mother–infant bonding.

Study variables	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	*M (SD)*
1. History of depression symptoms	–										2.44 (1.05)
2. History of anxiety symptoms	0.75***	–									2.27 (1.03)
3. Self-criticism (inadequate-self)	0.37***	0.39***	–								1.24 (0.89)
4. Self-criticism (hated-self)	0.30***	0.32***	0.60***	–							0.29 (0.60)
5. Self-criticism (reassuring self)	−0.40***	−0.40***	−0.49***	−0.41***	–						1.89 (0.92)
6. PPD symptoms	0.38***	0.38***	0.60***	0.61***	−0.44***	–					4.82 (6.54)
7. Postpartum anxiety symptoms	0.36***	0.42***	0.40***	0.44***	−0.36***	0.67***	–				3.82 (5.55)
8. Mother–infant bonding	0.22***	0.23***	0.30***	0.22***	−0.18**	0.34***	0.25***	–			0.37 (0.34)
9. Infants' age (months)	−0.02	0.01	−0.01	−0.03	0.02	0.05	0.09*	0.12**	–		8.57 (6.51)
10. Mothers' age (years)	−0.09*	−0.09*	−0.05	−0.10*	0.08	−0.09*	−0.09*	−0.07	0.11*	–	32.71 (5.19)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

RESULTS

Correlations between study variables are shown in **Table 2**. All study variables were significantly correlated with each other. Results show a high association between having a history of depression and anxiety symptoms, before and during pregnancy. History of depression and anxiety symptoms were positively correlated with the dimensions of self-criticism inadequate-self and hated-self, but negatively with reassuring self. High inadequate-self and hated-self and lower reassuring self-criticism was associated with higher levels of PPD and anxiety symptoms. Moreover, higher levels of self-criticism (hated and inadequate) were associated with higher problems in bonding. In the opposite direction, reassuring-self was negatively associated with bonding problems. Depression symptoms before and after partum, and anxiety symptoms before and after partum, were positively related to problems in mother–infant bonding.

History of Depression and Mother–Infant Bonding

In mediational analyses, findings (**Table 3**) show that having a history of depression symptoms influences the dimensions of self-criticism as it increases mothers' sense of inadequate-self and hated-self, while it reduces the levels of reassuring-self. Both harsh self-criticism dimensions, inadequate-self and hated-self, are associated with increased PPD symptoms. Reassuring-self is associated with decreased PPD symptoms. Finally, when controlling for all the variables in the model, PPD symptoms are positively associated with impaired mother–infant bonding, and the direct effect of history of depression symptoms on mother-infant bonding decreases and becomes non-significant.

The model testing the indirect effect of the history of depression symptoms on mother–infant bonding (**Figure 3**) showed significant indirect effects through the chain of mediators considered (see **Table 4**). As such, we found the following indirect effects of the serial mediation models. (1) First, through the self-criticism dimension of inadequate-self and through PPD symptoms; (2) second, through the self-criticism dimension of hated-self, and through PPD symptoms; and (3) finally through the self-criticism dimension of reassuring-self followed by PPD symptoms.

History of Anxiety and Mother–Infant Bonding

Results (**Table 5**) show a significant effect of mother's history of anxiety symptoms on the three dimensions of self-criticism, as it increases mother's sense of inadequate-self and hated-self, while it reduces the levels of reassuring self-criticism. Different from Model 1, in Model 2, only the self-criticism dimensions of the hated-self and the reassuring-self are significantly associated with postpartum anxiety symptoms, although in different directions. Accordingly, the greater the feelings of hated self, the greater the postpartum anxiety, while greater levels of mother's reassurance are associated with lower levels of postpartum anxiety symptoms. Finally, regarding the second-step mediator, postpartum anxiety is positively associated with impaired mother–infant bonding. When controlling for all the mediators in the model, in relation to the total effect, the direct effect of the history of anxiety symptoms on mother–infant bonding decreases and becomes non-significant. Also, when testing the indirect effects of the history of anxiety symptoms on mother–infant bonding (**Figure 4**) through the overall chain of mediators, there are no significant indirect effects (see **Table 6**). Results show that inadequate-self is, alone, a significant mediator of the relation between history of anxiety symptoms and infant–mother bonding.

DISCUSSION

This study analyzed if maternal history of depression symptoms predicted mother–infant bonding and if this relation was mediated sequentially by mother's self-criticism and present symptoms of depression. The same model was explored for anxiety, including history of anxiety symptoms as a predictor and present symptoms as mediator.

The results evidenced a high association between having a history of depression and anxiety symptoms, before and during pregnancy, which is in line with the vast literature that describes the overlapping and comorbid relations between these two frequent psychological conditions. Similarly, the positive associations were found between the history of depression symptoms and the PPD symptoms, and between

TABLE 3 | Standardized regression coefficients (β), unstandardized regression coefficients (b), standard errors (SE), and model summary information for the tested serial–parallel mediation Model 1.

	Inadequate-self				**Hated-self**				**Reassuring-self**				**PPD symptoms**				**Mother–infant bonding**				**Mother–infant bonding**			
																	(Total effect model)				**(Serial–parallel mediation model)**			
Antecedent	***β***	***b***	***SE***	***P***	***β***	***b***	***SE***	***P***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***
History of depression symptoms (IV)	0.19	0.17	0.05	0.001	0.134	0.08	0.04	0.029	−0.23	−0.20	0.05	0.000	0.09	0.29	0.15	0.058	0.15	0.05	0.20	0.018	0.08	0.03	0.02	0.204
Inadequate-self (M1)	–	–	–	–	–	–	–	–	–	–	–	–	0.26	0.94	0.16	0.000	–	–	–	–	0.12	0.05	0.02	0.032
Hated-self (M2)	–	–	–	–	–	–	–	–	–	–	–	–	0.37	1.99	0.22	0.000	–	–	–	–	−0.02	−0.01	0.03	0.770
Reassuring-self (M3)	–	–	–	–	–	–	–	–	–	–	–	–	−0.10	−0.36	0.13	0.008	–	–	–	–	0.02	0.01	0.02	0.706
PPD symptoms (M4)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.25	0.03	0.01	0.000
Constant	–	0.40	0.26	0.120	–	−0.20	0.18	0.261	–	2.50	0.26	0.000	–	0.77	0.83	0.354	–	−0.13	0.10	0.216	–	−0.17	0.11	0.107
History of anxiety symptoms (cov)	0.25	0.22	0.05	0.000	0.20	0.12	0.04	0.001	−0.22	−0.19	0.05	0.000	0.05	0.14	0.15	0.351	0.14	0.05	0.02	0.025	0.07	0.02	0.02	0.282
Mothers' age (cov)	−0.02	−0.004	0.01	0.617	−0.05	−0.01	0.00	0.214	0.02	0.00	0.01	0.624	−0.02	−0.01	0.02	0.552	0.06	0.04	0.00	0.153	0.07	0.00	0.00	0.073
Infants' age (cov)	−0.01	−0.001	0.01	0.802	−0.02	0.00	0.00	0.618	0.01	0.00	0.01	0.825	0.07	0.04	0.02	0.020	0.11	0.01	0.00	0.010	0.09	0.00	0.00	0.021
Gestational complications (cov)	0.01	0.02	0.07	0.837	0.00	0.00	0.05	0.931	−0.01	−0.01	0.07	0.865	0.01	0.09	0.21	0.665	−0.03	−0.02	0.03	0.446	−0.04	−0.02	0.03	0.362
Income (cov)	0.03	0.02	0.02	0.478	−0.09	−0.03	0.02	0.040	0.08	0.04	0.02	0.042	−0.05	−0.10	0.06	0.135	0.12	0.02	0.01	0.005	0.14	0.03	0.01	0.001
	$R^2 = 0.17$				$R^2 = 0.12$				$R^2 = 0.19$				$R^2 = 0.48$				$R^2 = 0.10$				$R^2 = 0.17$			
	$F_{(6,535)} = 18.59, p < 0.001$				$F_{(6,535)} = 12.23, p < 0.001$				$F_{(6,535)} = 21.14, p < 0.001$				$F_{(9,532)} = 54.88, p < 0.001$				$F_{(6,535)} = 9.44, p < 0.001$				$F\ (10,531) = 11.19, p < 0.001$			

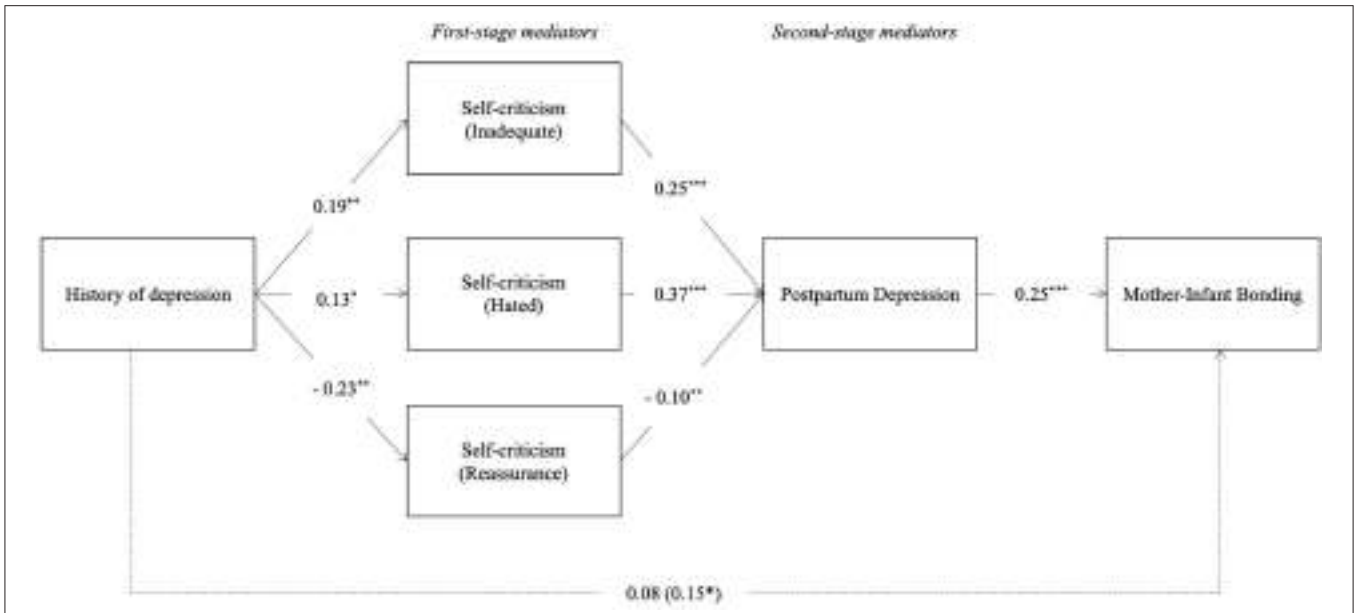

FIGURE 3 | Serial–parallel mediation model with standardized path coefficients: History of depression symptoms, inadequate-self, hated-self and reassuring-self dimensions of self-criticism, PPD Symptoms and mother–infant bonding (M1). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. The coefficients of the total effects appear in parentheses. Dashed lines are not-significant paths.

TABLE 4 | Standardized coefficients (β), unstandardized coefficients (b), unstandardized boot standard errors, and boot 95% confidence intervals of the unstandardized indirect effects of history of depression symptoms on mother–infant bonding, through inadequate-self, hated-self, reassuring-self, PPD symptoms (Model 1).

Specific indirect effect (mediators)	β	*b*	Boot SE	Boot 95% CI
History of depression symptoms → Inadequate-self → Mother–infant bonding	0.023	0.008	0.006	[−0.001, 0.020]
History of depression symptoms → Hated-self → Mother–infant bonding	−0.002	−0.001	0.003	[−0.007, 0.008]
History of depression symptoms → Reassuring-self → Mother–infant bonding	−0.004	−0.001	0.003	[−0.008, 0.005]
History of depression symptoms → PPD symptoms → Mother–infant bonding	0.023	0.007	0.005	[−0.0001, 0.018]
History of depression symptoms → Inadequate-self → PPD symptoms → Mother–infant bonding	0.012	0.004	0.002	[0.001, 0.009]
History of depression symptoms → Hated-self → PPD symptoms → Mother–infant bonding	0.012	0.004	0.003	[0.0002, 0.010]
History of depression symptoms → Reassuring-self → PPD symptoms → Mother–infant bonding	0.006	0.002	0.001	[0.0003, 0.005]

the history of anxiety symptoms and postpartum anxiety symptoms, highlighting the continuity of these risk factors during the peripartum period. These findings were in line with previous studies that showed the co-occurrence and the positive association between anxiety and depressive symptoms during PPD (e.g., Heron et al., 2004).

As for the first model of our study, the results have demonstrated that the history of depression symptoms showed significant indirect effects on mother–infant bonding through the chain of mediators, in line with the studies showing that mothers with a psychiatric history are at a higher risk of PPD symptoms and bonding problems (Lefkowitz et al., 2010; de Kruijff et al., 2019; Nakić Radoš et al., 2020; Tolja et al., 2020).

In addition, findings show that having a history of depression symptoms is associated with higher levels of inadequate-self and hated-self, and lower levels of self-reassurance, which is consistent with previous studies showing positive associations of inadequate-self and hated-self with psychopathology (Castilho et al., 2017) and a negative association of self-reassurance with psychopathology (Gilbert et al., 2004; Werner et al., 2019). The relationship between the inadequate self, hated-self and reassuring self, and PPD symptoms showed a similar pattern. This is consistent with the existing research that showed that the self-criticism had a negative effect on PPD symptoms (e.g., Vliegen and Luyten, 2009) and on those feelings of self-inadequacy mediated the stress-depression relationship (e.g., Kotera et al., 2021). Also, a stronger positive relationship between hated-self and depression was found, which is consistent with evidence showing hated-self to be consistently more highly associated with psychopathology than the inadequate self (Gilbert et al., 2004; Castilho et al., 2017; Werner et al., 2019).

Finally, higher levels of postpartum depressive symptoms were associated with higher problems in bonding, which confirms previous evidence from other studies (Edhborg et al., 2011; Dubber et al., 2015; Nakić Radoš et al., 2020; Tolja et al., 2020; Handelzalts et al., 2021). This finding is important since

TABLE 5 | Standardized regression coefficients (β), unstandardized regression coefficients (b), standard errors (SE), and model summary information for the tested serial–parallel mediation Model 2.

	Inadequate-self				**Hated-self**				**Reassuring-self**				**Postpartum Anxiety**				**Mother–infant bonding**				**Mother–infant bonding**			
																	(Total effect model)				**(Serial–parallel mediation model)**			
Antecedent	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***	***β***	***b***	***SE***	***p***
History of anxiety symptoms (IV)	0.25	0.22	0.05	0.00	0.20	0.12	0.04	0.001	−0.22	−0.19	0.05	0.000	0.221	0.60	0.15	0.00	0.14	0.05	0.02	0.025	0.050	0.02	0.02	0.43
Inadequate-self (M1)	–	–	–	–	–	–	–	–	–	–	–	–	0.096	0.30	0.15	0.05	–	–	–	–	0.172	0.06	0.02	0.00
Hated-self (M2)	–	–	–	–	–	–	–	–	–	–	–	–	0.262	1.21	0.21	0.00	–	–	–	–	0.043	0.02	0.03	0.41
Reassuring-self (M3)	–	–	–	–	–	–	–	–	–	–	–	–	−0.096	−0.29	0.13	0.28	–	–	–	–	0.005	0.00	0.02	0.92
Postpartum anxiety symptoms (M4)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.121	0.01	0.01	0.01
Constant	–	0.40	0.26	0.12	–	0.20	0.18	0.261	–	2.50	0.26	0.000	–	0.49	0.80	0.54	–	0.13	0.10	0.216	–	−0.16	0.11	0.14
History of depression symptoms (cov)	0.19	0.17	0.05	0.00	0.13	0.08	0.04	0.029	−0.23	−0.20	0.05	0.000	0.033	0.09	0.15	0.54	0.15	0.05	0.02	0.018	0.096	0.03	0.02	0.11
Mothers' age (cov)	−0.02	0.00	0.01	0.62	−0.05	−0.01	0.00	0.214	0.02	0.00	0.01	0.624	−0.058	−0.03	0.02	0.11	0.06	0.00	0.00	0.153	0.076	0.01	0.00	0.07
Infants' age (cov)	−0.01	0.00	0.01	0.80	−0.02	0.00	0.00	0.618	0.01	0.00	0.01	0.825	0.115	0.05	0.02	0.00	0.11	0.01	0.00	0.010	0.097	0.01	0.00	0.02
Gestational complications (cov)	0.01	0.01	0.07	0.84	0.00	0.00	0.05	0.931	−0.01	−0.01	0.07	0.865	0.104	0.59	0.20	0.00	−0.02	−0.02	0.03	0.446	−0.046	−0.03	0.03	0.26
Income (cov)	0.03	0.02	0.02	0.48	−0.09	−0.03	0.02	0.040	0.08	0.04	0.02	0.042	−0.011	−0.02	0.06	0.78	0.12	0.02	0.01	0.005	0.125	0.02	0.01	0.00
	$R^2 = 0.17$				$R^2 = 0.12$				$R^2 = 0.19$				$R^2 = 0.33$				$R^2 = 0.10$				$R^2 = 0.15$			
	$F_{(6,535)} = 18.59, p < 0.001$				$F_{(6,535)} = 12.23, p < 0.001$				$F_{(6,535)} = 21.14, p < 0.001$				$F_{(9,532)} = 28.56, p < 0.001$				$F_{(6,535)} = 9.44, p < 0.001$				$F\ (10,531) = 9.53, p < 0.001$			

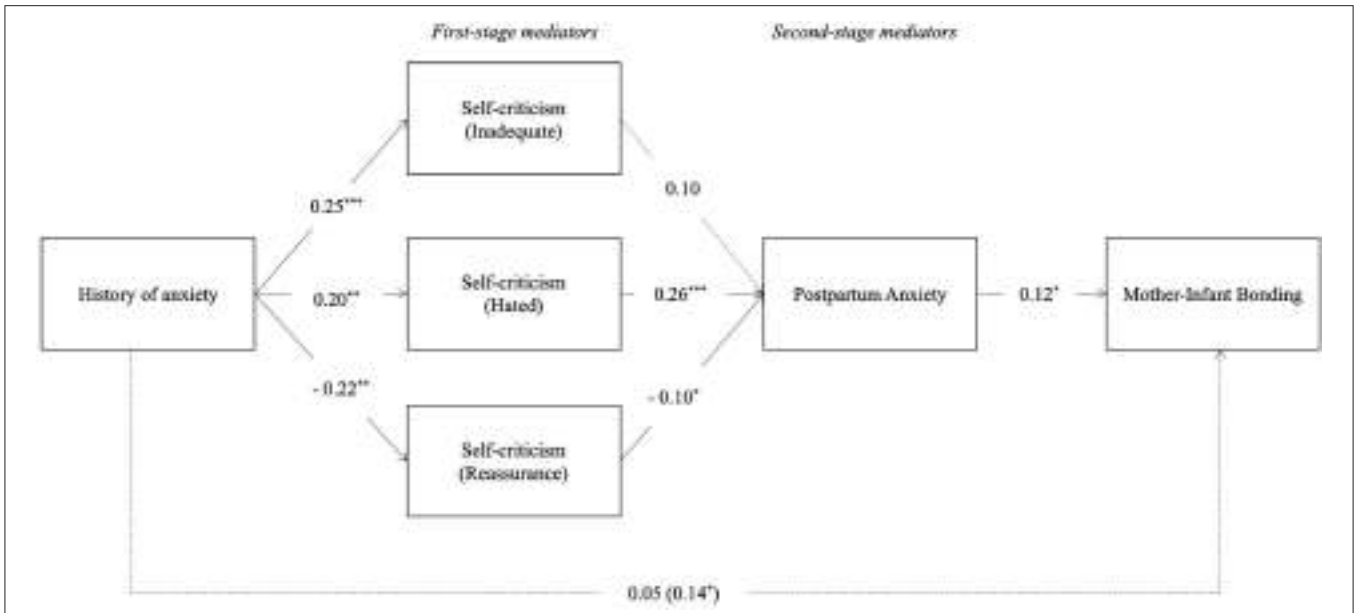

FIGURE 4 | Serial–parallel mediation model with standardized path coefficients: History of anxiety symptoms, inadequate-self, hated-self, and reassuring-self dimensions of self-criticism, postpartum anxiety symptoms and mother–infant bonding (M1). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. The coefficients of the total effects appear in parentheses. Dashed lines are not-significant paths.

TABLE 6 | Standardized coefficients (β), unstandardized coefficients (b), unstandardized boot standard errors, and boot 95% confidence intervals of the unstandardized indirect effects history of anxiety symptoms on mother–infant bonding, through inadequate-self, hated-self, reassuring-self, postpartum anxiety symptoms (Model 2).

Specific indirect effect (mediators)	β	b	Boot SE	Boot 95% CI
History of anxiety symptoms → Inadequate-self → Mother–infant bonding	0.041	0.014	0.007	[0.003, 0.030]
History of anxiety symptoms → Hated-self → Mother–infant bonding	0.009	0.003	0.005	[−0.007, 0.012]
History of anxiety symptoms → Reassuring-self → Mother–infant bonding	−0.001	−0.001	0.003	[−0.007, 0.007]
History of anxiety symptoms → Postpartum anxiety symptoms → Mother–infant bonding	0.027	0.009	0.006	[−0.0002, 0.023]
History of anxiety symptoms→ Inadequate-self → Postpartum anxiety symptoms → Mother–infant bonding	0.003	0.001	0.001	[−0.0004, 0.003]
History of anxiety symptoms → Hated-self → Postpartum anxiety symptoms → Mother–infant bonding	0.006	0.002	0.002	[−0.0001, 0.006]
History of anxiety symptoms → Reassuring-self → Postpartum anxiety symptoms → Mother–infant bonding	0.003	0.001	0.001	[−0.0000, 0.003]

it facilitates understanding of how maternal depression might impact bonding and further outcomes on infant health. Maternal depression might affect maternal bonding (Noorlander et al., 2008) and might lead to an insensitive caretaking environment (Nicol-Harper et al., 2007; Kaitz et al., 2010; Müller et al., 2016). Insensitive caretaking which can be seen in PPD symptoms might be affecting the difficulties in self-regulation of the infant (Manian and Bornstein, 2009).

As for the second model of our study, history of anxiety symptoms showed no significant indirect effects on mother–infant bonding through the overall chain of mediators. Furthermore, in our study, the direct effect of history of anxiety symptoms decreases and becomes non-significant on mother–infant bonding. Considering that there are very few studies examining the relationship between postpartum anxiety symptoms and bonding, and studies examining the relationship between the history of anxiety symptoms and bonding are even rarer and have heterogeneous results (Dubber et al., 2015; Göbel et al., 2018), this finding can be considered as a reflection of another aspect of maternal feelings on bonding before and during pregnancy. It can be evaluated that anxiety before and during pregnancy might be somehow functional in terms of bonding during the transition to parenthood (e.g., serving to protect the baby) (Figueiredo and Conde, 2011). Therefore, this finding between the history of anxiety and bonding may have been obtained. With respect to the link between postpartum anxiety symptoms and bonding, as expected, higher levels of postpartum anxiety symptoms were associated with higher problems in bonding, which confirms previous evidence from other studies (Edhborg et al., 2011; Tietz et al., 2014; Dubber et al., 2015). Mothers experiencing anxiety might show more difficulty in self-regulating, and in interacting sensitively and regulating the child (Feldman et al., 1997; Tietz et al., 2014).

In addition, consistent with previous studies on the links between self-criticism and psychopathology (Gilbert et al.,

2004; Castilho et al., 2017; Werner et al., 2019), having a history of anxiety symptoms was associated with higher levels of inadequate-self and hated-self, and lower levels of self-reassurance. The same was true with regards to the relationship between the inadequate self and reassuring self, and postpartum anxiety symptoms, which is in line with previous studies showing a negative effect of self-criticism in anxiety in the postpartum period (e.g., Vliegen and Luyten, 2009; Kotera et al., 2021). Therefore, individual attempts to cope with one's feelings of inadequacy can play an important role in the experience of anxiety in the postpartum period. Furthermore, no relationship regarding hated-self and anxiety was found. This is somewhat surprising, given evidence showing that the hated-self is more detrimental to mental health than the inadequate self (Gilbert et al., 2004; Castilho et al., 2017; Werner et al., 2019). Studies investigating the association between self-criticism and psychopathology have mostly used clinical samples (McIntyre et al., 2018; Werner et al., 2019); therefore, the fact that we used a community sample might contribute to explaining these unexpected findings regarding anxiety. Further studies that are conducted with non-clinical samples that explore the relationship between self-criticism and anxiety postpartum are needed.

Limitations and Recommendations for Future Studies

The studies presented several limitations that must be addressed. First, since this was a cross-sectional study, no causality could be inferred based on the analyses performed. Also, although the participants were instructed the exact time point to answer, the collection of data in one point could be considered as a limitation in terms of observer bias, perhaps calling into question if perhaps maternal perceptions of their previous mood as well as cognitions about the self and bonding with their child are not a function of their mood at the time of data collection. Therefore, some caution is needed when interpreting our findings. Future studies should include longitudinal designs to overcome this limitation. For instance, self-criticism, postpartum negative symptoms, and perception of infant–mother bonding of mothers with negative symptoms before and during pregnancy should be assessed 3–9 months after childbirth and, ideally, 1–2 years after childbirth to infer the possible causality and the identification of trajectories related to the impact of the history of depression and anxiety symptoms across diverse phases of postpartum period. Second, our non-probabilistic sampling procedures (i.e., convenience and snowball techniques and data collection based on social application's advertisements) might have influenced the characteristics of the sample and attracted mothers more motivated to respond to this large protocol, more digitally proficient, and with less particular impairments (psychical or neuropsychological). Also, the discrepancy between Cronbach α between the hated-self (0.74) and the inadequate self (0.92) should be noted, even though it is coherent with previous studies (e.g., Castilho et al., 2015).

Third, although the literature has highlighted the existence of high comorbidity between PPD and anxiety symptoms, our results are only focused on symptoms of PPD and anxiety, separately. Future studies could consider testing similar models with symptoms of anxiety and depression together. Moreover, self-report measures might be biased by social desirability, especially concerning mother–infant bonding.

Fourth, certain key variables are highly correlated as given in the following: History of depression symptoms and history of anxiety symptoms; PPD and postpartum anxiety symptoms; PPD symptoms and hated-self; PPD symptoms and inadequate-self. Also, although the participants were instructed the exact time point to answer, the collection of data in one point can be considered as a limitation in terms of observer bias, perhaps calling into question if perhaps maternal perceptions of their previous mood as well as cognitions about the self and bonding with their child are not a function of their mood at the time of data collection. Therefore, some cautions are needed when interpreting our findings.

Fifth, the factors concerning the context (e.g., partner's, family's or professional's support, and infant temperament and characteristics) were left out of the analyses. Future research must include their possible impact on maternal negative affect and on mother–infant bonding during the postpartum period. In addition, only intrapersonal variables are considered in the models, neither contextual nor "child" variables are included. Future research should take this into account and have more information about and from other informants and sources.

Also, the future research should test whether the proposed models apply to both common and clinically significant levels of anxiety and depression. Furthermore, the symptoms across the postpartum period, limited data exist about the stability and specific trajectories of these symptoms, and even less about the evolution of anxiety symptoms during postpartum. For that reason, the wide range of infants' ages requires caution in the interpretation of the results. Future research should consider a limited range of age, but also should characterize the pathways associated with emotional symptomatology across the postpartum period.

Finally, our study focused on depressive and anxious symptoms and on different types of self-criticism as mediating mechanisms. As such, our results should explore the cognitions, the coping mechanisms, and the emotions, associated with self-criticism, that are more prevalent in women with both depression and anxiety symptoms, and the differences among them. Moreover, the role of self-reassuring styles and self-compassion should be studied as possible protective factors for anxiety and depression in postpartum, and for the quality of mother–child bonding. Further exploration on the mechanisms through which self-critical thinking might impact psychopathology in postpartum would be important, especially regarding anxiety in which knowledge is still limited.

Strengths and Implications

This study adds to the existing research by examining both retrospectively self-reported levels of depression and anxiety symptoms before and during pregnancy, and the current (postpartum) levels of depression and anxiety symptoms in a large community sample in Portugal. The previous studies of self-criticism have been implicated in a range of

psychopathologies (McIntyre et al., 2018). Similarly, our findings also evidence the possible transdiagnostic role of self-criticism in the comprehension and maintenance of anxiety and depression during postpartum and bonding. Furthermore, we controlled the effect of depression and anxiety on each model, evidencing the differential contribution of anxiety and depression to bonding problems. Thus, they should be addressed as comorbid, despite being distinct phenotypic conditions.

The results from this study have important specific clinical implications. Given that the history of both depression and anxiety symptoms have predicted negative affect and bonding, concrete screening assessment delivered on mental care and general health institutions during pregnancy should address the existence of depressive and anxious symptoms prior and during pregnancy to help women at risk of postpartum distress and provide specific interventions. Furthermore, our findings suggest that decreasing maternal self-criticism should be targeted in preventive and therapeutic psychological interventions, and self-reassurance, which represents a self-compassionate attitude, should be promoted as a buffer mechanism to reduce the incidence of negative symptoms and bonding problems during the postpartum period. In this way, cultivating a self-accepting, mindful and non-judgmental mindset might help future and recent new mothers to adapt to changes and difficulties from this period with lower levels of self-criticism and less negative affect. Feeling less depressed and anxious might prevent bonding difficulties and less risk factors for mental health and wellbeing in mothers and children.

CONCLUSIONS

Maternal depression and other psychological problems have been described in literature as having considerable consequences on bonding during the postpartum period and afterward. This study added new insights on this previous evidence, revealing that the quality of mother–infant bonding in postpartum might be affected by the history of depression symptoms in mothers, but especially, that self-criticism and consequently the depressive symptoms might play a role in this relation. Further, the history of anxiety symptoms also has an impact on bonding but only is mediated by hated-self and, in an opposite way, by reassuring self. Our results highlight the importance of assessing previous history of maternal psychological symptoms and psychopathology, as they might represent an important risk factor for bonding in the postpartum period. Further, interventions might need to promote more self-compassionate attitudes in mothers to prevent maladaptation after the birth of a child.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical and Deontological Committee for Scientific Research of the School of Psychology and Life Sciences (CEDIC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB and LC contributed to the conception and design of the study. AB, SA, and LC organized the database. LC and ÁS performed the statistical analysis and wrote sections of the manuscript. AB, SA, and BK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Prospective Associations of Lifetime Post-traumatic Stress Disorder and Birth-Related Traumatization With Maternal and Infant Outcomes

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Objective: Many women experience traumatic events already prior to or during pregnancy, and delivery of a child may also be perceived as a traumatic event, especially in women with prior post-traumatic stress disorder (PTSD). Birth-related PTSD might be unique in several ways, and it seems important to distinguish between lifetime PTSD and birth-related traumatization in order to examine specific consequences for mother and child. This *post-hoc* analysis aims to prospectively examine the relation of both, lifetime PTSD (with/without interpersonal trauma) and birth-related traumatization (with/without postpartum depression) with specific maternal and infant outcomes.

Methods: In the prospective-longitudinal Maternal in Relation to Infants' Development (MARI) study, $N = 306$ women were repeatedly assessed across the peripartum period. Maternal lifetime PTSD and birth-related traumatization were assessed with the Composite International Diagnostic Interview for women. Maternal health during the peripartum period (incl. birth experience, breastfeeding, anxiety, and depression) and infant outcomes (e.g., gestational age, birth weight, neuropsychological development, and regulatory disorders) were assessed *via* standardized diagnostic interviews, questionnaires, medical records, and standardized observations.

Results: A history of lifetime PTSD prior to or during pregnancy was reported by 25 women who indicated a less favorable psycho-social situation (lower educational level, less social support, a higher rate of nicotine consumption during pregnancy). Lifetime PTSD was associated with pregnancy-related anxieties, traumatic birth experience, and anxiety and depressive disorders after delivery (and in case of interpersonal trauma additionally associated with infant feeding disorder). Compared to the reference group,

women with birth-related traumatization ($N = 35$) indicated numerous adverse maternal and infant outcomes (e.g., child-related fears, sexual problems, impaired bonding). Birth-related traumatization and postpartum depression was additionally associated with infant feeding and sleeping problems.

Conclusion: Findings suggest that both lifetime PTSD and birth-related traumatization are important for maternal and infant health outcomes across the peripartum period. Larger prospective studies are warranted.

Implications: Women with lifetime PTSD and/or birth related traumatization should be closely monitored and supported. They may benefit from early targeted interventions to prevent traumatic birth experience, an escalation of psychopathology during the peripartum period, and adverse infant outcomes, which in turn may prevent transgenerational transmission of trauma in the long term.

Keywords: lifetime PTSD, birth-related traumatization, pregnancy, postpartum, infant outcomes

INTRODUCTION

Many women experience traumatic events already prior to or during pregnancy, and delivery of a child may also be perceived as a traumatic event, especially in women with prior post-traumatic stress disorder (PTSD). PTSD is one of the most debilitating mental disorders and the 12-month prevalence in the German general population is 2.3% (95%CI: 1.8–2.9) (1). Women are more often affected by PTSD than men (12 month-rate in women and men: 3.6%; 95%CI: 2.8–4.7; and 0.9%, 95%CI: 0.6–1.5) and most of them experience traumatic events already prior to pregnancy (1). Still, the peripartum period is considered to be a vulnerable time frame for the onset, recurrence, and exacerbation of PTSD symptoms and other mental disorders in women (e.g., peripartum anxiety and depressive disorders) (2). Due to traumatic experiences prior to or during pregnancy about 3.3% of pregnant women suffer from PTSD and prevalence rates in risk populations (e.g., history of intimate partner violence) are even higher (about 18%) (3). In addition, up to one-third of women who have recently given birth describe their birth experience as traumatic (4), up to 10% suffer from clinically relevant posttraumatic stress symptoms during the first weeks thereafter (5–8), and up to 4% develop the full clinical picture of PTSD (3, 7, 9, 10). The prevalence of postpartum PTSD is even higher in at-risk populations (e.g., up to 19% after preterm delivery, emergency cesarean section, or still birth) (3, 7, 9, 10).

Birth-related PTSD might be unique in several ways, and it seems important to distinguish between lifetime PTSD and birth-related traumatization. Birth experience may become traumatic if the birth involves actual or threatened death or an injury for a woman or for the infant (2, 11, 12). Birth-related traumatization affects the mother-child-dyad and childcare of the baby might trigger maternal traumatic memories of birth. Given that childcare is usually associated with an increased vigilance, the hyperarousal criteria should be considered with caution. Risk factors of birth-related traumatization are a history of sexual trauma and intimate partner violence, depression or anxiety in pregnancy, fear of childbirth, complications during pregnancy, obstetric interventions/ operative delivery, peripartum infant complications, a subjective negative birth experience, and perception of inadequate intrapartum care or lack of social support (5, 11–14).

Both, lifetime PTSD and birth-related traumatization may be associated with postpartum depressive and anxiety disorders, whereas the relation to pregnancy- and child-related fears is less studied (5, 15–17). Moreover, PTSD in the context of pregnancy and childbirth might affect the partnership (e.g., sexual problems) and the mother-child-dyad (e.g., bonding) (16, 18, 19). For instance, traumatic memories or re-experiencing of the childbirth might reduce emotional availability of the mother to the infant, especially if the infant serves as a trigger of the event. This, in turn, could be crucial for the type of attachment the infant develops to the mother. Mother-child dyads may be further fragiled by the numbness affected women are likely to perceive (20). Some studies showed that birth-related PTSD symptoms are associated with bonding and breastfeeding difficulties that may have long-term health implications for infants (21, 22). In addition, symptoms of hyperarousal and intrusion might lead to impaired childcare and interaction with the child (e.g., angry or intrusive interaction) (19, 23, 24) and comorbid maternal depression might contribute additionally to parenting impairment (25, 26). A review by Christie et al. (27) found that parental PTSD was associated with impaired functioning across various parenting domains and less optimal parent-child relationships (27). The Perinatal Interactional Model of Intergenerational transmission of traumatization proposes that maternal PTSD leads to suboptimal caregiving behavior and parent-child interactions, which undermine child regulatory capacity and increase distress leading to poorer social-emotional outcomes for offspring of parents with PTSD (28). Moreover, Pat-Horenczyk et al. (29) suggested the idea of relational emotional regulation in which difficulties with emotion regulation pass from mother faced with trauma to the child (29). In line with this, Davies and colleagues showed that women with postpartum PTSD symptoms following childbirth and postpartum depression perceive their attachment relationships to be less optimal and

rated their infants as being temperamentally more difficult and less easy to soothe as compared to non-symptomatic women (9). Moreover, some prospective studies found maternal postpartum PTSD to be associated with difficult temperament and/ or poorer cognitive and social-emotional development in infants up to 2 years (19, 30). Especially interpersonal trauma might be crucial for the relation between mother and child and for early child development (e.g., neuropsychological development) (2, 31, 32).

Aims of the Study

In sum there is evidence that PTSD prior to and during pregnancy as well as birth-related traumatization are associated with adverse maternal and infant outcomes. As it has been argued that birth-related PTSD might be unique in several ways it seems important to distinguish between lifetime PTSD and birth-related traumatization in order to examine specific consequences for the mother and child (31, 33, 34). A *post-hoc* analysis of the data of the *Ma*ternal *A*nxiety in *R*elation to *I*nfant Development (MARI) study was conducted to examine specific associations of lifetime PTSD and birth-related traumatization with the above mentioned outcomes. In the prospective-longitudinal MARI study (35, 36) women were recruited already during early pregnancy and reported their lifetime diagnostic status prior to pregnancy. Participants were followed up three times during pregnancy and three times after delivery within this multi-wave and multi-method study. Given that anxiety and depressive disorders occur frequently in expectant mothers and may be also relevant for the considered outcomes, we chose expectant mothers with no anxiety and/or depressive disorders prior to or during pregnancy as reference group. This allows the examination of specific associations of lifetime PTSD and birth-related traumatization with the specific outcomes.

Using the data of the MARI study we were able to examine (1) whether women with PTSD prior to or during pregnancy were at higher risk for poor maternal health during the peripartum period (e.g., pregnancy-related fears, maternal anxiety and depressive disorder, operative delivery), for a traumatic birth experience, and adverse gestational and infant outcomes (e.g., regulatory disorders, attachment, neuropsychological development) as compared to women with neither anxiety nor depressive disorder until third trimester of pregnancy. Further, we examined (2) whether women suffering from birth-related traumatization were at higher risk for adverse maternal and infant outcomes (e.g., child-related fears, maternal anxiety and depressive disorder, maternal sexual problems, infant regulatory disorders) as compared to women with no anxiety or depressive disorder prior to delivery and no birth-related traumatization. Here we additionally investigated the role of postpartum depression at 2, 4 or 16 month postpartum (25).

METHODS

Procedure

The prospective-longitudinal MARI Study was conducted among $N = 306$ expectant mothers, sampled from the community in gynecological outpatient settings in Dresden, Germany (study period: 01/2009 – 09/2012). Participating pregnant women (and their infants) completed up to seven assessments: T1 (baseline): week 10 to 12 of gestation; T2: week 22 to 24 of gestation; T3: week 35 to 37 of gestation; T4: 10 days postpartum; T5: 2 months postpartum; T6: 4 months postpartum; T7: 16 months postpartum (36).

Informed consent was obtained from all participants and all legal guardians of the infants. The MARI Study was carried out in accordance with the Helsinki Declaration (2013) and was reviewed by the Ethics Committee of the Technische Universität Dresden (No: EK 94042007). More detailed information including objectives, methods, design, and a detailed study flow chart has been published elsewhere (35, 36).

Participants

Overall, $N = 533$ pregnant women were approached by the study team in gynecological outpatient settings in Dresden (Germany) and screened for inclusion and exclusion criteria. Fifty women were excluded based on the exclusion criteria, which were as follows: gestational age >12 weeks ($n = 8$), younger than 18 or older than 40 years ($n = 8$), multiple pregnancy ($n = 2$), history of more than three spontaneous abortions/(induced) terminations of pregnancy/stillbirths or infant impairment ($n = 2$), invasive fertility treatment ($n = 9$), severe physical disease/microsomnia/skeletal malformation ($n = 6$), substance abuse or heroin substitution during the past 6 months ($n = 0$), severe psychiatric illness ($n = 2$), expectation to leave the area of Dresden ($n = 6$), and insufficient mastery of German language ($n = 7$). Additional 9 women did not participate due to spontaneous abortion before the baseline interview (T1), 10 due to lacking consent of the father of the infant, 154 due to lack of time, and 4 due to unknown reasons (36).

Overall, data of 306 women were eligible for the MARI study. Due to spontaneous abortion/induced termination of pregnancy, the participation of $n = 8$ women ended after T1. During the study, $n = 3$ women moved away, $n = 5$ women could not be reached any more by phone, postal, or personal contact, $n = 9$ women reported lack of time or interest for further participation, and $n = 7$ women refused contact for follow-up assessment. Overall, retention rate until 16 months after delivery (T7) was 89.5% ($n = 274$). Some women did not participate at single assessments, e.g. due to preterm delivery, own/infant sickness, or lack of time (T2: $n = 0$, T3: $n = 10$, T4: $n = 2$, T5: $n = 5$, T6: $n = 1$, T7: $n = 7$) (a detailed flow chart of the MARI study was presented by Martini et al. (36).

Measures and Procedures

Figure 1 presents the assessment points of the MARI study and predictors and outcomes of the present analyses. A Computer-Assisted Personal Interview (CAPI) version of the Composite International Diagnostic Interview for Women (CIDI-V) (37) was applied at each assessment wave except for T4 (10 days postpartum). Due to the special situation after delivery, questionnaires were used at T4 instead of the diagnostic interview to assess mode of delivery, birth experience, neonatal outcomes, and postpartum adjustment.

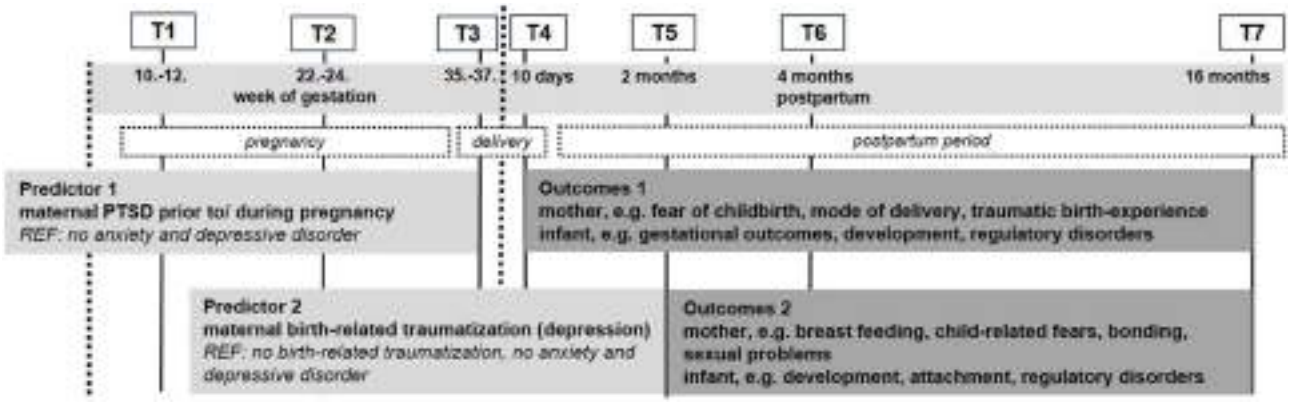

FIGURE 1 | Assessment waves, measures and outcomes for the *post-hoc* analyses of lifetime PTSD and birth-related traumatization with maternal and infant outcomes.

Predictors: PTSD Prior to or During Pregnancy and Birth-Related Traumatization

Maternal post-traumatic stress disorder as well as anxiety and depressive disorder were assessed using the CIDI lifetime version at baseline (T1) and the CIDI interval version at follow-up (T2, T3, T5, T6, T7). The CIDI-V is a modified version of the World Health Organization CIDI (WHO-CIDI) (38) that allows for a fully standardized assessment of DSM-IV-TR mental disorders in women (with specifying ICD-10 codes). Psychometric properties of the CIDI were modest to very good (39, 40). Diagnostic interviews were conducted by psychologists having received 1 week of intensive training and conducting a series of supervised interviews. Interviewers were closely monitored throughout the field period by experienced supervisors (clinical psychologists) (36).

Lifetime PTSD was assessed at Baseline (T1) and in Follow-up (T2, T3, T5, T6, and T7) interviews using the questions of the CIDI-V (Section N). Overall, $n = 25$ participants suffered from PTSD prior to or during pregnancy (35).

Birth-related traumatization was assessed at T5, T6, and T7 using adapted questions and lists of section N relating to the birth. It was defined as traumatic birth experience (A1: delivery as traumatic event or A2: intense fear, helplessness, or horror) AND hyperarousal or re-experiencing delivery or avoidance at T5, T6, or T7. Birth-related traumatization was indicated by $N = 35$ women. Of those women, $N = 19$ additionally indicated postpartum depression.

Since only $N = 4$ women indicated both PTSD prior to or during pregnancy and birth-related traumatization, this small group could not be analyzed in more detail.

Maternal and Infant Outcomes

Fear of childbirth during pregnancy and experience of childbirth was measured based on the German version of the Wijma Delivery Expectancy/ Experience Questionnaire (W-DEQ, Version A, Version B) (41–43). The W-DEQ is a reliable and valid 33-item questionnaire, with scores ranging from 'not at all' (0) to 'extremely' (5), yielding a minimum score of 0 and a maximum score of 165 (some items have to be reversed and a higher score indicates more intense fear of childbirth) (44, 45).

Maternal pregnancy- and child related fears were assessed at the end of the CIDI-V section on anxiety disorders with embedded questions and lists (37). During the assessments in pregnancy (T1–T3) the participants were instructed to read a list with pregnancy-related fears (e.g., rumination about current pregnancy, fear of labor pain, fear of vaginal delivery) and at T6 and T7 a list with child-related fears was provided (e.g., fear of mistakes concerning child care, fear of financial problems, fear of age-inappropriate development). The participants were asked "Have you ever ("Since the last interview, have you…") had a strong fear or avoidance of any of the situations/things in the list?" If the participants indicated one or more of these fears, they were asked whether the fear was excessive or stronger compared to other women and to evaluate the burden of the reported fears. Further questions on the presentation of associated anxiety symptoms (e.g., racing heart, sweating, trembling/shaking, dry mouth, difficult breathing, sensation of choking), frequency (sometimes or most of the time vs. only once), and interference with daily live (not at all or somewhat vs. a lot or very much) were asked.

Information on *gestational age*, *preterm delivery* (<37 + 0 week of gestation), *infant birth weight*, and *mode of delivery* was collected via medical records (46).

Sexual problems were assessed at T7 using the German version of the Massachusetts General Hospital Sexual Function Questionnaire (MGH) (47, 48). The MGH is a five-item screening instrument that assesses sexual problems with respect to sexual interest, arousal, orgasm, lubrication, and overall sexual satisfaction: (i) "How has your interest in sex been over the past month?"; (ii) "How has your ability to become sexually aroused or excited been over the past month?"; (iii) "How has your ability to achieve orgasm been over the past month?"; (iv) "How has your ability to become or remain lubricated been over the past month?"; (v) "How would you rate your overall sexual satisfaction over the past month?". Items are labeled: 1: greater than normal; 2: normal; 3: minimally diminished; 4: moderately diminished; 5: markedly diminished; and 6: totally absent. Based

on previous studies (47), a cutoff score of three was used to differentiate normal sexual functioning (≤3) from putative sexual problems or dysfunctions (>3) on each item. Concurrent and predictive validity (with respect to sexual functioning and sexual dysfunctions assessed by other self-reports and diagnostic instruments) of the MGH have been shown to be high (47, 49).

Duration of breastfeeding and *infant regulatory disorders* were assessed with a structured diagnostic interview (Baby-DIPS) at T5, T6, and T7 (50). *Excessive infant crying* was defined according to the "rule of three" by Wessel et al. (51) as crying for ≥3 h per day on ≥3 days per week for ≥3 weeks (51). *Feeding problems* were defined as any feeding problem (from a list of 16 feeding problems), failure-to-thrive, or mothers worrying (a lot or very much) about infant growth over a period of at least 4 weeks. *Sleeping problems* were defined as difficulties in initiating or maintaining sleep for ≥3 nights per week for ≥3 months while the mother was somewhat, a lot, or very much impaired by her infant's sleeping difficulties between 6 and 16 months (52). Cases that were attributable to a concurrent medical condition were excluded. The Baby-DIPS comprises good to excellent inter-rater reliability as well as high acceptance rates for interviewers and participants (53). Rates and co-occurrence of regulatory problems in the MARI sample were comparable to rates reported by others (52, 54).

Maternal bonding was assessed with the German Version of the Postpartum Bonding Instrument (PBQ) at T5 (55). This self-report questionnaire consists of 25 items assessing impaired bonding, rejection and anger, anxiety about care, and risk of abuse (42, 56). The very good psychometric properties were confirmed for the German Version (55). For this analysis, the scales impaired bonding as well as rejection and anger were relevant.

Observations of the mothers and their infants were conducted using standardized observation paradigms to assess infants' temperament (57), neuropsychological development (58), and the quality of infant attachment (59). Standardized observations were conducted by two female psychologists who were blinded to the diagnosis of the mother and had received 2 weeks of training. All observations were recorded by three cameras and supervised to ensure a high assessment quality. Video coding was conducted with the software "Interact" (Mangold).

Neuropsychological development was assessed at T6 and T7 with the standardized procedure by Petermann and Renziehausen (58). The tasks allow for an assessment of developmental deficits in different areas (movement control, fine motor skills, visual perception, exploration behavior, receptive and expressive language, cognitive performance). Coding was conducted by graduate and postgraduate psychology students according to the manual guidelines (58).

Temperament was measured with the procedures developed by Kagan et al. (60). For the assessment of *infant's reactivity* at T6, the infants sat in a reclining cushioned seat and heard some taped sentences, saw three different colorful mobiles move back and forth, had a cotton swab dipped in dilute butyl alcohol placed under the nostrils, heard a female voice speaking different syllables, and saw a colored umbrella spread out. During these procedures the mother was out of view of the infant. Videotapes were coded for high motor activity (multiple arm, leg, and back movements) and crying (high percentage of time spent crying) in response to the stimuli. Infants were classified as "highly reactive" (high motor activity and crying), "low reactive" (low motor activity and crying), or neither (either high motor activity and low crying amount or the opposite). The assessment of *behavioral inhibition* at T7 involved the presentation of inanimate stimuli to the child (a spinning bingo wheel with noisy objects inside, rotating toys, a puppet show, and sweet and sour tastes). Moreover, strangers (a woman dressed in a white laboratory coat and surgical face mask and a woman with a black cloth over her head and shoulders) attempted to interact with the child. Video coding was conducted by graduate and postgraduate psychology students who were blinded and had received a training of 2 weeks for coding the infant's reactivity and behavioral inhibition (60). The average coding time was 45 min for reactivity and behavioral inhibition. At least 10 videos were coded during training sessions to yield an adequate observer agreement (kappa >0.8) and about 10% of all videos were randomly selected and re-analyzed for quality check to ensure observer agreement with satisfying results (61).

Attachment: At T7 mother-infant-dyads participated in the Strange Situation Procedure (59), which consisted of eight episodes, including two brief separations and reunions of the infant from/with the mother. Following the procedures described by Ainsworth et al. (59) and Main and Solomon (62), the attachment group classification was based primarily on the infant's reactions to the mother's return (59, 62). Infants who actively greeted and/or sought contact with the mother upon reunion and returned to exploration within 3 min were classified as secure (Typ B: secure). Infants who actively averted gaze or avoided or ignored the mother immediately upon reunion (Typ A: avoidant) and infants who sought to reunite with the mother but displayed ineffective proximity and contact-seeking behavior, showing anger and active resistance to contact or prolonged fussiness and persistent low-level distress (Typ C: ambivalent/resistant) were classified as insecure. Video coding was conducted by graduate and postgraduate psychology students who were blinded and had received the coding training. The average coding time for attachment videos was 60 min. Cohen's kappa coefficient for the secure and insecure (avoidant and resistant) attachment classifications was based on 20% of randomly selected and independently scored videotapes of the Strange Situation Test (63). Interrater reliability was conducted on 20% of the sample ($\kappa = 1.00$ for ABC classification). Final scores for difficult tapes and coder disagreements were based on consensus [for more information see (64)].

Statistical Analyses

All analyses were performed using STATA version 14 (65). For research question (1) linear and logistic regression analyses were conducted to examine concurrent and prospective associations (Beta, ß and odds ratios, OR) of maternal PTSD prior to or during pregnancy with and without interpersonal trauma with maternal and infant health outcomes (reference: women with neither anxiety nor depressive disorder until T3). For research question (2) linear and logistic regression analyses were conducted to examine betas/ORs including 95% confidence intervals (CI) of maternal birth-related traumatization (with and

TABLE 1 | Sociodemographic and gynecological characteristics of women with any PTSD until T3 (with/without interpersonal trauma) ($N = 25$) as compared to women with neither anxiety nor depressive disorder until T3 ($N = 100$).

	Women with neither anxiety nor depressive disorder until T3 ($N = 100$)	**PTSD prior to or during pregnancy with/without interpersonal trauma ($N = 25$)**	**Significant group differences**
	***N*, % or M, SD**	***N*, % or M, SD**	
Age (M, SD)	27.9 (4.6)	27.1 (3.7)	
Educational status (*n*, %)			
Lower education (≤10 years)	25 (25.0)	**13 (52.0)**	**Chi²=6.891, $p = 0.009$**
Higher education (>10 years)	75 (75.0)	**12 (48.0)**	
Marital status (*n*, %)			
Not married	64 (64.0)	18 (72.0)	
Married	36 (36.0)	7 (28.0)	
Cohabitation (*n*, %)			
Not living together	6 (6.0)	0 (0.0)	
Living together	94 (94.0)	25 (100.0)	
Working time at baseline (*n*, %)			
Full-time job	37 (37.0)	8 (32.0)	
Part-time job	26 (26.0)	4 (16.0)	
Currently not working	37 (37.0)	13 (52.0)	
Monthly household income after taxes (*n*, %)			
< 500€	9 (9.0)	1 (4.0)	
500–1,500€	34 (34.0)	11 (44.0)	
1,500–2,500€	27 (27.0)	9 (36.0)	
2,500–3,500€	19 (19.0)	2 (8.0)	
3,500–4,500€	8 (8.0)	2 (8.0)	
>4,500€	3 (3.0)	0 (0.0)	
Parity (*n*, %)			
Primipara	60 (60.0)	11 (44.0)	
Multipara	40 (40.0)	14 (56.0)	
Pregnancy planned/ desired: yes (*n*, %)	86 (94.5)	22 (95.7)	
Prior spontaneous abortions (*n*, %)			
No	79 (79.0)	16 (64.0)	
Yes	21 (21.0)	9 (36.0)	
Any nicotine consumption during pregnancy (*n*, %)	3 (3.0)	**4 (16.0)**	**Chi²=6.394, $p = 0.011$**
Any alcohol consumption during pregnancy (*n*, %)	31 (31.0)	7 (28.0)	
Social support during pregnancy (F-SozU, T2) (M, SD)	4.5 (0.4)	**4.1 (0.7)**	**$t = 3.122$, $p > 0.001$**
Partnership quality during pregnancy (PFB, T2) (M, SD)	72.8 (10.5)	68.5 (18.1)	

T3, MARI assessment during third trimester of pregnancy; REF, reference; PTSD, post-traumatic stress disorder; n, number; %, percentage; M, mean; SD, standard deviation; Chi², Chi-squared test; t, t-test; p, p-value. Bold: significant group differences.

without depression) with maternal and infant health outcomes (reference: neither anxiety nor depressive disorder prior to or during pregnancy and no birth-related traumatization). Separate analyses were conducted for each outcome and no adjustment for multiple testing was applied, because the individual tests were related to individual hypotheses. Statistical significance was evaluated two-sided at the 5% level ($p < 0.05$).

RESULTS

To investigate research question 1, analyses were based on the following three diagnostic groups:

- Reference: neither anxiety nor depressive disorder prior to or during pregnancy (until T3) ($N = 100$)
- PTSD prior to or during pregnancy (cumulative lifetime diagnosis until T3) ($N = 25$)
- PTSD prior to or during pregnancy with interpersonal traumata (cumulative lifetime diagnosis until T3) ($N = 17$)

Women with PTSD prior to or during pregnancy were characterized by a lower educational level (education: ≤10 years: reference: 25.0%, PTSD prior to or during pregnancy: 52.0%; Chi²=6.891, $p = 0.009$) compared to women with neither anxiety nor depressive disorder until delivery (**Table 1**). Moreover, women with PTSD prior to or during pregnancy

TABLE 2 | Maternal and infant outcomes in women with PTSD prior to or during pregnancy (with interpersonal trauma) compared to women with neither anxiety nor depressive disorder until T3.

	Reference group: Neither anxiety nor depressive disorder prior to or during pregnancy (until T3) (*N* = 100)	**PTSD prior to or during pregnancy (w/wo interpersonal trauma) (*N* = 25)**		**PTSD prior to or during pregnancy with interpersonal traumata (until T3) (*N* = 17)**	
	***N*, % or M, SD**	***N,* % or M, SD**	**OR (95%CI) or ß (95%CI)**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**
Maternal health during pregnancy and birth experience					
Fear of childbirth (W-DEQ-A, T3) (M, SD)	57.9 (21.5)	**69.3 (22.1)**	**ß = 11.40 (1.21–21.59)**	**69.7 (19.0)**	**ß = 11.80 (0.08–23.51)**
Birth experience (W-DEQ-B, T4) (M, SD)	62.8 (21.8)	67.3 (18.2)		65.8 (18.8)	
Pregnancy-related anxiety (*n*, %)					
Fear of labor pain	19 (19.0)	8 (32.0)		5 (29.4)	
Fear of vaginal delivery	26 (26.0)	10 (40.0)		8 (47.1)	
Fear of perineal rupture/episiotomy	27 (27.0)	6 (24.0)		5 (29.4)	
Fear of epidural anesthesia	8 (8.0)	**10 (40.0)**	**OR = 7.67 (2.61–22.53)**	**7 (41.2)**	**OR = 8.05 (2.41–26.89)**
Excessive pregnancy-related fear	7 (7.0)	*5 (20.0)*		3 (17.7)	
Presentation of anxiety symptoms	8 (8.0)	4 (16.0)		3 (17.7)	
Interference with daily live	3 (3.0)	**6 (24.0)**	**OR = 10.21 (2.35–44.43)**	**3 (17.7)**	**OR = 6.93 (1.27–37.76)**
Evaluation of fears as frequent	9 (9.0)	4 (16.0)		3 (17.7)	
Mode of delivery (*n*, %)					
Spontaneous delivery	78 (85.7)	20 (87.0)		14 (87.5)	
C-section/ Operative vaginal delivery	13 (14.3)	3 (13.4)		2 (12.5)	
Support and control during delivery (M, SD)					
Internal control (SCIB)	32.2 (8.1)	28.7 (9.2)		27.9 (9.4)	
External control (SCIB)	38.1 (8.9)	38.0 (8.2)		38.4 (8.7)	
Support (SCIB)	46.9 (8.6)	46.7 (11.3)		44.6 (12.0)	
DSM-VI criteria for traumatic birth experience (*n*, %)					
A1: delivery as traumatic event	11 (12.1)	**9 (42.9)**	**OR = 5.45 (1.87–15.90)**	**6 (42.9)**	**OR = 5.45 (1.59–18.70)**
A2: intense fear, helplessness, or horror	15 (16.5)	**8 (38.1)**	**OR = 3.12 (1.10–8.82)**	**6 (42.9)**	**OR = 3.80 (1.15–12.55)**
B: re–experiencing delivery	1 (1.0)	**4 (16.0)**	**OR = 18.85 (2.00–177.37)**	**2 (11.8)**	**OR = 13.20 (1.13–154.68)**
C: avoidance of recollection due to delivery	0 (0.0)	0 (0.0)	omitted	0 (0.0)	omitted
E: alterations in arousal following delivery	6 (6.0)	2 (8.0)		0 (0.0)	omitted
Any postpartum anxiety disorder (*n*, %)	8 (8.8)	**11 (47.8)**	**OR = 9.51 (3.19–28.39)**	**7 (43.8)**	**OR = 8.07 (2.37–27.49)**
Postpartum depression (*n*, %)	0 (0.0)	7 (30.4)	omitted	5 (31.3)	omitted
Infant health outcomes					
Gestational age (M, SD)	39.5 (1.5)	39.4 (1.2)		39.4 (1.2)	
Birth weight (M, SD)	3,403.2 (58.1)	3.510.7 (440.7)		3,494.1 (440.6)	
Excessive crying (*n*, %)	6/91 (6.6)	3/23 (13.0)		2/16 (12.5)	
Feeding problems (*n*, %)	24/91 (26.4)	10/23 (43.5)		**9/16 (56.3)**	**OR = 3.59 (1.20–10.70)**
Sleeping problems (*n*, %)	9/91 (9.9)	4/23 (17.4)		4/16 (25.0)	

(Continued)

TABLE 2 | Continued

	Reference group: Neither anxiety nor depressive disorder prior to or during pregnancy (until T3) (*N* = 100)	**PTSD prior to or during pregnancy (w/wo interpersonal trauma) (*N* = 25)**		**PTSD prior to or during pregnancy with interpersonal traumata (until T3) (*N* = 17)**	
	***N*, % or M, SD**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**
Neuropsychological development (T6) (M, SD)	11.6 (0.8)	11.6 (0.6)		11.6 (0.6)	
Neuropsychological development (T7) (M, SD)	13.3 (1.8)	13.6 (1.6)		13.1 (1.7)	
Temperament: highly reactive (T6) (*n*, %)	9/83 (10.8)	5/22 (22.7)		4/15 (26.7)	
Temperament: Behavioral Inhibition (T7) (*n*, %)	38/84 (45.2)	5/20 (25.0)		5/13 (38.5)	
Insecure attachment (Strange Situation) (T7) (*n*, %)	29/82 (35.4)	7/20 (35.0)		4/13 (30.8)	

T3, 3rd assessment during third trimester of pregnancy; T5, 5th assessment 2 months postpartum; T6, 6th assessment 4 months postpartum; T7, 7th assessment 16 months postpartum; REF, reference; Any PTSD until T3, women with any PTSD until T3, Any PTSD + man-made trauma until T3, women with any PTSD with manmade trauma until T3, W-DEQ, Wijma Delivery Expectancy/Experience Questionnaire; PBQ, Postpartum Bonding Questionnaire; N, number; %, percentage; M, mean; SD, standard deviation; OR, odds ratio; 95%CI, 95% confidence interval. Bold: significant group differences.

reported more often nicotine consumption during pregnancy (16.0% vs. 3.0%; Chi^2=6.394, $p = 0.001$) and lower social support during pregnancy (F-Sozu: M=4.1, SD=0.7 vs. M=4.5, SD=0.4; $t = 3.122$, $p > 0.001$) as compared to the reference group. There were no significant differences between the groups with regard to age, marital status, and monthly household income (**Table 1**).

Table 2 shows maternal and infant outcomes in women with PTSD prior to or during pregnancy compared with or without interpersonal trauma ($N = 25$) to women with neither anxiety nor depressive disorder until T3 ($N = 100$). Women with history of PTSD reported more fear of childbirth and fear of epidural anesthesia and perceived delivery more often as traumatic (including re-experiencing delivery later on). Moreover, infants of women with PTSD prior to delivery and interpersonal trauma ($N = 17$) were at higher risk for feeding problems.

To investigate research question 2, analyses were based on the following three diagnostic groups:

- Reference: neither anxiety nor depressive disorder prior to or during pregnancy (until T3) and no birth-related traumatization (traumatic birth experience (A1 or A2) AND no hyperarousal/ re-experiencing/ avoidance) ($N = 70$)
- birth-related traumatization (traumatic birth experience (A1 or A2) AND hyperarousal or re-experiencing or avoidance) ($N = 35$)
- birth-related traumatization (traumatic birth experience (A1 or A2) AND hyperarousal or re-experiencing or avoidance) AND depression ($N = 19$)

Table 3 shows maternal and infant outcomes in women with birth-related traumatization compared to women with neither anxiety nor depressive disorder until T3 and no birth-related traumatization. A higher risk for child-related fears, postpartum anxiety disorders, and sexual problems was reported by women with birth-related traumatization. Moreover, infants of mothers with birth-related traumatization and postpartum depression were at higher risk for feeding and sleeping problems.

DISCUSSION

This prospective longitudinal study demonstrated that (1) women with PTSD prior to or during pregnancy presented with a disadvantageous psycho-social situation, reported more pronounced fear of childbirth, and indicated more often a traumatic birth experience compared to women without anxiety and depressive disorder prior to delivery. Moreover, infants of women with PTSD and interpersonal trauma, had a higher risk for feeding problems. (2) Women with birth-related traumatization indicated numerous adverse outcomes (e.g., postpartum anxiety and depression, child-related fears, sexual problems), and in case of additional postpartum depression, the infants were more often affected by feeding and sleeping problems.

The first research question examined the associations of PTSD prior to or during pregnancy with specific maternal and infant outcomes. As expected and in line with previous research, women with PTSD prior to or during pregnancy reported more often pregnancy- and child-related fears and they were further at higher risk for a traumatic birth experience compared to women without anxiety and depressive disorder prior to delivery (12). Moreover, those women presented with a disadvantageous psycho-social situation (lower educational level, less social support) and indicated more often nicotine consumption during pregnancy (66, 67). These factors can be associated with a cascade of behavioral health and neuroendocrine changes that

TABLE 3 | Maternal and infant outcomes in women with birth-related traumatization (and depression) after delivery compared to women with neither anxiety nor depressive disorder until T3 and no birth-related traumatization.

	Reference group: Neither anxiety nor depressive disorder until T3 and no birth-related traumatization (*N* = 70)	**Birth-related traumatization: Traumatic birth experience (A1/ A2) + (hyperarousal/ re-experiencing/ avoidance) (*N* = 35)**		**Birth-related traumatization: Traumatic birth experience (A1/ A2) + (hyperarousal/ re-experiencing/ avoidance) + depression (*N* = 19)**	
	***N*, % or M, SD**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**
Maternal health during postpartum period					
Duration of breastfeeding (M, SD)	9.4 (4.6)	9.6 (4.5)		8.8 (4.7)	
Maternal impaired bonding (T5) (PBQ) (M,SD)	4.3 (4.1)	5.3 (4.3)		5.5 (4.1)	
Maternal rejection and anger (T5) (PBQ) (M,SD)	1.5 (2.0)	1.7 (2.2)		1.8 (1.9)	
Child-related fears/ anxiety (*n*, %)					
Fear of mistakes concerning child care	9 (12.9)	**11 (31.4)**	**OR = 3.11 (1.14–8.44)**	6 (31.6)	
Fear of mistakes concerning child feeding	12 (17.1)	**14 (40.0)**	**OR = 3.22 (1.29–8.07)**	7 (36.8)	
Fear of financial problems	2 (2.9)	2 (5.7)		2 (10.5)	
Fear of mistakes concerning child rearing	3 (4.3)	**10 (28.6)**	**OR = 8.93 (2.27–35.14)**	**6 (31.6)**	**OR = 10.31 (2.28–46.56)**
Fear concerning quality of day care*	7 (10.3)	8 (23.5)		3 (16.7)	
Fear that child suffers from familial conflicts*	0 (0.0)	4 (11.8)	omitted	1 (5.6)	omitted
Fear of separation from child	3 (4.4)	**7 (20.6)**	**OR = 5.62 (1.35–23.36)**	3 (16.7)	
Fear of age-inappropriate infant development	5 (7.1)	5 (14.3)		**5 (26.3)**	**OR = 4.64 (1.18–18.23)**
Fear of viral or other infection/ disease	8 (11.4)	8 (22.9)		4 (21.1)	
Fear of infant injury	11 (15.7)	9 (25.7)		3 (15.8)	
Fear of infant death	13 (18.6)	**16 (45.7)**	**OR = 3.69 (1.51–9.06)**	**9 (47.4)**	**OR = 3.95 (1.34–11.66)**
Evaluation of fear as excessive	30 (42.9)	**23 (65.7)**	**OR = 2.56 (1.10–5.94)**	13 (68.4)	
Presentation of anxiety symptoms	7 (10.0)	**10 (28.6)**	**OR = 3.60 (1.23–10.51)**	5 (26.3)	
Evaluation of fears as frequent	6 (8.6)	**9 (25.7)**	**OR = 3.69 (1.19–11.42)**	4 (21.1)	
Interference with daily life	2 (2.86)	**5 (14.3)**	**OR = 5.67 (1.04–30.87)**	**4 (21.1)**	**OR = 9.07 (1.52–54.15)**
Any anxiety disorder postpartum	6 (8.6)	**14 (40.0)**	**OR = 7.11 (2.43–20.86)**	**8 (42.1)**	**OR = 7.76 (2.25–26.72)**
Postpartum depression	0 (0.0)	19 (54.3)	omitted	*19 (100.0)*	*group definition*
Sexual problems (T7) (M, SD)					
Sexual interest	3.2 (1.4)	**3.9 (1.3)**	**ß = 0.76 (0.18–1.33)**	**4.2 (1.2)**	**ß = 1.02 (0.30–1.75)**
Sexual arousal	2.8 (1.4)	**3.4 (1.4)**	**ß = 0.60 (0.02–1.19)**	3.5 (1.4)	
Orgasm	2.7 (1.4)	**3.6 (1.7)**	**ß = 0.90 (0.26–1.53)**	**3.8 (1.8)**	**ß = 1.10 (0.29–1.91)**
Lubrication	2.3 (0.9)	**3.0 (1.4)**	**ß = 0.76 (0.28–1.24)**	**2.9 (1.4)**	**ß = 0.67 (0.09–1.25)**
Overall sexual satisfaction	2.8 (1.3)	**3.9 (1.5)**	**ß = 1.1 (0.50–1.67)**	**4.4 (1.5)**	**ß = 1.57 (0.84–2.29)**
Infant Health and infant outcomes					
Excessive crying (*n*, %)	5/70 (7.1)	4/35 (11.4)		3/19 (15.8)	
Feeding problems (*n*, %)	17/70 (24.3)	15/35 (42.9)		**12/19 (63.2)**	**OR = 5.34 (1.81–15.74)**
Sleeping problems (*n*, %)	8/70 (11.4)	9/35 (25.7)		**8/19 (42.1)**	**OR = 5.64 (1.75–18.18)**
Neuropsychological development (T6) (M, SD)	11.4 (0.9)	11.6 (0.8)		11.7 (0.8)	
Neuropsychological development (T7) (M, SD)	13.3 (1.9)	13.1 (2.0)		12.9 (2.3)	

(Continued)

TABLE 3 | Continued

	Reference group: Neither anxiety nor depressive disorder until T3 and no birth-related traumatization (*N* = 70)	**Birth-related traumatization: Traumatic birth experience (A1/ A2) + (hyperarousal/ re-experiencing/ avoidance) (*N* = 35)**		**Birth-related traumatization: Traumatic birth experience (A1/ A2) + (hyperarousal/ re-experiencing/ avoidance) + depression (*N* = 19)**	
	***N*, % or M, SD**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**	***N*, % or M, SD**	**OR (95%CI) or ß (95%CI)**
Temperament: highly reactive (T6) (*n*, %)	7/63 (11.1)	5/32 (15.6)		2/17 (11.8)	
Temperament: behavioral Inhibition (T7) (*n*, %)	32/66 (48.5)	14/31 (45.2)		7/16 (43.8)	
Insecure attachment (Strange Situation) (T7) (*n*, %)	26/65 (40.0)	15/31 (48.4)		8/16 (50.0)	

*T5, 5th assessment 2 months postpartum; T6, 6th assessment 4 months postpartum; T7, 7th assessment 16 months postpartum; REF, reference; A1, DSM–IV PTSD criteria A1; A2, DSM–IV PTSD criteria A2; PBQ, Postpartum Bonding Questionnaire; N, number; %, percentage; M, mean; SD, standard deviation; OR, odds ratio; ß, Beta-coefficient; 95%CI, 95% confidence interval; * Data of N = 267 participants available only. Bold: significant group differences.*

may not only have negative consequences for the affected women, but also for the infants (68, 69). Regarding the current discussion on intergenerational transmission of trauma effects it is particularly interesting that women with lifetime PTSD reported more pronounced pregnancy-related fears (70). Yehuda and Lehrner recently highlighted that preconception trauma in parents might be associated with epigenetic changes and developmentally programmed effects that can result from offspring's early environmental in utero and postnatal exposures leading to an increased susceptibility of the infant to later environmental distress (70, 71). We found a higher risk for infant regulatory disorders (feeding problems) in mothers with PTSD prior to or during pregnancy and interpersonal traumata (2, 28, 29, 31, 32). However, no significant associations were seen for e.g., temperament, neuropsychological development, or bonding. One explanation could be that lifetime PTSD was not present anymore during the perinatal period in some of the women due to recovery or successful therapy. However, it still seems to be relevant for the development of infant feeding problems in case of interpersonal trauma. Another explanation might be the limited statistical power to detect differences between the respective groups (see limitations section).

The second research question pertains to birth-related traumatization. As expected, women with birth-related traumatization reported more often sexual problems as compared to the reference group (12). Given that sexual problems impede the partnership or interfere with further family planning, affected women might profit from targeted early interventions supporting them and their partners to successfully cope with sexual dysfunctions and associated problems (18, 72). In line with previous evidence, women with birth-related traumatization reported more often postpartum anxiety and depressive disorders as compared to the reference group (12). This is important to note, since traumatic birth experience might change the way affected mothers interact with their infants, especially if postpartum depression is also present (e.g., avoiding contact with or being emotionally unavailable for the infant) (73, 74). Moreover, we saw a higher risk for infant regulatory disorders (sleeping and feeding problems) in mothers with birth-related traumatization and postpartum depression. This was in line with the results by Garthus-Niegel and colleagues who reported an association of PTSD and impaired child sleep (75). However, no significant associations were seen for e.g., temperament, neuropsychological development, or bonding. This was surprising since other prospective studies found maternal postpartum PTSD to be associated with poorer cognitive and social-emotional development in infants up to 2 years (19, 30). However, Garthus-Niegel et al. (19) did not find significant associations with other domains of child development (fine/gross motor or communication development) which was also not seen in our sample (19).

Taken together, our findings highlight the importance of early targeted prevention and intervention for affected women (20) and the peripartum period represents an opportunity to interrupt the pattern of intergenerational transmission of trauma. Knowledge of PTSD prior to or during pregnancy that is also associated with a higher risk of traumatic birth experience (e.g., experience of fear, helplessness or horror, or re-experiencing delivery) is crucial for health-care providers to be alert of when they treat these high-risk women (20, 76). Moreover, trauma-informed interventions should be developed and tested especially for women with PTSD and a history of interpersonal trauma or comorbid depression (74, 77). Targets that should be addressed are prevention of re-traumatization during delivery, improvement of maternal partnership problems and social support, and sensitivity training to encourage mother-child-interaction and bonding/ attachment (78–80). First evidence shows that cognitive behavioral therapy (81) and Eye Movement

Desensitization and Reprocessing approaches (82–84) may improve PTSD status but require investigation in randomized controlled trials (85). Debriefing may only be successful if women are requesting it themselves (86). Since PTSD can also affect the developing relationship with the child, mother-infant bonding problems should also be addressed (20, 23). For some mothers, their infants are a reminder of their traumatic birth and may therefore trigger avoidance behaviors (i.e., non-initiation of breastfeeding) (21). Here, Mother Baby Connections, a program involving interaction therapy, has brought first promising results (87).

Strengths and Limitations

A particular feature of this investigation was the recruitment already during early pregnancy and the consideration of lifetime diagnostic status. To our knowledge this is the first study investigating both, lifetime PTSD and birth-related traumatization, with associated maternal and infant outcomes. Strengths of this study include the prospective multi-wave design and the long follow-up period. Findings are limited by small cell sizes in some clinical groups. This limits power to detect differences between the respective groups. Thus, the absence of significant differences between infants of mothers with no anxiety and depressive disorder as compared to mothers with lifetime PTSD or birth-related traumatization regarding, e.g., temperament, neuropsychological development, or bonding, should not be interpreted as indicative of negative results. It was also not possible to explore the putative cumulative risk of lifetime PTSD and birth-related traumatization on maternal and infant outcomes. Moreover, sample size prohibited examination of third variables that might also be relevant (e.g., income, education, birth outcomes) (88).

CONCLUSION

The study shows that PTSD is a highly debilitating disorder and affected (expectant) mothers might profit from early interventions already during pregnancy and the initial postpartum period (89). Our results highlight the crucial role of early identification and treatment of affected women. Women's health care providers should screen for PTSD and subsyndromal posttraumatic stress symptoms in routine assessments during and after pregnancy, especially in women with a reported history of trauma. Such screening will allow women to receive needed treatment and referrals and mitigate the potentially negative sequelae of PTSD (14). However, screening without sufficient services is not helpful and could be triggering for both professionals and families. Thus, a fully trauma informed perinatal system and effective trauma specific interventions during pregnancy and immediately after traumatic births is warranted to ensure that the families receive help for parenting and early bonding (77).

Finally, this *post-hoc* analysis was conducted with the aim of generating hypotheses for future research. Larger prospective studies are warranted to examine why interpersonal trauma is especially harmful for perinatal outcomes, and to disentangle whether this is driven by the interpersonal trauma in general, or trauma related to mothers' own childhood attachment relationships. It will be important to examine the role of hormonal alterations and other biological or psychosocial factors in the context of perinatal PTSD and to include a comprehensive assessment on psychotherapeutic and pharmacological treatments. Finally, it is important to note, that paternal PTSD after childbirth is a highly understudied and unrecognized problem that should receive more attention.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because after consulting the Ethics Committee and due to the sensitive nature of the questions asked in this study, participants were assured that all raw data would remain confidential and would not be shared. Therefore, no openly assessable data files are attached. Further information on the data can be obtained from the corresponding author (JM, email: julia.martini@tu-dresden.de), the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (email: ethikkommission@mailbox.tu-dresden.de), and the Institute of Clinical Psychology and Psychotherapy of the Technische Universität Dresden.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Technische Universität Dresden (No: EK 94042007). Written informed consent to participate in this study was provided by the participants' legal guardian.

AUTHOR CONTRIBUTIONS

JM conceptualized and designed the study, designed the data collection instruments, collected data for the study, carried out the statistical analyses and the interpretation of the data, drafted the initial manuscript, and approved the final manuscript as submitted. EA, SK, KW, JR, and SG-N critically reviewed the manuscript and approved the final manuscript as submitted. All authors contributed to the article and approved the submitted version.

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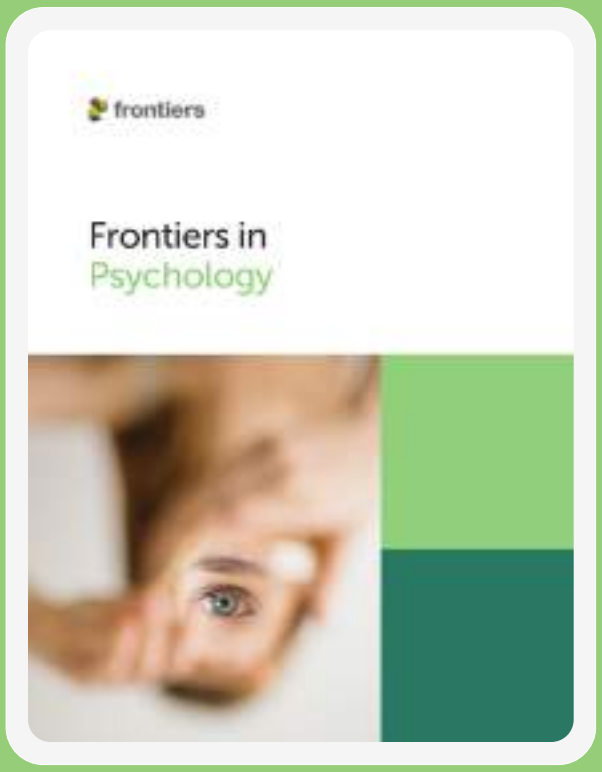

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Editorial

Life in a post-pandemic world: What to expect of anxiety-related conditions and their treatment

When the current pandemic comes to an end, as it eventually will, many people will have lived through all kinds of stresses and losses, including the loss of friends and loved ones due to the novel coronavirus, the loss of jobs, the bankruptcy of businesses, and foreclosures on homes. For some people, marriages and other relationships will have crumbled under the stress of self-isolation and mounting financial hardships. If the research on natural disasters serves as a guide, as a result of the current pandemic an estimated 10 % of people will develop severe psychological problems, such as mood disorders, anxiety disorders, or posttraumatic stress disorder (PTSD) (Galatzer-Levy, Huang, & Bonanno, 2018). But the percentage could be much higher. In the wake of the SARS outbreak in 2003, a number of people developed PTSD. A four-year follow-up study of 70 survivors of SARS, for example, found that 44 % developed PTSD. Even after recovering from SARS, PTSD persisted for years in almost all (82 %) of these sufferers. PTSD symptoms tended to be more severe in people who had a high perceived life threat, low social support, and more close relatives who suffered from, or died, from SARS (Hong et al., 2009). Other studies of SARS have reported similar findings (Gardner & Moallef, 2015). It is likely that the current coronavirus will also lead to cases of PTSD. Isolation and confinement, even if only for a few weeks, can cause lasting psychological problems (Brooks et al., 2020). People quarantined for prolonged periods in cramped accommodation, sharing a bedroom with multiple occupants, or trapped at home in an abusive or coercive relationship, may be especially vulnerable to developing PTSD symptoms (Hong et al., 2009) during and after the outbreak (Taylor, 2019, Taylor, 2017). Emerging evidence also suggests it is likely that many medical and non-medical health care workers will develop PTSD (Tan et al., 2020).

Our research suggests that, during the current pandemic, some people have developed a COVID Stress Syndrome, characterized by fear of infection, fear of touching surfaces or objects that might be contaminated with the novel coronavirus, xenophobia (i.e., fear that foreigners might be infected with the virus), COVID-related checking and reassurance seeking, and COVID-related traumatic stress symptoms (e.g., COVID-related intrusive thoughts and nightmares). The COVID Stress Scales, a set of measures developed to better understand and assess COVID-19-related distress, are introduced in this volume in the article by Taylor et al. (2020). It appears that people who develop COVID Stress Syndrome have pre-existing psychopathology, particularly pre-existing high levels of health anxiety and obsessive-compulsive checking and contamination symptoms. It remains to be seen whether the COVID Stress Syndrome is simply an adjustment disorder, abating once the pandemic is over, or whether it will become chronic for some individuals.

As a result of the current pandemic there may also be an increase in hikikomori, a syndrome that superficially resembles agoraphobia in which people become recluses, reluctant to leave their living quarters. Hikikomori, defined as severe social withdrawal lasting 6 months or longer (Teo, 2010), was once regarded as a syndrome limited to Japan but has become increasingly recognized in other countries (Bowker, Bowker et al., 2019). COVID-19 is likely to increase the prevalence of hikikomori, as health-anxious people retreat from a coronavirus contaminated outside world into the safety of their apartments or homes. Advances in technology have made it increasingly easier for people to withdraw into their homes. There are trends—even before COVID-19—for people to increasingly work from home (U.S. Census Bureau, 2013), to watch movies at home instead of going to the cinema (Plaugic, 2018), to shop online instead of going to stores (U.S. Census Bureau, 2014), and to use home delivery food services instead of going to restaurants (Singh, 2019). These trends will likely be accentuated in the era of COVID-19, where homes have increasingly become havens of safety from a pathogen infested outside world.

In the wake of the current pandemic, even people who do not become housebound may become fastidious germaphobes, striving to avoid touching “contaminated” surfaces or hugging people or shaking hands. Germ phobias, which are typically features of obsessive-compulsive disorder, arise from a combination of genetic and environmental factors (Lopez-Sola et al., 2016). These factors interact with one another (Taylor, 2011). In other words, when a person with a particular genetic makeup has a traumatic experience involving the threat of infection, a germ phobia may develop. Such phobias are typically chronic (Visser, van Oppen, van Megen, Eikelenboom, & van Balkom, 2014), although milder phobias may be short-lived. All this suggests that some people will become germaphobes as a result of COVID-19. At this point, it is not possible to say how many people will become germaphobes.

There may be other, subtle, after-effects of COVID-19. Just like survivors of the Great Depression in the 1930s (McManus, 2010), some survivors of the current pandemic may become more frugal and self-sufficient, making sure to have a back-up supply of non-perishable foods and other supplies. There is also the question concerning the neuropsychiatric sequelae of COVID-19. Anecdotal evidence suggests that in the aftermath of COVID-19 infection, some people have persistence chronic fatigue and other neuropsychiatric problems (Troyer, Kohn, & Hong, 2020). The prevalence, severity, and chronicity of such problems as well as their association with anxiety-related conditions remains to be determined.

But the news is not all bad. Research on resilience (Galatzer-Levy et al., 2018) suggests that two-thirds of people will be resilient to the stresses of COVID-19. Some of these people will experience renewed purpose and meaning in their lives, through helping others during the pandemic. But, despite this good news, there is concern that there may be insufficient mental health resources to treat the many people left suffering in the wake of the pandemic, whether they be those who had

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pre-existing anxiety-related disorders, those who had other pre-existing mental health conditions, or those who developed COVID Stress Syndrome or related conditions as a result of COVID-19. Online mental health resources have proliferated in the past few months, primarily out of the necessity for delivering mental health services in the context of physical distancing. While it is defensible to suggest that the current pandemic may be a turning point in the wider application of e-mental health (Wind, Rijkeboer, Andersson, & Riper, 2020), it remains to be determined whether the application of online interventions targeting general anxiety symptoms and management strategies will be sufficient to alleviate the effects of anxiety-related conditions arising as a result of COVID-19. Specifically targeted interventions delivered in a stepped- or blended-care approach may be necessary for those with more severe presentations, both now and in the context of future pandemics.

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Review

Perinatal Origins of Adult Disease and Opportunities for Health Promotion: A Narrative Review

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Review

Perinatal Origins of Adult Disease and Opportunities for Health Promotion: A Narrative Review

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Abstract: The "developmental origins of health and disease" (DOHaD) hypothesis refers to the influence of early developmental exposures and fetal growth on the risk of chronic diseases in later periods. During fetal and early postnatal life, cell differentiation and tissue formation are influenced by several factors. The interaction between genes and environment in prenatal and early postnatal periods appears to be critical for the onset of multiple diseases in adulthood. Important factors influencing this interaction include genetic predisposition, regulation of gene expression, and changes in microbiota. Premature birth and intrauterine growth restriction (IUGR) are other important factors considered by the DOHaD hypothesis. Preterm birth is associated with impaired or arrested structural or functional development of key organs/systems, making preterm infants vulnerable to cardiovascular, respiratory, and chronic renal diseases during adulthood. Growth restriction, defined as impaired fetal growth compared to expected biological potential in utero, is an additional negative factor increasing the risk of subsequent diseases. Environmental factors implicated in the developmental programming of diseases include exposure to pollution, stress, drugs, toxic agents, nutrition, and exercise. The DOHaD may explain numerous conditions, including cardiovascular, metabolic, respiratory, neuropsychiatric, and renal diseases. Potential antenatal and postnatal preventive measures, interventions, and future directions are discussed.

Keywords: disease; origin; development; developmental programming; perinatal; health

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1. Introduction

The concept that early life events predict adult health and disease was initially proposed in 1986, when Barker et al. showed that adults who had low birth weight (<2.5 kg) were at higher risk of cardiovascular disease [1]. Since then, the concept of developmental programming has been extended to other organs and systems. The "developmental origins of health and disease" (DOHaD) hypothesis refers to the influence of early developmental exposures and fetal growth on the risk of chronic diseases in later periods. Cell differentiation and tissue formation occur in fetal and early postnatal life under the influence of several factors. It is increasingly recognized that perinatal period is of paramount importance for the development and the prevention of subsequent diseases. Neonatologists and pediatricians have an important "window of opportunity" to prevent and cure several diseases and, importantly, promote adult health.

In this narrative review, we will propose examples of diseases and discuss potential preventive measures with potential long-term impacts.

2. Developmental Programming of Diseases and Relative Mechanisms

Critical perinatal factors influencing organogenesis and predisposition to disease include genetic factors, interaction between genes and environment, duration of gestation, and maternal–fetal interactions.

The interaction between genes and the environment in prenatal and early postnatal periods appears to be critical for the onset of diseases in adulthood and has the potential to be modified by interventions. Important factors influencing this interaction include regulation of gene expression and changes in microbiota (individual microorganisms) and microbiome (their collective genomes) [2]. Across perinatal periods, multiple epigenetic mechanisms regulate gene expression without exerting modifications in the DNA sequence: examples are DNA methylation, histone modifications, chromatin remodeling, and transmission of small non-coding RNA. Maternal and paternal contributions to inheritance by means of epigenetic changes in response to nutritional factors and exposure to environmental agents (i.e., drugs, radiations) have recently been reported [3].

Premature birth and intrauterine growth restriction (IUGR) are other important factors considered by the the DOHaD hypothesis. Preterm birth is associated with impaired or arrested structural or functional development of key organs/systems, making preterm infants vulnerable to several diseases at adulthood [4].

Another implication of preterm birth is the lack of hormonal supply with steroid hormones (estradiol and progesterone), which is typically observed among term infants. Both hormones increase up to 100-fold during pregnancy in the mother and the fetus. After preterm birth, these hormones drop dramatically in the mother and the newborn within hours. This is a physiological event at term, but the very preterm infant is disrupted from this huge hormonal supply at a much earlier developmental stage. Preliminary clinical data showed that the replacement of estradiol and progesterone in very preterm infants may improve lung development and neurological outcome [5,6].

Growth restriction, defined as impaired fetal growth compared to expected biological potential in utero, is an additional negative factor increasing the risk of subsequent diseases [7]. Fetal growth is determined by a complex interplay between genetic factors, nutrient and oxygen availability from the placenta, environmental factors, and endocrine modulation of these interactions [7].

True IUGR, compared to constitutional smallness, is a pathological condition in which the placenta fails to deliver an adequate supply of oxygen and nutrients to the developing fetus [8]. Differential expression of growth factors, proteins, and mRNA in placentas of women who delivered growth-restricted fetuses have been reported, suggesting the activation of compensatory mechanisms aimed at maximizing fetal growth [9].

Infants with IUGR, compared appropriately grown gestational age infants, have a significantly higher risk of mortality and neonatal complications with long-term consequences [10–12]. The etiology of these complications is due to fetal chronic hypoxia and nutrient deprivation due to placental dysfunction, with impaired fetal hemodynamic adaptations and subsequently altered organ structure and function [13]. For the prevention of IUGR, there is evidence that aspirin modestly reduces small-for-gestational-age (SGA) pregnancy in women at high risk and that a dose of $\geq$100 mg should be recommended and start at or before 16 weeks of gestation [14]. However, the optimal strategy to identify women who may benefit from prophylactic aspirin still has to be determined.

Changes in microbial population and their interactions with genes and the environment in different organs (i.e., intestine, lungs) have been linked to the development of several diseases, including metabolic syndrome, cardiovascular diseases, and respiratory and psychiatric disorders [2,15].

Suboptimal nutrition and extrauterine growth restriction also increase the risk of complications of prematurity [16]. However, excessive catch-up growth may have negative effects on lifespan [17]. Epigenetic alterations, altered insulin sensitivity, and antioxidant capacity resulting in tissue remodeling and telomere shortening seem to play a significant role in these complications [18,19].

Environmental factors implicated in the developmental programming of diseases include exposure to pollution, stress, drugs, toxic agents, exercise, and nutrients [20–22].

3. Cardiovascular, Renal and Metabolic Disease

Preterm birth and IUGR can result in structural changes of the cardiovascular system, such as the development of short sarcomeres in cardiomyocytes and vascular remodeling (muscularization), resulting in increased arterial stiffness. IUGR and preterm birth are independent risk factors for the development of subsequent cardiovascular disease and **hypertension** [23–25]. The cause of hypertension is likely multifactorial (i.e., reduced nephron number, increased arterial stiffness) and affected by both prenatal and postnatal events. Protein malnutrition, pharmacologic exposures, and hypoxia are important causes of a reduction in glomeruli, and reduced nephron number due to altered programming has been considered an important factor associated with elevated blood pressure [4,26].

According to a recent study, young adults born preterm have evidence of greater diffuse myocardial fibrosis in the left ventriculum that relates to the degree of prematurity, resulting in impaired diastolic function [27]. Greater diffuse myocardial fibrosis may underlie part of the increased cardiovascular risk in this population, including heart failure, ischemic heart disease, and early cardiovascular-related mortality.

Infants born afterIUGR have increased vascular stiffness and increased intima-media thickness, resulting in decreased vascular compliance and impaired endothelial-dependent vasodilation. These vascular alterations may increase myocardial workload and contribute to the development of hypertension in adulthood [28–30].

Bassareo et al. suggested that central aortic elasticity in former extremely preterm infants is impaired when compared with that of term-born controls, particularly in the context of intrauterine growth restriction [31]. Animal models of intrauterine growth restriction demonstrated an altered elastin to collagen ratio (with less elastin and increased collagen engagement, which is 100–1000 times stiffer than elastin), which in turn led to increased arterial stiffness [32]. Elastin slowly accumulates during late gestation and early neonatal period, and slowly involves during aging, with resulting progressive collagen increase [33]. Furthermore, previous reports highlighted that subjects who were born preterm may develop an early peripheral arterial dysfunction—that is, the first manifestation of atherosclerosis, preceding structural changes in the vascular wall [34]. Johansson et al. showed an increase of blood pressure in adults born preterm, adjusted for birth weight and current body mass index [35]. Hypertension has both an early onset, with up to 70% of preterm infants having elevated systolic blood pressure in infancy, and a prolonged duration, with hypertension remaining a significant concern into adulthood, particularly in the presence of adult obesity [36,37].

The postnatal environment plays an important role in reducing or enhancing the likelihood of disease expression: proposed postnatal factors include nutrient availability and stress [38]. In their longitudinal study, Barker et al. reported that children who developed hypertension later in life were characterized by slow fetal growth, followed by rapid compensatory growth in childhood [39]. Neonatal growth acceleration increases the risk of obesity-related hypertension [40], whereas continued growth failure increases the risk of hypertension beyond the effect of IUGR alone [41,42].

In a meta-analysis by Horta et al., breastfeeding, regardless of IUGR status, decreased the likelihood of developing major cardiovascular risk factors, including type 2 diabetes and obesity; however, no association was observed with blood pressure [43]. Lindberg et al. hypothesized that the association between low birth weight and increased risk of hypertension in adulthood may be modifiable with micronutrient interventions in infancy such as iron supplements, highlighting the need for ongoing nutritional assessment [44]. However, the role of perinatal micronutrient and iron deficiencies in relation to blood pressure level in adulthood is still under investigation.

Prematurity is also a major risk factor also for **obesity**, and the risk increases with decreasing gestational age [45]. Among others, the postnatal period is characterized by the fastest growth. It represents a critical window of tissue and organ development wherein several regulatory mechanisms continue to develop after birth. Variations in this process may have long-lasting effects on health. The association between weight gain in infancy

and obesity in childhood, adolescence, and adulthood has been widely recognized [46]. Abdominal adipose tissue, an endocrine organ, secretes adipocytokines and vasoactive substances that can influence the risk of developing metabolic traits [47].

In addition to family history and unhealthy lifestyle factors, early life exposures have been identified as potential risk factors for the development of **diabetes** later in life. Preterm and early term birth were associated with up to 1.5-fold increased risk of type 1 and type 2 diabetes from childhood into early to mid-adulthood in a large population-based cohort [48]. These findings may have multiple underlying mechanisms that involve pancreatic beta cell function and insulin resistance. Preterm birth interrupts the development of pancreatic beta cells, which are formed predominantly in the third trimester of pregnancy, and might permanently reduce their number or function [49]. Preterm birth also alters immune function including T cell response, which may potentially mediate its association with type 1 diabetes, consistent with its autoimmune etiology [50]. Other contributing factors may include exposure to antenatal corticosteroids and rapid catch-up growth in infancy, leading to visceral adiposity and insulin resistance [51].

Most studies show a 30–40% reduction in insulin sensitivity in children and young adults born very preterm (<32 weeks' gestation) in comparison with those born at term [52]. Another study showed that adults born even moderately preterm (32–36 weeks' gestation) have an isolated reduction in insulin sensitivity but normal β-cell function [53].

Stroke is one of the most common causes of disability among adults worldwide. Previous studies have indicated that low birth weight is associated with an increased risk of adult stroke in men and that birth weight is inversely associated with the risk of stroke in women [54,55]. The risk of both ischemic and hemorrhagic stroke is associated with preterm birth [56]. Some studies have demonstrated increasing trends in the incidence of low birth weight and ischemic stroke among young adults also in middle- and low-income countries [57], making the identification of new risk factors and preventive measures a research priority.

In humans 60% of the nephrons develop during the third trimester of gestation, mostly between 28 and 34 weeks of gestation. The final endowment of nephrons is both dependent on gestational age at birth and intrauterine environment. The principal factor, among others, which determines nephron number is birth weight [58]. An event occurring during the early stage of nephrogenesis can have dramatic effects on the final nephron number. However, the number of nephrons can be 'reprogrammed' through various interventions (including nutritional interventions) applied during pregnancies at risk [59].

Chronic kidney disease (CKD) is defined as the reduction of reduced glomerular filtration rate (GFR) up to end-stage renal disease (ESRD), proteinuria, or both. Prevalence of ESRD is increasing worldwide. Reduced nephron endowment has been proposed as playing a determinant role in the pathogenesis of CKD [26]. Reduced nephron number is responsible for an adaptive glomerular hyperfiltration, resulting in renal hypertrophy and glomerular capillary enlargement. The consecutive glomerular hypertension may lead over time to renal injury, proteinuria, impaired GFR, and systemic hypertension [60]. Concomitant salt retention, increased peripheral vascular resistance and cardiac changes may lead to glomerular sclerosis, impaired GFR, and systemic hypertension. Eventually, inflammation, upregulation of the renin angiotensin system, and the production of nitric oxide and reactive species worsen renal injury [61]. Low birth weight and intrauterine growth restriction are both associated with a decreased nephron number, the latter condition reducing it by an average of 30–35%, whereas the effects of preterm birth are still unknown [62]. In preterm infants, nephrogenesis is expected to continue in a potentially unfavorable environment.

While rapid postnatal growth and/or overfeeding enhances the "vulnerability state" acquired in utero and accelerates the development of adult diseases ("mismatch hypothesis"), slow postnatal growth and breastfeeding in particular (possibly through reduced protein and sodium intakes) tend to prevent such diseases [63]. Nephron endowment may

result from a complex process which integrates the interaction of the fetal environment (or postnatal environment in preterm infants) and the genetic background.

4. Respiratory Disease

Conditions such as prematurity and its complications, fetal growth restriction, and inflammation have been associated with long-term pulmonary morbidity, including **asthma**, in up to 75% of infants born below 30 weeks of gestation [64,65]. Premature delivery results in loss of the normal structural complexity of the lung and greater susceptibility to subsequent injury from infection or environmental factors such as smoking. Genetic susceptibility factors also play a role in reduced immunologic regulation needed for normal lung development and function [66]. Proposed mechanisms by which preterm birth may affect subsequent risk of asthma include genetic, perinatal, and environmental factors.

Early-life inflammatory insults, as in neonatal respiratory distress and bronchopulmonary dysplasia (BPD), may hamper the development of properly organized pulmonary interstitium, with consequences for acinar structure and function, peribronchial airway support, and elastic recoil pressures [67]. Early onset **chronic obstructive pulmonary disease** (COPD) has been observed in subsets of extremely preterm-born adults, as lung function will commence its normal age-related decline from subnormal levels, possibly at steeper trajectories [68]. It has been hypothesized that young adults born preterm, having failed to reach optimal peak lung function, will decline during adulthood with a steeper trajectory than those born at term, and that external factors including pollution, infection, and smoking could have a further detrimental effect on this decline [69]. Structural changes of the lungs following IUGR and inflammation (impaired alveolar and vascular development, muscularization of lung vessels, endothelial dysfunction) have been related to development of **BPD** and pulmonary hypertension [70]. BPD has been associated with significant pulmonary morbidity beyond the neonatal period, including the use of bronchodilators up to two years of age, frequent diagnosis of asthma later in childhood, and persistence of abnormal baseline spirometry at 11 years of age compared with full-term controls [71]. Patients with BPD are also more likely to be hospitalized after discharge from the neonatal intensive care unit and use outpatient services more frequently than premature patients without BPD [72,73]. However, according to other studies, premature infants without BPD are also at risk of developing pulmonary morbidity beyond the neonatal period as compared with term infants. An equal incidence of wheezing-related illnesses among patients born prematurely regardless of the presence of BPD was reported [64]. In a study of 25-year-old adults born extremely preterm in the early 1980s, exercise capacity was 10% lower than in a control group born at term (but still within a range considered normal) and was positively associated with self-reported physical activity and unrelated to neonatal factors and current airway obstruction [74].

Difficulties in this research area, characterized by a long time span between birth and the occurrence of complications, include the rapid evolution of obstetric and neonatal care (i.e., improved survival, implementation of preventive strategies such as prenatal steroids and caffeine, maternal metabolic control, newborn practices among others) that can have an important influence on long-term outcomes.

5. Neuropsychiatric Conditions

Increased risk of impaired neurodevelopment and psychological dysfunctions in the first four decades of life were reported in preterm infants, in small for gestational age (SGA) infants compared to appropriate for gestational age (AGA) infants and in pregnancies complicated by maternal diabetes [75–77]. Underlying mechanisms could be reduced brain volume, organizational differences, oxidative stress, and hypoxia of the fetus. In a Swedish cohort study, individuals who were born preterm were more likely to be prescribed psychotropic medications during young adulthood than individuals who were born full term [78]. Moreover, chronic diseases (i.e., Alzheimer's disease, schizophrenia) may be

associated with epigenetic factors, nutritional deficiency, and exposure to toxic agents occurring during gestation [79].

6. Potential Preventive Measures, Interventions and Future Directions

Several preventive measures can be identified and considered to promote long-term health. Examples of useful **antenatal** measures are: improved identification of subjects with increased risk of complications (i.e., earlier/more frequent ecographic growth assessment), dietary modifications during pregnancy to ensure normalization of body weight, zinc and iron levels, glycemia and blood pressure control, lifestyle measures (i.e., avoidance of alcohol and tobacco, maximization of maternal education), reduced stress and exposure to pollution), and management of chronic diseases. Some of these measures are currently being evaluated in the context of clinical studies [80–88].

The prevention of preterm birth and enhanced maturation (optimal antenatal steroid administration) is of paramount importance. Global policies to enhance health, particularly in low-income countries have been advocated [89]. Specific dietary interventions, including the supplementation of folic acid, zinc, long-chain polyunsaturated fatty acids, and vitamin D, which are possibly associated with favorable epigenetic changes, are under assessment [15].

Finally, the administration of drugs during high-risk pregnancies (i.e., when IUGR is demonstrated) is another potential measure: sildenafil has been investigated but increased fetal death in a clinical trial has led to discontinuation of the study [90]; vascular endothelial growth factor is currently under investigation to promote angiogenesis [91], insulin-like growth factor 1 (IGF-1), antioxidants and melatonin have been tested in preclinical studies [92–94]. The identification of the optimal timing of delivery in pathologic conditions (such as IUGR) is another important aspect, and studies are underway in this regard [95].

Postnatal interventions in the early phases of life include promotion of breastfeeding, optimization of nutrition and growth (potentially with administration of hormones/growth factors such as IGF-1 analogues, cautious use and therapeutic drug monitoring of toxic drugs (i.e., nephrotoxic antibiotics, systemic steroids with potential heart and brain toxicity), adequate follow-up of patients at high risk, appropriate resource allocation [89]. The change of maternal and offspring microbiota by dietary modifications (i.e., dietary supplementation with docosahexaenoic acid and arachidonic acid to improve neurodevelopmental outcomes) [83], pre-probiotics, and possibly other factors is a potential intervention needing further studies.

Novel drugs under investigation include lactoferrin and stem cell administration [96,97].

Knowledge translation, the process of putting knowledge into action, is of paramount importance to ensure the use of research findings in decision-making [98]. In fact, the prevention of preterm birth, IUGR, and their long-term complications, as here discussed, is highly relevant for individual and public health. One approach could be to analyze and compare strengths and characteristics of different health systems to inform clinical decision-making, research, and healthcare policy, as recently performed by Japanese and Canadian researchers regarding the prevention and management of preterm birth [99].

In conclusion, developmental programming is emerging as a new concept for the explanation of several diseases in children and adults. The characterization of underlying mechanisms and the identification of preventive measures and treatment are of great importance in order to promote health and prevent the development of several chronic diseases.

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Original Investigation | Psychiatry

Association of Preeclampsia and Perinatal Complications With Offspring Neurodevelopmental and Psychiatric Disorders

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Abstract

IMPORTANCE Maternal preeclampsia has been reported to increase the risk of autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), and intellectual disability in offspring. However, the association between maternal preeclampsia combined with perinatal complications and neurodevelopmental and psychiatric disorders in offspring is less well documented.

OBJECTIVE To examine the association of maternal preeclampsia, separately and together with perinatal complications, with neurodevelopmental and psychiatric disorders in offspring.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study used data from nationwide registries in Finland to assess all singleton live births (N = 1 012 723) between January 1, 1996, and December 31, 2014. Offspring were followed up until December 31, 2018 (when the oldest reached age 22 years). Exclusion criteria were maternal inpatient psychiatric diagnoses and pregestational diabetes. The study and data analysis were conducted from May 1, 2020, to June 1, 2021.

EXPOSURES Preeclampsia and perinatal complications (delivery earlier than 34 weeks' gestation and/or small for gestational age).

MAIN OUTCOMES AND MEASURES The primary outcomes were neurodevelopmental and psychiatric diagnoses and dispensation of psychotropic drugs among offspring until December 31, 2018. Cox proportional hazards regression analyses were performed to assess the associations.

RESULTS Of 1 012 723 singleton live births (51.1% boys; mean [SD] maternal age at birth, 30.0 [5.4] years; specific data on race and ethnicity were not available in the data set), 21 010 children (2.1%) were exposed to preeclampsia alone, 33 625 children (3.3%) were exposed to perinatal complications alone, and 4891 children (0.5%) were exposed to both preeclampsia and perinatal complications. A total of 93 281 children (9.2%) were diagnosed with a neurodevelopmental or psychiatric disorder. Offspring exposed to both preeclampsia and perinatal complications had an increased risk of any neurodevelopmental or psychiatric disorder after adjusting for potential confounding (adjusted hazard ratio [aHR], 2.11; 95% CI, 1.96-2.26) compared with those not exposed to either preeclampsia or perinatal complications; this risk was higher than exposure to either preeclampsia alone (aHR, 1.18; 95% CI, 1.12-1.23) or perinatal complications alone (aHR, 1.77; 95% CI, 1.72-1.82). Sibling pair analyses did not detect any increase in the risk of neurodevelopmental or psychiatric disorders after exposure to preeclampsia alone, but offspring exposed to both preeclampsia and perinatal complications had increased risks of intellectual disabilities (aHR, 3.24; 95% CI, 1.05-10.06), specific developmental disorders (aHR, 3.56; 95% CI, 2.35-5.41), ADHD and conduct disorders (aHR, 2.42; 95% CI, 1.09-5.39), and other behavioral and emotional disorders (aHR, 2.45; 95% CI, 1.17-5.13). The risk estimates for specific developmental disorders (aHR, 2.82; 95% CI, 2.60-3.05) and ADHD and conduct disorders (aHR, 1.88; 95% CI, 1.65-2.14) were higher

(continued)

Key Points

Question Is maternal preeclampsia, alone or together with perinatal complications (preterm birth and/or small birth size) associated with an increased risk of neurodevelopmental and psychiatric disorders in offspring?

Findings In this cohort study of 1 012 723 singleton live births in Finland, exposure to both maternal preeclampsia and perinatal complications was associated with higher risks of specific neurodevelopmental disorders as well as attention-deficit/hyperactivity disorder and conduct disorders in offspring compared with exposure to either preeclampsia or perinatal complications alone.

Meaning These results suggest that children exposed to both preeclampsia in utero and perinatal complications have modestly increased risks of developing specific neurodevelopmental disorders as well as attention-deficit/hyperactivity disorder and conduct disorders.

+ Multimedia

+ Supplemental content

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Abstract (continued)

among offspring exposed to both preeclampsia and perinatal complications compared with those exposed to perinatal complications alone (aHR, 2.26 [95% CI, 2.18-2.33] and 1.60 [95% CI, 1.52-1.68], respectively).

CONCLUSIONS AND RELEVANCE In this study, exposure to both maternal preeclampsia and perinatal complications was associated with intellectual disabilities, specific developmental disorders, ADHD and conduct disorders, and other behavioral and emotional disorders in offspring. For specific developmental disorders and ADHD and conduct disorders, the risk estimates were higher among offspring exposed to both preeclampsia and perinatal complications compared with those exposed to perinatal complications only.

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Introduction

Preeclampsia, occurring in 3% to 5% of pregnancies worldwide, is characterized by new-onset hypertension along with proteinuria after 20 weeks' gestation and is often accompanied by uteroplacental dysfunction with abnormal blood vessel development and other maternal organ dysfunction.[1-3] Preeclampsia is a major factor associated with maternal and perinatal morbidity and mortality associated with eclampsia, stroke, and kidney failure as well as hemolysis, elevated liver enzymes, and low platelet syndrome.[4] In addition, preeclampsia has been associated with long-term endocrine and cardiovascular morbidity in offspring.[5-7] However, preeclampsia may present with or without severe features. Although diagnostic criteria for severe preeclampsia are included in the *International Classification of Diseases, Tenth Revision* (*ICD-10*), recent clinical care guidelines recommend avoiding early classification of preeclampsia as mild or severe because the condition can deteriorate rapidly.[3] Given that delivery is the only effective treatment for preeclampsia, delivery before 34 weeks' gestation is often used as a retrospective proxy for severe preeclampsia.[8] In addition, because small for gestational age (SGA) status at birth is associated with uteroplacental dysfunction, preeclampsia combined with SGA status is also considered a severe condition.[9,10]

Preeclampsia has been associated with increased risks of several neurodevelopmental disorders in offspring, including autism spectrum disorder (ASD), attention-deficit/ hyperactivity disorder (ADHD), schizophrenia, intellectual disability, epilepsy, and cerebral palsy.[9-15] Several systematic reviews[16-18] reported that preeclampsia was associated with increases of 50% in the risk of ASD, 30% in the risk of ADHD, and 40% in the risk of schizophrenia among offspring. In 1 meta-analysis,[18] only a few studies of ASD and ADHD assessed familial confounding by including siblings. A recent study[19] in Finland followed up 4743 offspring to age 10 years and grouped offspring diagnoses, finding that maternal preeclampsia, but not other maternal hypertensive disorders, was associated with an increased risk of both psychological developmental disorders (*ICD-10* codes F80-F89, with code F84 indicating ASD) and emotional and behavioral disorders (*ICD-10* codes F90-F98, with code F90 indicating ADHD). This study[19] also found effect sizes had a propensity to be larger for severe preeclampsia (*ICD-10* code O14.1) than for mild to moderate preeclampsia (*ICD-10* code O14.0) and suggested through findings from hierarchical regression analyses that maternal and paternal mental disorders did not have an impact for these effect sizes. Additive consequences were also detected, with a higher number of maternal metabolic and hypertensive disorders (including obesity, diabetes, and hypertension; 0-3 disorders) being associated with a greater risk of neuropsychiatric diagnoses in children. Furthermore, the authors suggested that preterm birth and SGA status partially mediated some of the associations between preeclampsia and child diagnoses.[19] These findings were consistent with those of similar studies included in a systematic review.[18]

In the present cohort study, we extended these findings with the aim of assessing the effect sizes of exposure to maternal preeclampsia together with perinatal complications for a wide range of

individual neurodevelopmental and psychiatric diagnoses among offspring followed up to age 22 years. We used a recommended indicator of severe preeclampsia that was based on preterm birth (earlier than 34 weeks' gestation) and/or SGA status,[8-10] and we compared the effect sizes of exposure to both preeclampsia and perinatal complications with those of exposure to preeclampsia or perinatal complications alone. Moreover, we performed sibling analyses to examine whether detected associations could be explained by familial confounding. To conduct these analyses, we used data from more than 1 million live births recorded in nationwide registers in Finland and followed up offspring to age 22 years.

Methods

Study Population and Data Sources

This population-based cohort study included all 1 012 723 singleton live births in Finland from January 1, 1996, to December 31, 2014, that were recorded in the Drugs and Pregnancy Database,[20,21] which contains data from the Medical Birth Register,[22,23] the Register on Induced Abortions,[24,25] and the Register of Congenital Malformations,[26] all of which are maintained by the Finnish Institute for Health and Welfare.[20] Registers are described in eMethods in the Supplement. This study was approved by the Drugs and Pregnancy Database steering committee and the data protection authority in Finland. Register linkages were conducted as specified in the agreement between the register administrators (the Social Insurance Institution of Finland and the Finnish Institute for Health and Welfare). Data were obtained from Finnish administrative registers. According to Finnish law, informed consent is not required for the use of data from these registers. All data were deidentified, and no registered person (mother or child) was contacted. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

The study and data analysis were conducted from May 1, 2020, to June 1, 2021. All offspring were followed up until December 31, 2018 (when the oldest reached age 22 years). The exclusion criteria were maternal pregestational diabetes (n = 25 901) and maternal in-hospital psychiatric history (n = 20 486) before or during pregnancy because these exposures could have increased the risks of neurodevelopmental and psychiatric disorders in offspring, with moderate to high effect sizes.[27,28] In all analyses, with the exception of sibling analyses, mothers with chronic hypertension (n = 16 434) and gestational hypertension (n = 17 469) were excluded from the group with no exposure to either preeclampsia or perinatal complications (reference group) because they could have produced bias in the main results.[9,10]

Main Exposures

Main exposures included maternal preeclampsia (identified through *ICD-10* code O11 [14 726 participants] or O14 [11 175 participants] in the Finnish Care Registers for Health Care[29]) and perinatal complications, including SGA status and/or delivery earlier than 34 weeks' gestation (identified through the Drugs and Pregnancy Database). Small for gestational age was defined as birth weight and/or length more than 2 SDs lower than the sex-specific and gestational age–specific mean in the Finnish population[30] based on criteria from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society.[31]

Outcomes and Covariates

Offspring neurodevelopmental and psychiatric disorders between 1996 and 2018, as defined by *ICD-10* codes from the Finnish Care Registers for Health Care, were used as outcome variables. These variables included psychotic disorders (*ICD-10* codes F20-F29), mood disorders (*ICD-10* codes F30-F39 and F92), anxiety disorders (*ICD-10* codes F40-F43 and F93), eating disorders (*ICD-10* code F50), sleeping disorders (*ICD-10* code F51), personality disorders (*ICD-10* codes F60-F69), intellectual disabilities (*ICD-10* codes F70-F79), specific developmental disorders (*ICD-10* codes

F80-F83), ASD (*ICD-10* code F84), ADHD and conduct disorders (*ICD-10* codes F90 and F91), and other behavioral and emotional disorders (*ICD-10* code F98) (eTable 1 in the Supplement). Data on dispensation of psychotropic drugs prescribed to offspring were extracted using Anatomical Therapeutic Chemical (ATC) classification system codes from the Finnish Register on Reimbursement Drugs. Drugs included antipsychotic, anxiolytic, hypnotic, and sedative medications (ATC group N05); antidepressant medications (ATC group N06A); and psychostimulant and nootropic medications (ATC group N06B).

The covariates included offspring birth year, offspring sex, and maternal factors, including age at delivery, country of birth (Finland or other), married at birth (yes or no), occupation (upper white collar worker, lower white collar worker, blue collar worker, or other status), smoking status (yes or no), parity (0 or ≥1 births to a fetus with gestational age ≥24 weeks, regardless of whether the child was born alive or stillborn) identified through the Drugs and Pregnancy Database, obesity (*ICD-10* codes E65 and E66; yes or no), gestational diabetes (yes or no), outpatient psychiatric disorders (*ICD-10* codes F00-F99; yes or no), systemic inflammatory disease (*ICD-10* codes M30-M36; yes or no) identified through the Finnish Care Registers for Health Care, use of psychotropic medication during pregnancy (yes or no) identified through the Finnish Register on Reimbursement Drugs, and interval between pregnancies.

Statistical Analysis

Cox proportional hazards modeling was used to examine the association of maternal preeclampsia and perinatal complications with the diagnosis of neurodevelopmental and psychiatric disorders in offspring and the dispensation of psychotropic drugs (sensitivity analysis) to offspring after adjusting for potential confounding. The proportional hazards assumption was tested.

Sibling pair analyses were also performed to investigate whether any associations between exposure to maternal preeclampsia with perinatal complications and neurodevelopmental and psychiatric disorders in offspring were explained by familial confounding. All singleton sibling pairs from consecutive pregnancies were included. In a sensitivity analysis, only the first 2 subsequent singleton pregnancies of the same mother during the study period were included. The risk of neuropsychiatric disorders for the second (younger) sibling was estimated after stratifying for both the first and second siblings' exposure or nonexposure to preeclampsia and/or perinatal complications. The reference group comprised unexposed second siblings with first siblings who were also unexposed. Second siblings were followed up for psychiatric diagnosis outcomes and dispensation of psychotropic medication until December 31, 2018. Exposure-based sibling pair stratification allowed us to calculate the risk estimates for outcomes among exposed second siblings and compare those results with risk estimates among unexposed second siblings who had exposed older siblings. In model 2, the first sibling was also followed up for outcomes. Model 2 was further adjusted for the corresponding psychiatric diagnosis or dispensation of psychotropic medication for the first sibling, irrespective of the exposure to the first sibling, as an attempt to reduce genetic confounding. Overall, this sibling pair analysis approach enabled detection of exposure-specific associations among second siblings that were not explained by exposure in the first siblings only, thereby excluding complete familial confounding.

Hazard ratios (HRs) with 95% CIs were reported for the risks of neurodevelopmental and psychiatric outcomes. Two-sided $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Among 1 012 723 singleton live births, 517 923 (51.1%) were boys, and 494 800 (48.9%) were girls; the mean (SD) maternal age at birth was 30.0 (5.4) years. Specific data on race and ethnicity were not available in the data set. A total of 21 010 children (2.1%) were exposed to preeclampsia alone, 33 625 children (3.3%) were exposed to perinatal complications alone, and 4891 children (0.5%) were

exposed to both preeclampsia and perinatal complications (**Table 1**). Offspring were followed up for a mean (SD) of 12.4 (5.7) years, corresponding to 12.6 million person-years. Overall, 93 281 children (9.2%) were diagnosed with a neurodevelopmental or psychiatric disorder between 1996 and 2018. Specific developmental disorders were most common (55 326 children [5.5%]) followed by anxiety disorders (50 731 children [5.0%]), mood disorders (38 293 children [3.8%]), and ADHD and conduct disorders (30 115 children [3.0%]) (eTable 2 in the Supplement). The cumulative incidences of several neurodevelopmental and psychiatric disorders among offspring exposed to both maternal preeclampsia and perinatal complications were higher than those of offspring exposed to preeclampsia alone and those of offspring not exposed to either preeclampsia or perinatal complications, which was exemplified by the incidence of specific developmental disorders (preeclampsia and perinatal complications: 638 of 4891 children [13.0%]; preeclampsia alone: 1357 of 21 030 children [6.5%]; neither preeclampsia nor perinatal complications: 49 442 of 953 197 children [5.2%]) and ADHD and conduct disorders (preeclampsia and perinatal complications: 239 of 4891 children [4.9%]; preeclampsia alone: 744 of 21 030 children [3.5%]; neither preeclampsia nor perinatal complications: 27 461 of 953 197 children [2.9%]) (**Figure 1**; eTable 2 and eTable 3 in the Supplement).

Compared with offspring unexposed to preeclampsia and perinatal complications, those exposed to preeclampsia alone had an 18% higher likelihood (adjusted HR [aHR], 1.18; 95% CI, 1.12-1.23) of any neuropsychiatric disorder after adjusting for potential confounding, whereas the aHR for neuropsychiatric disorders among offspring exposed to perinatal complications alone was 1.77 (95% CI, 1.72-1.82) (**Figure 2**; eTable 4 in the Supplement). Exposure to preeclampsia alone was associated with an increased risk of all neuropsychiatric disorders (ranging from an aHR of 1.10 [95% CI, 1.02-1.18] for mood disorders to 1.24 [95% CI, 1.18-1.31] for specific developmental disorders), with the exception of psychotic disorders (aHR, 0.97; 95% CI, 0.73-1.28), eating disorders (aHR, 1.13; 95% CI, 0.94-1.36), and personality disorders (aHR, 1.12; 95% CI, 0.86-1.46). Exposure to perinatal complications alone was also associated with an increased risk of all neurodevelopmental and psychiatric disorders, with aHRs ranging from 1.22 (95% CI, 1.07-1.38) for sleeping disorders to 4.22 (95% CI, 3.95-4.52) for intellectual disabilities (Figure 2; eTable 4 in the Supplement). A similar pattern was observed for unadjusted HRs (eTable 4 in the Supplement).

Offspring exposed to both preeclampsia and perinatal complications had a more than 2-fold risk of developing any neurodevelopmental or psychiatric disorder (aHR, 2.11; 95% CI, 1.96-2.26), which was higher than the risk of those exposed to either preeclampsia alone (aHR, 1.18; 95% CI, 1.12-1.23) or perinatal complications alone (aHR, 1.77; 95% CI, 1.72-1.82). Exposure to both preeclampsia and perinatal complications was also associated with specific developmental disorders (aHR, 2.82; 95% CI, 2.60-3.05) and ADHD and conduct disorders (aHR, 1.88; 95% CI, 1.65-2.14); these risk estimates were higher than exposure to preeclampsia alone (specific developmental disorders: aHR, 1.24 [95% CI, 1.18-1.31]; ADHD and conduct disorders: aHR, 1.22 [95% CI, 1.13-1.31]) and perinatal complications alone (specific developmental disorders: aHR, 2.26 [95% CI, 2.18-2.33]; ADHD and conduct disorders: aHR, 1.60 [95% CI, 1.52-1.68]) (Figure 2; eTable 4 in the Supplement). In addition, exposure to both preeclampsia and perinatal complications vs exposure to preeclampsia alone was associated with a higher risk of psychotic disorders (aHR, 1.60 [95% CI, 1.03-2.49] vs 0.97 [95% CI, 0.73-1.28]), anxiety disorders (aHR, 1.28 [95% CI, 1.14-1.45] vs 1.13 [95% CI, 1.06-1.20]), intellectual disabilities (aHR, 3.34 [95% CI, 2.75-4.06] vs 1.22 [95% CI, 1.05-1.42]), ASD (aHR, 1.73 [95% CI, 1.40-2.13] vs 1.23 [95% CI, 1.09-1.39]) and other behavioral and emotional disorders (aHR, 2.04 [95% CI, 1.80-2.32] vs 1.14 [95% CI, 1.06-1.24]). However, the risk estimates for exposure to both preeclampsia and perinatal complications were equal to or lower than exposure to perinatal complications only (psychotic disorders: aHR, 1.40 [95% CI, 1.19-1.65]; anxiety disorders: aHR, 1.28 [95% CI, 1.23-1.34]; intellectual disabilities: aHR, 4.22 [95% CI, 3.95-4.52]; ASD: aHR, 1.67 [95% CI, 1.53-1.81]; other behavioral and emotional disorders: aHR, 1.81 [95% CI, 1.71-1.90]) (Figure 2; eTable 4 in the Supplement). No association was found between exposure to both preeclampsia and perinatal complications and eating disorders (aHR, 1.40; 95% CI, 0.99-1.95), sleeping disorders (aHR, 0.64;

Table 1. Demographic Characteristics of Singleton Live Births in Finland Between 1996 and 2014 Stratified by Preeclampsia and Perinatal Complications

Variables[a]	No preeclampsia with no perinatal complications, No. (%)[b,c]	No preeclampsia with perinatal complications, No. (%)	Preeclampsia with no perinatal complications, No. (%)	Preeclampsia with perinatal complications, No. (%)
Total births, No.	953 197	33 625	21 010	4891
Decade of birth				
1996-1999	203 996 (21.4)	7104 (21.1)	2956 (14.1)	855 (17.5)
2000-2009	493 804 (51.8)	17 466 (51.9)	11 956 (56.9)	2650 (54.2)
2010-2014	255 397 (26.8)	9055 (26.9)	6098 (29.0)	1386 (28.3)
Offspring sex				
Boy	487 209 (51.1)	17 632 (52.4)	10 680 (50.8)	2402 (49.1)
Girl	465 988 (48.9)	15 993 (47.6)	10 330 (49.2)	2489 (50.9)
Maternal age, y				
<20	23 530 (2.5)	1371 (4.1)	682 (3.2)	133 (2.7)
20-24	152 166 (16.0)	6249 (18.6)	3957 (18.8)	759 (15.5)
25-29	306 375 (32.1)	10 031 (29.8)	6519 (31.0)	1365 (27.9)
30-34	299 677 (31.4)	9661 (28.7)	5897 (28.1)	1387 (28.4)
≥35	171 448 (18.0)	6313 (18.8)	3955 (18.8)	1247 (25.5)
Parity[d]				
0	379 725 (39.8)	19 094 (56.8)	12 721 (60.5)	3257 (66.6)
1	328 751 (34.5)	8179 (24.3)	5303 (25.2)	927 (19.0)
2	148 996 (15.6)	3747 (11.1)	1816 (8.6)	413 (8.4)
3	50 877 (5.3)	1441 (4.3)	618 (2.9)	148 (3.0)
4 or more	43 833 (4.6)	1137 (3.4)	512 (2.4)	142 (2.9)
Missing	1015 (0.1)	27 (0.1)	40 (0.2)	4 (0.1)
Maternal occupation				
Upper white collar	161 147 (16.9)	4810 (14.3)	3347 (15.9)	778 (15.9)
Lower white collar	340 383 (35.7)	11 248 (33.5)	7750 (36.9)	1834 (37.5)
Blue collar	136 880 (14.4)	5490 (16.3)	2955 (14.1)	715 (14.6)
Other	165 209 (17.3)	6132 (18.2)	3404 (16.2)	720 (14.7)
Missing	149 578 (15.7)	5945 (17.7)	3554 (16.9)	844 (17.3)
Mother's marital status				
Married	571 707 (60.0)	17 424 (51.8)	11 599 (55.2)	2548 (52.1)
Cohabiting	275 008 (28.9)	10 829 (32.2)	6934 (33.0)	1642 (33.6)
Other	88 238 (9.3)	4503 (13.4)	2179 (10.4)	601 (12.3)
Missing	18 244 (1.9)	869 (2.6)	298 (1.4)	100 (2.0)
Mother's country of birth				
Finland	875 408 (91.8)	30 019 (89.3)	19 824 (94.4)	4516 (92.3)
Other	77 789 (8.2)	3606 (10.7)	1186 (5.6)	375 (7.7)
Maternal smoking				
No	793 268 (83.2)	23 896 (71.1)	17 896 (85.2)	4027 (82.3)
Stopped in first trimester	34 953 (3.7)	1250 (3.7)	967 (4.6)	168 (3.4)
Continued during pregnancy	101 010 (10.6)	7455 (22.2)	1674 (8.0)	525 (10.7)
Missing	23 966 (2.5)	1024 (3.0)	473 (2.3)	171 (3.5)
Maternal systemic inflammatory disease[e]				
Yes	9566 (1.0)	478 (1.4)	271 (1.3)	83 (1.7)
No	943 631 (99.0)	33 147 (98.6)	20 739 (98.7)	4808 (98.3)

(continued)

Table 1. Demographic Characteristics of Singleton Live Births in Finland Between 1996 and 2014 Stratified by Preeclampsia and Perinatal Complications (continued)

Variables[a]	No preeclampsia with no perinatal complications, No. (%)[b,c]	No preeclampsia with perinatal complications, No. (%)	Preeclampsia with no perinatal complications, No. (%)	Preeclampsia with perinatal complications, No. (%)
Maternal psychiatric outpatient history (1998-2014)				
Yes	59 647 (6.3)	2971 (8.8)	1888 (9.0)	436 (8.9)
No	893 550 (93.7)	30 654 (91.2)	19 122 (91.0)	4455 (91.1)
Maternal receipt of psychotropic medication during pregnancy[f]				
Yes	36 997 (3.9)	1627 (4.8)	1070 (5.1)	222 (4.5)
No	916 200 (96.1)	31 998 (95.2)	19 940 (94.9)	4669 (95.5)
Maternal chronic hypertension[g]				
Yes	0	0	1973 (9.4)	676 (13.8)
No	953 197 (100.0)	33 625 (100.0)	19 037 (90.6)	4215 (86.2)
Maternal gestational hypertension[h]				
Yes	0	0	2966 (14.1)	615 (12.6)
No	953 197 (100.0)	33 625 (100.0)	18 044 (85.9)	4276 (87.4)
Maternal obesity[i]				
Yes	21 801 (2.3)	630 (1.9)	1072 (5.1)	212 (4.3)
No	931 396 (97.7)	32 995 (98.1)	19 938 (94.9)	4679 (95.7)
Maternal gestational diabetes[j]				
Yes	129 921 (13.6)	3214 (9.6)	4863 (23.1)	692 (14.1)
No	823 276 (86.4)	30 411 (90.4)	16 147 (76.9)	4199 (85.9)

[a] Mothers with in-hospital psychiatric disorders and pregestational diabetes were excluded.

[b] Preeclampsia based on *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnostic code O11 or O14.

[c] Perinatal complications defined as small for gestational age (defined as birth weight and/or length more than 2 SDs lower than the sex-specific and gestational age–specific mean of the Finnish population[1] based on criteria from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society[2]) and/or delivery earlier than 34 weeks' gestation.

[d] Parity defined as number of births to a fetus with gestational age of 24 weeks or more, regardless of whether the child was born alive or stillborn.

[e] Maternal systemic inflammatory disease based on *ICD-10* codes M30 to M36.

[f] Maternal use of psychotropic medications during pregnancy based on Anatomical Therapeutic Chemical classification system codes N05 and N06.

[g] Maternal chronic hypertension based on *ICD-10* codes I10 to I13 and O10.

[h] Maternal gestational hypertension based on *ICD-10* code O13.

[i] Maternal obesity based on *ICD-10* codes E65 and E66.

[j] Maternal gestational diabetes based on *ICD-10* code O24.4.

95% CI, 0.40-1.02), or personality disorders (aHR, 1.54; 95% CI, 0.98-2.42), whereas exposure to perinatal complications alone was associated with a higher risk of eating disorders (aHR, 1.44; 95% CI, 1.27-1.63), sleeping disorders (aHR, 1.22; 95% CI, 1.07-1.38), and personality disorders (aHR, 1.64; 95% CI, 1.41-1.92) (Figure 2; eTable 4 in the Supplement).

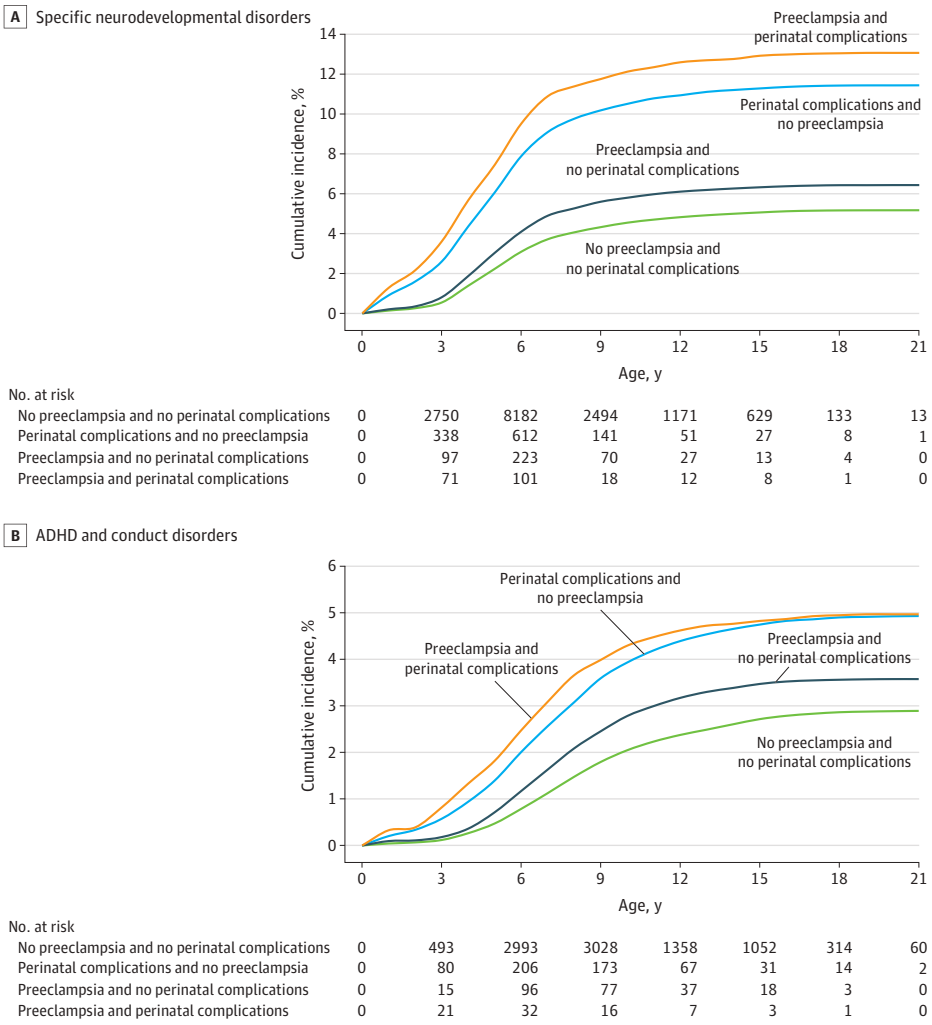
A total of 50 131 singleton live offspring (5.0%) received prescribed psychotropic medications, including antipsychotic and hypnotic or anxiolytic drugs (ATC group N05; 33 471 children), antidepressant drugs (ATC group N06A; 11 509 children), and stimulant drugs (ATC group N06B; 14 547 children) (eTable 5 in the Supplement). We examined the association between the exposures and the dispensation of psychotropic medications as an estimate of offspring neuropsychiatric disorders using a sensitivity analysis. After adjusting for potential confounding, exposure to preeclampsia only was associated with slightly higher risks of dispensation of any psychotropic medication (aHR, 1.09; 95% CI, 1.02-1.17) and stimulant medication (aHR, 1.25; 95% CI, 1.12-1.40). Exposure to both preeclampsia and perinatal complications was associated with a higher risk of dispensation of any psychotropic medication (aHR, 1.52; 95% CI, 1.35-1.71); antipsychotic, anxiolytic, hypnotic, and sedative drugs (aHR, 1.53; 95% CI, 1.33-1.76); antidepressant drugs (aHR, 1.34; 95% CI, 1.02-1.75); and stimulant drugs (aHR, 1.64; 95% CI, 1.33-2.02); however, the effect sizes were similar to those among offspring exposed to perinatal complications only (any psychotropic drug: aHR, 1.53 [95% CI, 1.47-1.59]; antipsychotic, anxiolytic, hypnotic, and sedative drugs: aHR, 1.55 [95% CI, 1.47-1.63]; antidepressant drugs: aHR, 1.25 [95% CI, 1.14-1.37]; stimulant drugs: aHR, 1.69 [95% CI, 1.57-1.81]) (eFigure 1 in the Supplement).

The results of sibling pair analyses suggested that the associations detected between exposure to both preeclampsia and perinatal complications and specific developmental disorders, ADHD and conduct disorders, intellectual disabilities, and other behavioral and emotional disorders were not confounded (**Table 2**; eTable 6 in the Supplement), and the associations with other neuropsychiatric diagnoses were explained by within-pair shared familial factors (eTable 7 and eTable 8 in the Supplement). The effect size for the risk of any neuropsychiatric diagnosis (ie, any *ICD-10* F code)

among second siblings who had unexposed first siblings (aHR, 2.02; 95% CI, 1.66-2.45) was similar to the effect size for risk in the whole cohort (aHR, 2.11; 95% CI, 1.96-2.26); however, when only the first sibling was exposed, the second sibling had no increased risk of any neuropsychiatric diagnosis (aHR, 0.90; 95% CI, 0.74-1.09) (Table 2). When both siblings in the pair were exposed to both preeclampsia and perinatal complications, the risk of any neuropsychiatric diagnosis was larger (aHR, 3.19; 95% CI, 2.14-4.77).

Sibling pair analysis of the effect sizes of exposure to perinatal complications alone revealed that the detected association between perinatal complications and the risk of any neuropsychiatric diagnosis was not explained only by familial confounding. When both siblings in the pair were exposed, the effect sizes for the risks of specific developmental disorders (aHR, 2.40; 95% CI, 2.09-2.76) and ADHD and conduct disorders (aHR, 2.14; 95% CI, 1.69-2.71) (**Table 3**) among those exposed to perinatal complications alone were smaller than the effect sizes among those exposed to both preeclampsia and perinatal complications (specific developmental disorders: aHR, 3.56 [95% CI, 2.35-5.41]; ADHD and conduct disorders: aHR, 2.42 [95% CI, 1.09-5.39]) (Table 2), which were consistent with the risk estimates for the whole cohort (specific developmental disorders: aHR, 2.26 [95% CI, 2.18-2.33]; ADHD and conduct disorders: aHR, 1.60 [95% CI, 1.52-1.68]) (Figure 2; eTable 4 in the Supplement). However, the detected associations between exposure to preeclampsia alone

Figure 1. Maternal Preeclampsia and Incidence of Neurodevelopmental and Psychiatric Disorders in Offspring

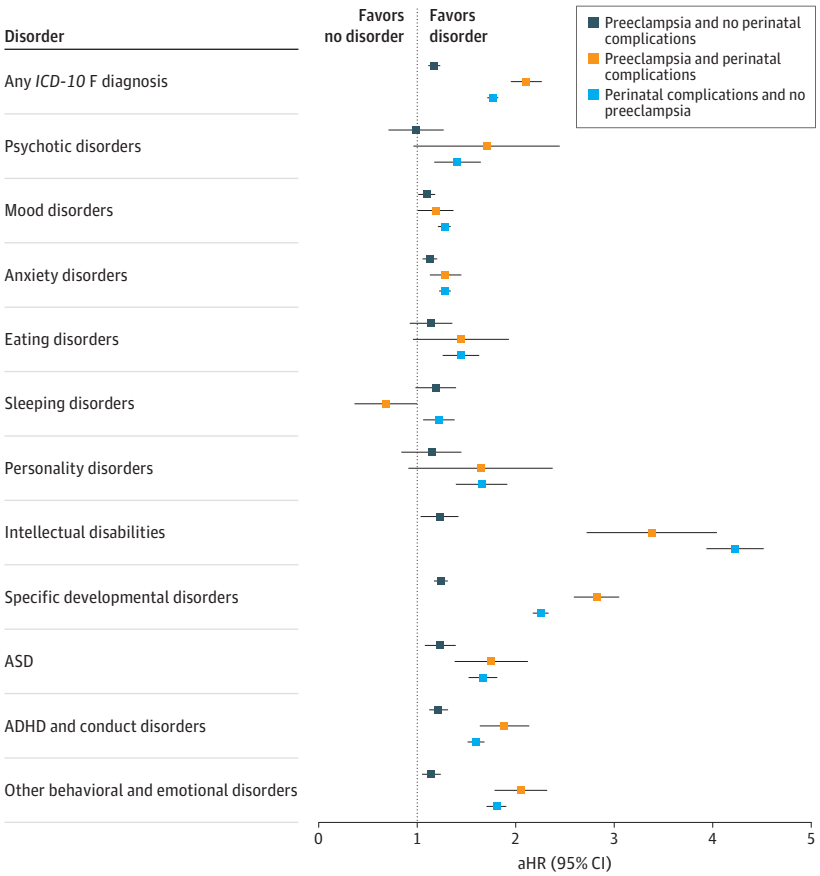


Preeclampsia was defined as *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnostic code O11 or O14. Perinatal complications were defined as small for gestational age (defined as birth weight and/or length more than 2 SDs lower than the sex-specific and gestational age–specific mean of the Finnish population[1] based on criteria from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society[2]) and/or birth earlier than 34 weeks' gestation. All offspring were followed up until December 2018. A, Specific developmental disorders include *ICD-10* codes F80 to F83. B, Attention-deficit/hyperactivity disorder (ADHD) and conduct disorders include *ICD-10* codes F90 and F91.

and the risk of any neuropsychiatric diagnosis were all explained by familial confounding (eTable 9 in the Supplement).

We also conducted sensitivity analyses of exposure diagnoses. Rather than using both *ICD-10* codes O14 (preeclampsia) and O11 (preexisting hypertension with preeclampsia) to define preeclampsia, we used only *ICD-10* code O14. The risk estimate pattern was similar to that of *ICD-10* codes O14 plus O11 (eg, risk of any neuropsychiatric diagnosis among those exposed to preeclampsia with perinatal complications: aHR, 2.51 [95% CI, 2.22-2.84] using *ICD-10* code O14 alone vs 2.11 [95% CI, 1.96-2.26] using *ICD-10* codes O14 and O11); however, because the number of mothers in the *ICD-10* code O14 group was smaller (43% of those in the *ICD-10* codes O14 plus O11 group), the 95% CIs were broader (eTable 10 and eTable 11 in the Supplement). Inclusion of mothers with inpatient psychiatric diagnoses and pregestational diabetes, and subsequent adjustment, did not substantially change the effect sizes (eg, risk of any neuropsychiatric diagnosis among those exposed to preeclampsia with perinatal complications: aHR, 2.08; 95% CI, 1.94-2.22]) (eTable 12 in the Supplement). We also estimated effect sizes for the association of exposure to gestational hypertension (*ICD-10* code O13), rather than preeclampsia, with neurodevelopmental and psychiatric disorders. Exposure to both gestational hypertension and perinatal complications vs preeclampsia and perinatal complications was associated with lower effect sizes for specific developmental disorders (aHR, 1.99 [95% CI, 1.65-2.40] vs 2.82 [95% CI, 2.60-3.05]), ASD (aHR, 1.14 [95% CI, 0.66-1.96] vs 1.73 [95% CI, 1.40-2.13]), and other behavioral and emotional disorders (aHR, 1.58 [95% CI, 1.17-2.14] vs 2.04 [95% CI, 1.80-2.32]) and a higher effect size for sleeping disorders (aHR, 3.09 [95%

Figure 2. Association of Maternal Preeclampsia and Perinatal Complications With Risks of Neurodevelopmental and Psychiatric Disorders in Offspring



Reference group comprised offspring who were not exposed to preeclampsia (*International Classification of Diseases, Tenth Revision* [*ICD-10*], diagnostic code O11 or O14) or perinatal complications (defined as small for gestational age [defined as birth weight and/or length more than 2 SDs lower than the sex-specific and gestational age–specific mean of the Finnish population[1] based on criteria from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society[2]] and/or birth at <34 weeks' gestation) after excluding maternal chronic hypertension and gestational hypertension. Analyses were adjusted for offspring birth year, offspring sex, and maternal factors, including age at delivery, country of birth (Finland or other), married at birth (yes or no), occupation (upper white collar worker, lower white collar worker, blue collar worker, or other status), smoking (yes or no), parity (0 or ≥1 births to a fetus with gestational age ≥24 weeks, regardless of whether the child was born alive or stillborn), obesity (*ICD-10* codes E65 and E66; yes or no), gestational diabetes (yes or no), outpatient psychiatric disorders (yes or no), dispensation of psychotropic medication (Anatomical Therapeutic Chemical classification system codes N05 and N06; yes or no), and systemic inflammatory disease (yes or no). All offspring were followed up until December 2018. ADHD indicates attention-deficit/hyperactivity disorders; aHR, adjusted hazard ratio; ASD, autism spectrum disorders.

CI, 1.92-4.98] vs 0.64 [95% CI, 0.40-1.02]). All other effect sizes were similar to those found for exposure to both preeclampsia and perinatal complications (eTable 13 in the Supplement).

The mediation analysis revealed that preterm birth and/or SGA status significantly mediated the association between maternal preeclampsia and any neuropsychiatric diagnosis in offspring (total association: HR, 1.05 [95% CI, 1.04-1.07]; direct association: HR, 1.01 [95% CI, 1.00-1.03]; by perinatal complications: HR, 1.04 [95% CI, 1.02-1.07]) (eTable 14 and eFigure 2 in the Supplement).

Discussion

This cohort study investigated the associations of prenatal exposure to preeclampsia and/or perinatal complications with neurodevelopmental and psychiatric disorders in offspring. Novel approaches of this study included (1) comparison of exposure to both preeclampsia and perinatal complications with exposure to preeclampsia alone and perinatal complications alone and (2) estimation of the risk of a wide spectrum of neurodevelopmental and psychiatric disorders in offspring. Using a large population-based cohort in Finland comprising more than 1 million singleton live births, we found an increased risk of specific developmental disorders (*ICD-10* codes F80-F83), ADHD and conduct disorders (*ICD-10* codes F90 and F91), intellectual disabilities (*ICD-10* codes F70-F79), and other

Table 2. Sibling Pair Analysis of Exposure to Both Maternal Preeclampsia and Perinatal Complications[a]

Exposure to preeclampsia with perinatal complications[c]	Total sibling pairs, No.	aHR (95% CI)[b]				
		Any neuropsychiatric diagnosis[d]	Intellectual disabilities[e]	Specific developmental disorders[f]	ADHD and conduct disorders[g]	Other behavioral and emotional disorders[h]
Model 1[i]						
Neither child/pregnancy in sibling pair exposed	435 997	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
First but not second child/pregnancy exposed	1614	0.96 (0.79-1.17)	0.72 (0.36-1.43)	1.02 (0.82-1.27)	0.93 (0.66-1.29)	1.04 (0.76-1.42)
Second but not first child/pregnancy exposed	873	2.08 (1.71-2.53)	3.17 (2.02-4.98)	2.82 (2.34-3.39)	1.81 (1.26-2.59)	1.52 (1.05-2.22)
Both children/pregnancies in sibling pair exposed	142	3.34 (2.24-5.00)	3.40 (1.10-10.55)	3.72 (2.45-5.64)	2.51 (1.13-5.59)	2.53 (1.21-5.30)
Model 2[j]						
Neither child/pregnancy in sibling pair exposed	435 997	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
First but not second child/pregnancy exposed	1614	0.90 (0.74-1.09)	0.66 (0.33-1.33)	0.95 (0.76-1.18)	0.86 (0.62-1.19)	0.98 (0.72-1.34)
Second but not first child/pregnancy exposed	873	2.02 (1.66-2.45)	3.05 (1.95-4.79)	2.71 (2.25-3.26)	1.73 (1.21-2.48)	1.49 (1.02-2.18)
Both children/pregnancies in sibling pair exposed	142	3.19 (2.14-4.77)	3.24 (1.05-10.06)	3.56 (2.35-5.41)	2.42 (1.09-5.39)	2.45 (1.17-5.13)

Abbreviations: ADHD, attention-deficit/hyperactivity disorders; aHR, adjusted hazard ratio.

[a] Sibling pair analysis of all 438 626 consecutive sibling pairs among 1 012 723 births in Finland between 1996 and 2014. All mothers with a singleton sibling pair were included. Mothers with in-hospital psychiatric disorders and pregestational diabetes were excluded.

[b] The aHRs for outcomes in the second child included diagnosis of any neurodevelopmental or psychiatric disorder (all F diagnostic codes from the *International Classification of Diseases, Tenth Revision* [*ICD-10*]) with regard to exposure of the sibling pair to preeclampsia with perinatal complications.

[c] Reference group comprised offspring who were not exposed to maternal preeclampsia (defined as *International Classification of Diseases, Tenth Revision* [*ICD-10*] code O11 or O14) or perinatal complications (defined as birth weight and/or length more than 2 SDs lower than the sex-specific and gestational age–specific mean of the Finnish population[1] based on criteria from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society[2] and/or delivery earlier than 34 weeks' gestation).

[d] Includes all *ICD-10* F codes.

[e] Includes *ICD-10* codes F70 to F79.

[f] Includes *ICD-10* codes F80 to F83.

[g] Includes *ICD-10* codes F90 and F91.

[h] Includes *ICD-10* code F98.

[i] Model 1 was adjusted for offspring birth year, offspring sex, and maternal factors, including age at delivery, country of birth (Finland or other country), married at birth (yes or no), occupation (upper white collar worker, lower white collar worker, blue collar worker, or other status), smoking (yes or no), parity (0 or ≥1 births to a fetus with gestational age ≥24 weeks, regardless of whether the child was born alive or stillborn), obesity (*ICD-10* codes E65 and E66; yes or no), gestational diabetes (yes or no), outpatient psychiatric disorders (yes or no), dispensation of psychotropic medication (Anatomical Therapeutic Chemical classification system codes N05 and N06; yes or no) during pregnancy (yes or no), systemic inflammatory disease (yes or no), and intrapregnancy interval.

[j] Model 2 was adjusted for all variables in model 1 plus the presence of a corresponding neurodevelopmental or psychiatric disorder or the dispensation of psychotropic medication to the first child.

behavior and emotional disorders (*ICD-10* code F98) in offspring exposed to both maternal preeclampsia and perinatal complications. These associations were not explained by measured confounders or unmeasured familial confounders. The risks of specific developmental disorders and ADHD and conduct disorders among offspring exposed to both preeclampsia and perinatal complications were higher than those of offspring exposed to perinatal complications only. The effect sizes for exposure to both preeclampsia and perinatal complications had aHRs ranging from 2 to 3. However, the associations between exposure to preeclampsia alone and offspring neurodevelopmental and psychiatric disorders were explained by unmeasured familial confounding, as revealed in our sibling pair analyses.

Gestational hypertension represents a more benign increase in blood pressure than preeclampsia.[32] In the present cohort, exposure to both gestational hypertension and perinatal

Table 3. Sibling Pair Analysis of Exposure to Perinatal Complications Only[a]

Exposure to perinatal complications only[c]	Total sibling pairs, No.	aHR (95% CI)[b]		
		Any neuropsychiatric diagnosis[d]	Specific developmental disorders[e]	ADHD and conduct disorders[f]
Model 1[g]				
Neither child/pregnancy in sibling pair exposed	417 922	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
First but not second child/ pregnancy exposed	15 730	1.06 (1.00-1.13)	1.07 (0.99-1.17)	1.04 (0.90-1.19)
Second but not first child/ pregnancy exposed	9392	1.96 (1.86-2.08)	2.66 (2.47-2.85)	1.90 (1.65-2.18)
Both children/pregnancies in sibling pair exposed	2483	2.02 (1.82-2.25)	2.61 (2.27-2.99)	2.37 (1.87-3.01)
Model 2[h]				
Neither child/pregnancy in sibling pair exposed	417 922	1.0 [Reference]	1.0 [Reference]	1,0 [Reference]
First but not second child/ pregnancy exposed	15 730	1.00 (0.94-1.06)	1.00 (0.92-1.09)	0.95 (0.83-1.10)
Second but not first child/ pregnancy exposed	9392	1.91 (1.80-2.02)	2.57 (2.39-2.76)	1.82 (1.58-2.09)
Both children/pregnancies in sibling pair exposed	2483	1.88 (1.68-2.09)	2.40 (2.09-2.76)	2.14 (1.69-2.71)

Abbreviations: ADHD, attention-deficit/hyperactivity disorders; aHR, adjusted hazard ratio.

[a] Sibling pair analysis of all 445 527 consecutive sibling pairs among 1 012 723 births in Finland between 1996 and 2014. All mothers with a singleton sibling pair were included. Mothers with in-hospital psychiatric disorders, pregestational diabetes, and preeclampsia (*ICD-10* code O11 or O14) were excluded. Sibling pairs with missing information on gestational age or birth weight for either sibling were also excluded.

[b] The aHRs for outcomes in the second child included diagnosis of any neurodevelopmental or psychiatric disorder (all F diagnostic codes from the *International Classification of Diseases, Tenth Revision* [*ICD-10*]) with regard to exposure of the sibling pair to perinatal complications.

[c] Reference group comprised offspring who were not exposed to maternal preeclampsia (defined as *International Classification of Diseases, Tenth Revision* [*ICD-10*] code O11 or O14) or perinatal complications (defined as birth weight and/or length more than 2 SDs lower than the sex-specific and gestational age–specific mean of the Finnish population[1] based on criteria from the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society[2] and/or delivery earlier than 34 weeks' gestation).

[d] Includes all *ICD-10* F codes.

[e] Includes *ICD-10* codes F80 to F83.

[f] Includes *ICD-10* codes F90 and F91.

[g] Model 1 was adjusted for offspring birth year, offspring sex, and maternal factors, including age at delivery, country of birth (Finland or other country), married at birth (yes or no), occupation (upper white collar worker, lower white collar worker, blue collar worker, or other status), smoking (yes or no), parity (0 or ≥1 births to a fetus with gestational age ≥24 weeks, regardless of whether the child was born alive or stillborn), obesity (*ICD-10* codes E65 and E66; yes or no), gestational diabetes (yes or no), outpatient psychiatric disorders (yes or no), dispensation of psychotropic medication (Anatomical Therapeutic Chemical classification system codes N05 and N06; yes or no) during pregnancy (yes or no), systemic inflammatory disease (yes or no), and intrapregnancy interval.

[h] Model 2 was adjusted for all variables in model 1 plus the presence of a corresponding neurodevelopmental or psychiatric disorder or the dispensation of psychotropic medication to the first child.

complications was associated with lower effect sizes for the risk of specific developmental disorders, ASD, and other behavioral and emotional disorders compared with exposure to both preeclampsia and perinatal complications. However, exposure to both gestational hypertension and perinatal complications had an unexpectedly higher effect size for the risk of sleeping disorders; however, all other effect sizes were similar to those among offspring exposed to both preeclampsia and perinatal complications, suggesting that this finding warrants further studies.

Meta-analyses[16,17] have reported that preeclampsia is associated with modest increases in the risk of ASD, ADHD, and schizophrenia. A large population-based cohort study in Sweden that examined the associations between preeclampsia and ASD using a severity indicator found that, among 2 842 230 singleton live births from 1982 to 2010, children exposed to preeclampsia had an increased risk of ASD (aHR, 1.25; 95% CI, 1.19-1.30), and children exposed to preeclampsia who were born SGA had an even higher risk of ASD (aHR, 1.66; 95% CI, 1.49-1.85); however, the risk estimate was comparable with that of children born SGA only.[10] Another Swedish national register–based study including 2 047 619 children reported that those exposed to preeclampsia had an increased risk of ADHD (aHR, 1.15; 95% CI, 1.12-1.19) compared with those not exposed to preeclampsia and SGA; after adjustment, the aHR for exposure to both preeclampsia and SGA was 1.43 (95% CI, 1.31-1.55), which was also comparable with that of exposure to SGA alone.[9] In addition, a Norwegian population-based study[11] including 980 560 children found that preeclampsia in term births was associated with increases in the risk of ADHD (adjusted odds ratio [AOR], 1.18; 95% CI, 1.05-1.33), ASD (AOR, 1.29; 95% CI, 1.08-1.54), and intellectual disability (AOR, 1.50; 95% CI, 1.13-1.97) after adjustment, but the researchers did not assess SGA exposure. A Swedish and Danish study[33] of 4 489 044 births reported aHRs of 1.6 for both ASD and ADHD and 2.5 for intellectual disabilities among offspring exposed to preeclampsia who were born earlier than 33 weeks' gestation; however, the aHR for exposure to preterm birth alone was not reported. Another Swedish and Danish study[12,13] found a 2- to 3-fold increase in the risk of offspring psychosis or schizophrenia after preeclampsia exposure. Our study found associations with modest effect sizes that were consistent with those studies,[9-13,33] but we also observed that the risk estimates for specific developmental disorders and ADHD and conduct disorders in offspring exposed to both preeclampsia and perinatal complications (ie, birth at <34 weeks' gestation and/or SGA status) were higher (aHR, 2.82 for birth at <34 weeks' gestation and 1.88 for SGA status) than those of offspring exposed to perinatal complications only, which is a novel finding.

Few studies have examined the association between exposure to preeclampsia and the risk of other neurodevelopmental and psychiatric disorders in offspring. A retrospective population-based cohort study[34] in Israel including 253 808 singletons reported that exposure to preeclampsia was associated with obstructive sleep apnea, epilepsy, and cerebral palsy in offspring, whereas no association was found with eating disorders. Our study similarly detected no association between exposure to preeclampsia and the risk of eating disorders in offspring; however, we did find an association between preeclampsia alone and the risk of sleeping disorders, although this association was explained by familial confounding, and epilepsy and cerebral palsy were not assessed. Furthermore, we found that offspring exposed to both preeclampsia and perinatal complications had a higher likelihood of developing other behavioral and emotional disorders (*ICD-10* code F98), which was not explained by familial confounding; however, the effect size was similar to that of exposure to perinatal complications only. Notably, for intellectual disabilities and sleeping disorders, the effect size of exposure to both preeclampsia and perinatal complications was lower than that of exposure to perinatal complications only, and this lower effect size remained after adjusting for gestational age and birth weight (data not shown). Although the sample of offspring with sleeping disorders was small and the risk estimate for sleeping disorders was therefore less reliable, we could not explain the lower effect size for the risk of intellectual disabilities among those exposed to both preeclampsia and perinatal complications compared with those exposed to perinatal complications only.

To our knowledge, only3 population-based studies of ASD, ADHD, and intellectual disabilities conducted in Sweden and Denmark[9,10,33] and 1 case control study of ASD conducted in Taiwan[35] have

assessed familial confounding by including sibling pairs who were discordant for preeclampsia, and no sibling-matched study has examined the associations between preeclampsia and other neuropsychiatric disorders. However, the findings of those studies[9,10,33,35] suggested that familial confounding did not explain the associations between maternal preeclampsia and ASD, ADHD, and intellectual disabilities because no marked difference in effect size was observed between the whole population and the differentially exposed siblings. Notably, our sibling pair analysis did not detect true associations between preeclampsia alone and neurodevelopmental and psychiatric disorders because the associations were explained by unmeasured familial confounding. However, the associations of exposure to both preeclampsia and perinatal complications or exposure to perinatal complications alone with intellectual disabilities, specific developmental disorders, ADHD and conduct disorders, and other behavioral and emotional disorders (*ICD-10* code F98) were not explained by familial confounding. Further large population–based research is warranted to verify our findings.

The etiologic factors underlying preeclampsia are not well known. However, there are a few mechanisms that may explain the association between maternal preeclampsia and fetal neurodevelopment. First, the placental insufficiency associated with preeclampsia[36] can lead to insufficient placental perfusion, hypoxia, and oxidative stress, which may have implications for neurodevelopment.[37-41] Second, impaired balance between circulating proangiogenic and antiangiogenic factors from the placenta has been reported in mothers with preeclampsia, with possible consequences for fetal vascular development, which in turn could plausibly impact both fetal cerebrovascular function and neurodevelopment and be further associated with cognitive and developmental functions in postnatal life.[42] Third, maternal inflammation may also play a mechanistic role.[43] Fetal exposure to maternal allergies, autoimmune diseases, and infections has been reported to be associated with both preeclampsia and offspring neurodevelopment.[16,43] In animal models, some maternal cytokines, such as C-reactive protein, interleukin 6, and interleukin 17, seem to be able to cross the placenta and enter fetal circulation, where they may regulate neuronal function and have consequences for later psychiatric and cognitive pathological characteristics.[44-46]

Limitations

This study has several limitations. Although the study adjusted for several putative confounding factors and performed sibling pair analyses, unknown and unmeasured confounding of sibling-discordant factors remains a limitation. The study also lacks data on paternal factors. In addition, exploration of factors moderating and mediating the association of exposure to both preeclampsia and perinatal complications with neurodevelopmental and psychiatric disorders in offspring is warranted. Although we identified all recorded diagnoses of neuropsychiatric disorders in offspring until the oldest were age 22 years, changes in diagnosis and comorbidities were not taken into account. Given that the mean follow-up duration was 12.4 years, the rate of late-onset disorders was underestimated (eTable 1 in the Supplement).

Conclusions

This cohort study found that offspring exposed to both maternal preeclampsia and perinatal complications had modestly increased risks of developing intellectual disabilities, specific developmental disorders, ADHD and conduct disorders, and other behavioral and emotional disorders. For specific developmental disorders and ADHD and conduct disorders, the risk estimates were higher among offspring exposed to both preeclampsia and perinatal complications compared with offspring exposed to perinatal complications only. Exposure to preeclampsia alone did not increase the risk of neurodevelopmental and psychiatric disorders because the detected associations were explainable by familial confounding. Further research is warranted to explore the complex mechanisms underlying the association between preeclampsia exposure and the development of these disorders.

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SUPPLEMENT.

5-2019

Trauma narratives in mental health interpreting : a qualitative study.

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TRAUMA NARRATIVES IN MENTAL HEALTH INTERPRETING: A QUALITATIVE STUDY

By

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B.A., University of Louisville, 2014

A Thesis
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in Spanish

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ABSTRACT

TRAUMA NARRATIVES IN MENTAL HEALTH INTERPRETING:

A QUALITATIVE STUDY

Miranda Hale

April 9, 2019

Interpreting Studies has seen an increase in research in mental health, but many questions have yet to be explored. This study seeks to contribute to the literature by considering how interpreters render trauma narratives that clients share in counseling sessions. Semi-structured interviews were conducted with two interpreters who have experience in the mental health setting and one counselor who has worked extensively with interpreters. A thematic analysis of these interviews contributes to a better understanding of the interpreted interactions in this setting, with key points highlighting aspects of the setting itself, the work environment, and interpreters' trauma awareness. It also demonstrates that some participants in these encounters already have a basic awareness of how trauma affects language. This study concludes that interpreters' renditions of these narratives can have diagnostic value in this setting. As a preliminary study, these findings can serve as a basis for further research on the topic.

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CHAPTER I

INTRODUCTION

Imagine that someone you know has just experienced a negative life-altering event: she was robbed at gunpoint and beaten by her assailants. After a short hospital stay, she survived the confrontation without lasting physical injuries. However, the incident has impacted her in other ways. She is trying her hardest to stay strong for her children, but every area of her life has been affected. As she tries to go on with her daily routine, she finds that it is difficult to do simple tasks. On top of this, she feels paralyzed by fear when she hears sounds that remind her of the attack. You know there are resources out there to help her, but there's one problem: she's only been in the United States for a year and doesn't speak English well enough to communicate with a therapist.

While the above anecdote is fictional, it mirrors the experience of many in this country who have experienced some sort of trauma and don't know where to turn for help. Many immigrants and refugees could benefit from receiving psychological services to cope with such debilitating circumstances, but a language barrier prevents them from accessing these services. A range of solutions exist, but one of the most common involves using interpreters to facilitate communication between the trauma survivor and the mental health professional. Although using interpreters is a valid solution, it poses its own challenges. Will the interpreter be able to tell the survivor's story well? Will the therapist be able to maintain control of the session in the presence of a third party? How

will the interpreter respond to the traumatic content they are hearing and subsequently interpreting?

The process of thinking through these questions and seeking answers to them has led to the TIMIS project (Trauma-Informed Mental Health Interpreting Services). This study was created with the two-fold approach of providing these interpreting services to victims of trauma and looking at these questions further. As I have sifted through some of these questions in my interpreting classes and while assisting with this study, I have developed an interest in a specific aspect of this issue: trauma narratives and their interpretations. In this thesis I will primarily look at trauma narratives and how they are interpreted, while situating it within the broader context of the TIMIS project.

Before diving into the details of this study, I would like to comment on the exceptional opportunity that interpreting provides. Whereas the theoretical nature of research can often feel far removed from the practical solutions it seeks to provide, applied research on interpreting has the potential to immediately impact the lives of those who receive interpreting services. As an interpreter and a researcher in this field, I can simultaneously be the voice for people like the woman mentioned above while also contributing to knowledge that will help others be better equipped to serve in the same capacity. There is a tension there, and it does come with its limitations, but it is a rewarding work. I resonate with the reflections of other researchers in neighboring fields: "I am aware of the potential problems involved in trying to fulfill two roles at the same time… I see myself as a researcher *and* a social activist, and I see these roles as complementary rather than contradictory (Phipps 2012)" (Ladegaard "Coping" 192).

1. Statement of the Problem

As previously mentioned, the TIMIS project was intentionally designed both to provide interpreting services to trauma survivors and to further the research on interpreting in mental health. The first problem it seeks to address is social in nature. Although Louisville, Kentucky has a large population of Spanish-speakers, there are very few mental health services available to them in their own language. Sometimes these services can be accessed through interpreters, but due to lack of funding and available resources, organizations may rely on bilinguals who are untrained in interpreting and in trauma-informed care. The TIMIS project makes it possible for this Spanish-speaking population to access these services for free using trained interpreters. The additional social benefit is that the interpreters receive further training and practice in interpreting in mental health, and counselors get the professional experience of learning to work with interpreters.

The second problem the TIMIS project seeks to address is scientific in nature. There is limited research on interpreters working in mental health. This is indicative of a broader trend within Interpreting Studies, as noted by scholars: "Indeed, the body of research in Interpreting, especially community interpreting, is so small that most questions are yet to be formulated and researched" (Hale and Napier 20). With this said, there are relatively numerous publications centering around legal and medical interpreting, but far fewer focusing on mental health. Most of the questions about interpreting in mental health have yet to be asked, and those that have been asked are accompanied by a scant body of research.

2. Research Questions

While the TIMIS project was designed to cover a broader scope of research questions about this setting, covering topics such as interpreter visibility, interpreter agency, and trauma-informed protocol, this thesis is addressing one area in particular: interpreting trauma narratives within this setting. How do interpreters process and then convey these trauma narratives from one language to another? Since trauma narratives have different linguistic characteristics than regular discourse, do interpreters unintentionally repair the message as they convey it? Does the rendered message maintain the same characteristics as the original, to the greatest extent possible? And, consequently, does this make a difference in the way mental healthcare professionals perceive, and possibly even diagnose, their clients with limited English proficiency?

Languages vary on many levels: lexicon (vocabulary), morphology (word-level), syntax (sentence-level), semantics (meaning), to name a few. As such, interpreters cannot produce an exact equivalence of what they heard in the source language, because the differences in languages do not allow for this. Beyond considering the words themselves, they must also take into account how they are spoken, which is represented in the paraverbal aspects of communication. My hypothesis is that interpreters may unintentionally try to repair language they hear and produce a rendition that is less accurate than desired. If the language sounds different or unnatural, on a verbal and paraverbal level, they may want to reproduce something that makes sense, but ends up losing some of the characteristics that made the original message distinct from ordinary speech.

Interpreters in mental healthcare are already facing a host of expectations and pressures: they must listen intently to stories of clients' most traumatic experiences and repeat them, they have to remain calm in the midst of such heavy content and emotional reactions from the clients, and they must conform to the counselor's therapeutic style, while simultaneously navigating other personal and professional pressures. Why should we put more pressure on them to get all the nuances and paraverbal aspects of these narratives correct? In mental healthcare, words are the only means professionals have to diagnose their clients' problems. The interpreter is the only one in the room who can hear the original message exactly as it is being said, nuance and all. In order to do their job well, to be the voice of the victim and give the counselor access to that voice, they must ensure that the voice is being conveyed accurately. If interpreters are not even aware that trauma narratives are distinct from everyday speech, and the implications this could ultimately have for diagnosis and treatment, they may not pay careful enough attention to produce a faithful rendition. This research is intended to better understand this problem and shape further training for interpreters who will interpret these narratives.

3. Purpose of the Study

The purpose of this study is to learn more about interpreters' and counselors' perceptions of interpreter-mediated counseling sessions, with the aim of gathering information about trauma narratives. To understand the research questions, it first looks at the interactions: who is participating, where the sessions are is taking place and how often, what they are like. Then it indirectly observes the trauma narratives that are shared during the sessions. It explores whether the listeners have perceived any differences in trauma narratives as compared to everyday speech. The study seeks to identify

characteristics of these narratives based on the literature and the perspective of interpreters and counselors. This research also looks to describe how interpreters have handled these narratives while interpreting and to make recommendations for future training.

4. Strengths & Limitations of the Study

The methodological approach to this study will be described in detail in chapter three; however, it is important to address some of the strengths and limitations early on. Semi-structured interviews were conducted with two interpreters and one counselor, all with at least one year of experience in the mental health setting. The study is qualitative in nature and, as such, some of its strengths are also limitations. While the sample size was relatively small, the method utilized allowed the participants to describe their experience with trauma narratives in depth.

As a researcher, I have personally had to wrestle with some of the limitations to this study. My original plan was to do discourse analysis on interpreted trauma narratives. These would have come from transcripts of real-life interpreted counseling sessions through the TIMIS project. I considered this to be the ideal approach because there are limitations to relying on reflections about interpreting instead of looking at the interpreted encounters themselves. Not only that, but since my hypothesis is that interpreters are unintentionally altering the messages, I was counting on having actual transcripts to answer my questions. If interpreters are unaware that they are doing something, they will not likely to be able to report on it. Although there are currently counseling sessions scheduled to happen through the project, at the time of writing these sessions have yet to take place due to various logistical challenges.

In thinking through this limitation and having to come to terms with the interview method I ultimately chose to utilize, I have noted a strength in it. With the transcripts, I would have been limited to data from a small number of counseling sessions, and trauma narratives may not have even appeared in those sessions. With the interview method, the participants were reflecting on years or even decades of experience that I would not have otherwise had access to. Even with the limitations, since this is such a new topic of study, the data collected is useful in determining the relevance of this issue, and will help pave the way for further research. .

5. Interdisciplinary Nature of Study and Organization

The primary aim of this paper is to contribute to the field of Interpreting Studies, an academic discipline which focuses on the oral or signed transfer of messages across languages. This will be accomplished by studying a specific linguistic phenomenon, trauma narratives, within a given context (mental health settings) and describing how interpreters have handled them in the past. This information will allow recommendations to be made for best practices in the future. The field of Interpreting Studies in and of itself is diverse, as highlighted by the broad range of categories researchers can study: medium, setting, mode, languages (cultures), discourse, participants, interpreter, and problem (Pöchhacker 23-24). Given the diversity of topics within the field, it naturally lends itself to interdisciplinary work (47-51).

This study, while maintaining Interpreting Studies as a central focus, will also pull from the fields of psychology and linguistics for foundational concepts, theories, and data analysis. This intersection happens organically. Looking at the list above, one can see how these research categories in Interpreting Studies overlap with other fields of study:

discourse is logically linked with linguistics, languages and cultures with cultural studies, interpreting settings such as legal or medical with their respective academic disciplines. The possibilities are endless. In an effort to narrow my study, I have chosen to limit its overlap primarily with psychology and linguistics because they are most relevant to the questions at hand. I do this with the awareness that some questions may be left unanswered, paving the way for more research in the future.

Psychology as a discipline is helpful in contextualizing both the setting and the problem in this study. Since trauma narratives are shared in therapeutic settings, the psychological branches of counseling psychology and clinical mental health psychology give a framework for understanding the communication that takes place in counseling. Scholarly work from psychologists provides a definition of trauma, a central theme in this study. They are also referenced to define trauma-informed care, a foundational basis for trauma-informed interpreting. Publications from psychology dealing with working with interpreters are mentioned. Lastly, psychological studies that have commented on unique features of trauma survivors' language are referenced, especially where linguistics has not yet done so as comprehensively.

The field of linguistics is consulted within this study to show the connection between language and trauma. This discipline helps shed light on which aspects of speech are affected by trauma and how trauma manifests itself in language. Of particular relevance are the subfields of discourse analysis, pragmatics, and applied linguistics. Although discourse analysis, used to study different aspects of naturally occurring speech, is not employed here as a methodological approach, prior work using discourse analysis on trauma narratives is mentioned to show the relevance of the problem.

Pragmatics, which studies the meaning of words within a given context beyond their semantic meaning, while not the main emphasis of the research, can play a role in helping understand how the trauma narratives and the interpreter's rendition of them are perceived in the counseling sessions. Lastly, the subfield of applied linguistics studies linguistic problems. This is applicable to this study because it examines the linguistic problem of how to interpret speech affected by trauma.

Works from the above disciplines make up the literature review, which covers the following topics: language and trauma, trauma-informed interpreting, interpreting in mental health, and mental healthcare's perspective on working with interpreters. A detailed overview of the methodology used for this study follows the literature review. Then, there is an analysis and discussion of the collected data. Before reviewing what the applicable literature from Interpreting Studies, psychology, and linguistics reports, some basic concepts are introduced in the following section to assist in an understanding and interpretation of the findings.

6. Basic Concepts and Terminology

6.1. Concepts from Interpreting Studies

In the following paragraphs I introduce some basic concepts found within Interpreting Studies, such as interpreting, the people involved in the interpreting encounter, modes, settings, codes of ethics, and protocols. Although interpreting is different from translation, it is common for laypeople to mistakenly refer to both as translation because of their similarities. Both involve transferring messages from one language (the source language) to another (the target language). Typically, translators and interpreters convert messages from their B language, a language they have a high level of

fluency in, into their A language, or native language. In spite of these commonalities between interpreting and translation, there are characteristics which distinguish them from one another in their respective professional and academic fields.

Interpreting is distinct from translation in that the language transfer always happens orally or, in the case of sign language interpreting, through signs. Interpreting also involves a personal, sometimes face-to-face, synchronous communication. In contrast, translation projects are typically worked on privately and asynchronously. The professional implication is that interpreters must be prepared to render messages on the spot, whereas translators can take more time and consult resources before translating the message. This is one of the key elements that distinguishes research in both fields. While translation studies naturally focuses more on texts, Interpreting Studies looks not only at the message that is conveyed, but also the interaction between the participants.

One of the most relevant factors shaping these interactions is the setting in which the interpreting takes place. A typical division of interpreting settings is as follows: legal, healthcare, public service/community, and conference. New settings continue to be added as the field expands, and these can include interpreting in asylum proceedings, mental health care, education, interpreting for the mass media and in conflict zones, amongst others (Mikkelson and Jourdenais). While there are some generally accepted principles about interpreter role and conduct, scholars often debate the finer nuances of these issues within the context of each setting. This is part of the reason why my study is limited to one setting: mental health. Although the mental health setting is sometimes included within the broader healthcare setting, I will later discuss why I think it should be kept separate.

Due to the different interactions that take place across these settings, interpreters must train and prepare themselves accordingly. Being bilingual is a first step to interpreting, but it is not enough. Typically, interpreters must engage in serious study to specialize in one or more of these settings, beyond learning basic interpreting skills. This is because, in additional to the specialized terminology they must learn, they must also be mindful of pragmatic considerations regarding communication. A lawyer in a courtroom could ask someone, "What happened?" seeking to elicit a guilty response from a defendant, whereas a doctor in a hospital could ask the very same question out of sincere concern for a patient. The interpreter must to learn to distinguish these types of communication being mindful of the setting. These skills can be learned through professional and academic training. The level of training required for interpreters to enter the profession may differ depending on the country and organization where they are working. There are also different institutional expectations and professional conduct and protocols required of them.

Since interpreters are engaged in a professional task, they often abide by codes of ethics. These vary slightly based on the setting and the perceived role of the interpreter within that setting. For example, interpreters are always supposed to be impartial, but this would be implemented more stringently in legal interpreting, which is inherently adversarial, than in a medical setting interpreting between a doctor and a patient.

Interpreters are also expected to be accurate, to render the message accurately and adequately, without any omissions, additions, or modifications. Again, these expectations can vary slightly by setting. In a courtroom, if witnesses hesitate on the stand and the interpreters do not include these hesitations in their renditions, they are not accurately

conveying what was said. This lack of accuracy could be detrimental to the cases. Medical interpreters would still seek to convey these hesitations to promote accuracy, but the consequences of not doing so in this setting would likely not be as grave. Closely aligned with interpreter codes of ethics are protocols, specific actions interpreters should take in determined situations. Sometimes codes of ethics will allude to these protocols, sometimes they are outlined elsewhere, and sometimes the interpreters simply use common sense to adapt to the situations.

Interpreters also use different modes of interpretation depending on the nature of the setting, the specific goals of communication, and the challenges presented in each situation. The modes are typically broken down into three types: consecutive, simultaneous, and sight translation. Consecutive interpretation occurs when one speaker conveys a message then pauses to give the interpreter time to interpret into the target language. In the second mode, simultaneous interpretation, the interpreter listens to the original message in the source language and reproduces it in the target language at the same time, with just a slight lag time. Sight translation occurs when an interpreter is presented with a written document and must reproduce its contents orally in the target language on the spot.

Dialogue interpreting, consisting of two-way back and forth conversations that are conveyed through interpreters, are typical to interpreting in public services. The most commonly used mode in these encounters is consecutive, since it best corresponds with the natural turn taking of a two-way conversation. In the study presented here, interpreters may choose to use either consecutive or simultaneous interpretation, depending on what is the best fit to meet the specific communicative goals of the

counseling sessions. In some cases, specifically when considering trauma narratives, which could involve longer segments than interpreters normally handle in consecutive interpreting, they may switch to the simultaneous mode so as not to omit any major parts of the narrative. Sight translation may also be used in these sessions if the counselors want to incorporate any documents that have not been translated into Spanish, or if they ask the clients to write something out in Spanish to then be read aloud and shared with the counselor.

The last major set of terms relevant to interpreting has to do with the participants involved in the communication. The interpreter has already been identified. In public service interpreting settings, there is a professional providing some type of service, such as social work or therapy. This person is referred to in a broad sense as the service provider. In this study, since it focuses on the mental health setting, I will generally refer to the mental health care providers under the broad umbrella of counselors. This is not intended to diminish any distinctions in training or approach, but rather will serve to simplify the discussion. The one who receives this service, while called a client or patient by the service provider, is often referred to in Interpreting as a service user. Since this study is contextualized in mental health, I will mostly refer to them as clients. Now that we have a foundational understanding of interpreting in its various settings and modes, interpreter ethics and protocols, and the parties involved in the exchanges, we can move towards an understanding of trauma from a psychological perspective.

6.2. Concepts from Psychology: Trauma and Therapy

Trauma is a broad concept and thus difficult to define. There are a plethora of definitions and each one has its own nuances. For the sake of this paper, the following

definition will be used: “Individual trauma results from an event, series of events, or set of circumstances that is experienced by an individual as physically or emotionally harmful or life threatening and that has lasting adverse effects on the individual’s functioning and mental, physical, social, emotional, or spiritual well-being” (SAMHSA 7). The three “e’s” are highlighted in this definition: events, experience, and effects. “Events” refers to the fact that trauma can happen as a result of a single or repeated occurrence. “Experience” refers to one individual’s experience and the fact that the same difficult event may be experienced as traumatic for one person and not for another. Lastly, the word “effects” corresponds with the adverse effects, which can happen immediately after the event or come about later, but are always present, affecting the person’s daily life (8). Examples of potentially traumatic experiences can range from but are not limited to sexual molestation, child abuse, domestic violence, wars, and natural or man-made disasters (van der Kolk 1).

Since trauma leaves such a profound impact on individuals, it has been the subject of psychological study and interest for over a century. Near the end of the 19th century, notable figures such as Jean-Martin Charcot, Pierre Janet, Josef Breuer, and Sigmund Freud began looking into this phenomenon. Freud and Breuer’s “talking cure”, getting patients to discuss their traumatic past events, was thought to be the solution for recovering from trauma and integrating back into daily life (van der Kolk 182). This idea has evolved over the years, but talking is still seen as a fundamental element of the widespread cognitive behavioral therapy (CBT) psychological technique (182).

Alongside the top down approach of talking through traumatic experiences through CBT or some other method, mental health professionals have other ways to help

treat trauma. They may approach treatment using medication to help mitigate trauma's effects on the mind and body. Sometimes, since trauma can have a sensory impact on the body, a bottom up physical approach is used. This can include involve promoting activities such as yoga, which are intended to help the patient focus on reconnecting with his or her body in positive, healthy ways (3). A combination of all three approaches can be used, but this particular study will highlight the talking approach as it is most relevant to interpreters and trauma narratives, and naturally connected to the linguistic nature of this study.

While trauma in and of itself is not a new topic of study, the concept of a trauma-informed approach to care has grown in recent years. A trauma-informed approach within an organization or system understands what trauma is and how it affects people, and adjusts its standard practices accordingly. It realizes that trauma has a widespread impact, recognizes its signs and symptoms, responds by developing trauma-awareness into their structures, and takes measures to avoid re-traumatization (SAMHSA 9-10).

Traditionally trauma-informed care has been associated with psychology-based professions, but it has gained more traction recently and has expanded into different professions and services. It is not uncommon to hear of trauma-informed medical practices, trauma-informed educational practices, or even trauma-informed policing. This trend will likely continue, since the events that can provoke trauma cover such a wide range of the human experience and there is a high likelihood of trauma victims accessing various services and institutions. The concept of trauma-informed interpreting that is rooted in this trend will be discussed in the literature review. While a trauma-informed approach in one domain differs from therapeutic practices focused specifically on

overcoming trauma, both are relevant to our discussion in terms of protocol and setting. Now that these basic concepts have been introduced, a literature review will follow to examine the works and theories relevant to this study.

CHAPTER II

LITERATURE REVIEW

1. Language and Trauma

For the aims of this paper, we are primarily concerned with theories specifically relating to the linguistic manifestation of trauma in spoken language and then to look at how this is handled by interpreters. When trauma was outlined in the above section, it was introduced initially as a concept of particular interest to psychological studies. However, trauma has also been an emphasis in other fields of academic studies, as it has been approached from within literature, cultural studies, sociology, medicine, social work, history, even theology, amongst other fields. Although it would not be productive to delve into all the existing theories on trauma from these disciplines, it has proven to be a topic of merit across them. This stands in contrast to the lack of work on trauma done from a linguistic perspective in comparison with other fields. Since trauma is often related orally through narrative form, it by nature should be of interest to linguists. At the time of writing there is not a comprehensive theory of the linguistic manifestation of trauma.

Many of the observations about trauma and language have come from psychological studies. It has been asserted that "traumatic events are almost impossible to put into words" (van der Kolk 231). Early on, trauma was associated with a lack of language, or an inability to describe their traumatic experience, and language was seen as an essential component to overcoming it (177-182). While those who have directly

worked with patients have seen the benefits and challenges of language in their treatment, it was not until the 1980s that some of the first comprehensive tests studying the connection between language and trauma were conducted (Pennebaker). The goal was to evaluate the effectiveness of language in treatment, but in the process of doing so, they noticed some interesting patterns in the language itself.

In these studies it was observed that, when subjects wrote about trauma, there was a notable change in their handwriting; it would go from one style to another, such as cursive to block letters. In the recorded spoken accounts, the participants' voices changed so much when recounting personal traumatic stories that the researchers questioned if it was the same person (van der Kolk 241-242). Although the emphasis has not yet been on specific linguistic units that can be analyzed, this "switching," or changing vocal patterns and the narrative style of trauma experiences, has been reported in clinical practices (241-242).

More recently, the events of September 11, 2001 caused interests in researching traumatic experiences to resurface. One study from a clinical perspective delved heavily into discourse as it relates to trauma (Brockmeier). This was a groundbreaking study, considering that even in 2015 it was noted that "most of the existing trauma narrative research has been done by people in the health professions, and these studies tend to pay little attention to language" (Ladegaard "Coping" 189-90). Surveys were distributed to eyewitnesses of the events of 9/11. The resulting analysis of the data showed a "traumatic gap" in their ability to recount these traumatic histories (Brockmeier 16). Observations were made about the linguistic resources people utilized, such as figurative speech and ignoring traditional structures of narrative coherence, even metalinguistic reflections of

how limited their words were to describe their experiences. The researcher speaks of traumatic experience as "a break not just with a particular form of representation but with the very possibility of representation at all. This representational break culminates in the breakdown of narrativity" (33). It is interesting to note that the observations made in this particular study are coming from written answers, when the people ideally had time to think about the answers they wanted to write down. How much more might this lack of narrative cohesivity come out in spoken accounts?

Even philosophers have examined the relationship between trauma and speech. One scholar, a trauma victim herself, says that through the process of experiencing trauma, victims feel as though they've lost their voice (Brison 48). Their sense of agency has been taken away from them as a result of being harmed by others, in the instance of trauma where a perpetrator is responsible. After the event, the victims are left with a traumatic memory, which is distinct from other types of memory in that it produces an involuntary emotional and physiological response in the victims (41-45). When memory itself has been affected, this naturally leads to an altered form of speech, which also manifests itself in incoherent narratives. Narrative memory, in contrast, is an active construction of past events, and victims want to try to transform traumatic memories into coherent, narrative ones (45-47). Working through this process reveals "the performative role of speech acts in recovering from trauma: under the right conditions, *saying* something about a traumatic memory *does* something to it" (48).

This gets at the heart of what many types of trauma therapy aim to do: to get people to explore their traumatic memories so they can overcome the trauma they experienced. It is a current practice in trauma therapy to ask clients to describe these

moments audibly or write about them and then read the stories aloud to the counselor (Briere and Scott 127). Through this process of revisiting the original memory, responding to follow-up questions from the counselor, and repeating those steps as many times as necessary, the clients are helped to think through these memories with more clarity. Clients with less coherent narratives--ones that are fragmented, lacking a clear timeline of events and cause-effect relationships--typically suffer from higher levels of anxiety, insecurity, and confusion (131). In the same way, "it is likely that narrative coherence is a sign of clinical improvement" (130). In other words, the characteristics of these narratives can be an indication of how much trauma is affecting them, where they currently are on the spectrum of healing.

The literature reviewed here has shown some of the ways trauma can manifest itself in language and its relevance in trauma-focused therapy. While it is true that most research on trauma and language has been done by researchers in psychology, some researchers are beginning to look at trauma narratives from a sociolinguistic perspective (Drakos; Grazia Guido; Ladegaard "Codeswitching", "Coping", "The Discourse"; Trinch "Recalling"). In spite of these growing efforts to further the study of trauma as a linguistic phenomenon, more research needs to be done to help us better understand how trauma manifests itself through language. This study hopes to not only contribute to a linguistic understanding of trauma, but also to an understanding of how this language is processed by and conveyed through interpreters. Some of the practical concerns of interpreting for trauma victims will be considered in the next section.

2. Trauma-Informed Interpreting

With an awareness of the commonality and profundity of trauma on the rise, the drive towards trauma-informed approaches in society has also begun to shape interpreting practice. The profession, often through trial and error, has recognized the need for interpreters to be equipped to respond to trauma proactively and reactively. These best practices address both the after-effect of the exposure to the emotional content shared by the service users and the linguistic and practical challenges that present themselves during interpreted encounters. In recent years, trauma-informed interpreting has been coined and defined as "a young yet vital… specialisation of interpreting that integrates research on trauma into the professional practice of interpreters" (Bancroft 195).

In this section, I will address the way emotional challenges related to trauma have been addressed in Interpreting Studies literature before this term was coined. I will look at the populations the discussion has centered around thus far. I will also highlight the recent trend towards a survivor-focused approach and, respectively, how trauma-informed protocols can support such an approach by preventing re-traumatization and encouraging communicative autonomy. Lastly, I will explain how these concepts are relevant to my study.

While trauma-informed interpreting in and of itself is a newer concept that is gaining traction, the literature has previously recognized the emotional and psychological strain of the profession on its practitioners. Various studies have considered different aspects of these emotional and psychological challenges, especially within public service interpreting (Loutan et al.; Baistow; Valero-Garcés "Emotional","The Impact"). Two themes that commonly arise in this conversation are interpreter burnout and vicarious

trauma (Knodel; Splevins). These are distinct experiences; whereas burnout is a gradual emotional wearing down from the job, vicarious trauma can affect someone instantaneously without warning (Harvey 89). Many interpreters find themselves surprised and unprepared for their personal emotional and psychological response to the traumatic content they are exposed to while interpreting.

Since trauma covers such a vast range of experiences, it comes up in conversations in the literature when talking about interpreting for distinct groups. This can center around a particular type of violence, such as gender violence, which has been addressed through the creation of resources to help interpreters work with these victims (Toledano Buendía and del Pozo Triviño). Others have highlighted the centrality of trauma awareness in the context of working with refugees, since this group is by definition seeking refuge from a dangerous situation (Crezee et al. "Issues"; Jiménez-Ivars and León-Pinilla). Some have argued for a subcategory of Interpreting in Refugee Contexts within Interpreting Studies that would expand across different settings, in large part due to common experience of trauma many refugees have faced (Jiménez-Ivars and León-Pinilla). Other studies on interpreting with refugees have also highlighted trauma as a primary concern both for interpreters and those they are interpreting for (Crezee et al "Issues").

This last study understood the essence of trauma-informed interpreting before the term was even used. This is twofold: it considers the impact on both the interpreter and on the survivor (Bancroft 210-211). Most of the studies mentioned above have centered around the psychological and emotional impact on the interpreter. This emphasis on interpreters is valid because it aims to raise awareness about the possibility of vicarious

traumatization, something that could potentially drive interpreters away from the profession. However, the interpreter is not the only one at risk, because trauma can continue to have adverse effects on the survivor, and this should be taken into account when interpreting for them. A central goal should be protecting them from re-traumatization, or reliving their traumatic experience (Crezee et al. "Issues"). One of the means by which interpreters can make these service user-centered decisions is by adjusting their protocol.

The concept of interpreter protocols was mentioned in the introduction. While these protocols vary depending on the situation, a case has been made for establishing trauma-informed protocols for interpreters (Bancroft et al. 206-224). These protocols would first and foremost make efforts to protect the survivors from re-traumatization (Bancroft 214). Specific adjustments could include being mindful of the seating arrangement, eye contact, and tone of voice (Bancroft et al. 211-215). These may deviate from what is typically expected behavior of interpreters. For example, whereas interpreters might typically decide the seating arrangement without consulting the service users, a trauma-informed approach could entail asking the service users which seating arrangement they are more comfortable with (211). Other protocols become more complex: in some situations where interpreters would typically be expected to seek clarification of an utterance, the service providers might actually prefer to take the responsibility in doing so, since they are the ones who best understand trauma and how it could have affected this person (Bancroft 206).

Along with taking the trauma-informed approach to try to prevent re-traumatization of the survivor, interpreters should also work proactively to promote the

survivor's communicative autonomy. Communicative autonomy can be nurtured when interpreters "support clear communication where all parties have the power and authority to make their own decisions without interference by the interpreter" (Bancroft 212). In situations where the interpreter is aware of the trauma, interpreters as compassionate human beings have a natural desire to want to help by giving unsolicited advice to the client or the service provider or acting as a cultural broker (201). While the interpreter's intentions are often good, this can contradict a trauma-informed approach, since one of the goals in working with trauma survivors is helping restore the autonomy that was taken away from them as a result of the traumatic event(s) (200-201). In trauma-informed interpreting, interpreters work alongside the service providers for the benefit of the service user.

While trauma-informed intervention and protocols have been addressed in some of the literature and detailed suggestions such as the ones listed above have been made, more research must be done to determine which approaches best protect all parties while allowing the interpreter to appropriately convey the needed information. There is a delicate balance when considering the emotional and psychological needs of the parties involved in the communication and the need for linguistic clarity provided by the interpreter. The training programs and manuals previously referenced (Bancroft, Bancroft et al.), while based on extensive research, are very recent seminal works in this self-proclaimed young specialization. These resources were created on the premise that few practicing interpreters had prior trauma-informed training because very few such programs were available, and even those in existence were not extensive (Bancroft 202). Thus, now that this training has been disseminated, further research is needed to see how

these suggestions play out and impact the involved parties in interpreter-mediated communication. The need for more research in this area is one of the reasons this project has been launched.

Another way this project fulfills a need in the literature is by focusing on a broader scope of trauma. As detailed above, oftentimes trauma is discussed in the context of refugees or a particular type of violence. However, we have seen that there is a vast range of traumatic events that people can experience, and it is not limited to refugees or violence. Interpreters should be better equipped to understand the different ways trauma can impact people and their language in a general sense. While this study will not be able to definitively address all types of trauma and all the populations it impacts, it hopes to broaden the conversation.

Specifically, the question about interpreting trauma narratives corresponds to the idea of communicative autonomy. If the goal is to help the survivor regain their voice by communicating directly with the service provider with as little interpreter intervention as possible, then one element of promoting that autonomy is through interpreting trauma narratives as the survivor has uttered them. While this concept is not unique to trauma-informed interpreting, it may have greater implications in this type of interpreting than in other situations, given its sensitive nature. This focus on communicative autonomy overlaps with the idea of accuracy, which will be addressed in the next section on interpreting in mental health. Up to this point, the discussion around trauma-informed interpreting has covered a range of settings, but I will now focus on interpreting in a mental health setting, where trauma is often the basis of the need for communication.

3. Interpreting in Mental Health

This study will address a specific need within Interpreting Studies for more research on interpreting in the mental health setting. It has only been in the past two decades that Interpreting Studies has begun to look extensively at this setting. The first article I found that specifically looks at interpreters in therapeutic encounters was published in 2001 (Wadensjö "Interpretng"). In the same year, the role of interpreters in mental health was addressed at the third annual *Critical Link* conference (Bot and Brunette). This foreshadowed the more extensive work that would be done in *Dialogue Interpreting in Mental Health*, the seminal monograph on the topic (Bot). There have been additional studies done in this setting, many focusing on role (Bot "Role"; Zimányi "Somebody"), but it has also been approached from the perspective of communication (Zimányi "Conflict"), pragmalinguistics (Echauri Galván), and even the recipiency based on eye tracking (Vranjes et al.). While mental health interpreting is a newer area of research for the field compared to other settings, we are beginning to see more researchers pay attention to it.

Mental health interpreting has traditionally been categorized under the broader category of healthcare interpreting. This categorization is still common, but more people are beginning to recognize its distinctions and moving towards viewing interpreting in mental healthcare as its own setting. We begin to see steps towards this shift in a 2010 article on the rapport between interpreters and service providers in healthcare, where a review of the literature points towards differing expectations of the mental health interpreters' actions on the part of the service providers due to the nature of the care given (Iglesias Fernández 219). In 2015, the book *Introduction to Healthcare for*

Spanish-speaking Interpreters and Translators, which encompasses healthcare interpreting in a broader sense, details the unique features of interpreting in the mental health setting while still categorizing it under the healthcare setting (Crezee 159).

The Routledge Handbook of Interpreting, published in the same year, seems to represent a change this trend, dedicating separate chapters to interpreting in healthcare and mental healthcare in the Settings section. However, upon a more careful reading of the text, the respective authors still categorize these settings together while highlighting their differences. Interpreting in mental health care is introduced as a subcategory of healthcare interpreting (Bot "Interpreting" 254). Meanwhile, interpreting in mental health is discussed in the healthcare chapter, but the authors predict that there will be a need for professional medical interpreters to specialize in mental health interpreting. They explain why this is so: "healthcare includes a broad set of services, with extensive specialized vocabulary, goals and techniques. The purpose of a primary care doctor's interview and that of a mental health practitioner are often not the same" (Roat and Crezee 250). If this specialization of the profession develops, it is feasible that academic research will follow suit and continue to distinguish them from one another. In this paper, I will refer to interpreting in mental health as its own setting.

Interpreter training in this setting focuses primarily on the nature of the counseling sessions that will take place and how the client may respond (Crezee et al. *Introduction* 159). Although interpreters should familiarize themselves with some terminology in the field, most of the sessions will use simple language (159). This is in direct contrast to legal or broader medical settings, where interpreters will inevitably encounter a vast range of specialized vocabulary from those areas. Interpreters who work

in mental health are, however, encouraged to study the difference in therapeutic approaches, professional titles and job descriptions of mental health service providers, and to understand the most common mental health disorders, along with their respective symptoms, causes and treatment (162-168). This training for interpreters places less emphasis on what words will be used, and instead on how they will be used pragmatically in this setting. "In general, in order to interpret the words in an encounter well, one should have knowledge of the encounter's interactional purposes and the specific conversational techniques that will be used to meet this purpose" (Bot "Interpreting" 261).

These encounters can be divided in two very broad categories, with many variations within the categories themselves: protocolized treatments which tend to be more structured, and counseling therapies, which in comparison are less structured (262). In regard to the terminology used in these sessions, the protocolized treatments may employ specialized terminology with meanings contextualized to that system of therapy. In contrast, in the less structured counseling therapies, talk is more spontaneous, although there is an emphasis on "re-wording experiences" (262). One way in which accuracy is evaluated within mental health interpreting has to do with the interpreter's rendition of this specialized terminology. Interpreters may hinder the effectiveness of the therapy if terms are not being translated as the counselor intended them to be within those protocolized treatments. This can happen when interpreters do not understand the goal of the session and the intended use of these terms (262).

Another consideration of accuracy in mental health interpreting is how well the client's message is conveyed by the interpreter. In this setting, language is used as a tool

for diagnosis; additional tests cannot be ordered to confirm what the patient has said (Crezee et al. *Introduction* 159-60). Thus, words in all of their nuance carry a weight that is not uniform in every interpreting setting. The literature has mentioned how this can be particularly challenging when clients are dealing with psychotic patients with more severe diagnoses than perhaps a typical client seeking therapy for grief of to mitigate the stress of life. The talk of these psychotic patients has been described as disorganized and incoherent, using words and expressions that may not be frequently used by others or even make sense (Bot "Interpreting" 262). These present challenges for the interpreters, but their accuracy matters because "the mental health practitioner is interested to hear what the patient has to say and how he says it" (262).

Aside from the interpreter's personal preparation, practical recommendations have been made to help improve interpreter performance in this setting. It is highly recommended that interpreters request a pre-session or briefing and debriefing session with the mental health provider. The pre-session can serve to orient the interpreter to the service provider's goal for that appointment and any information about the case that is relevant. In the debriefing, the two parties, especially the interpreter, can reflect on relevant details about the client's speech that may not have come out in the session itself (Crezee et al. *Introduction* 160).

Despite all of the recommendations for professional interpreters working in this setting, little research has been done to explore these issues in depth. Although medical and judicial interpreting research has grown since the 1990s, empirical research "in interpreting in mental health is still very rare" (Bot "Interpreting" 255). This study seeks to encourage research in this direction by further highlighting this setting as one of

academic merit. Moreover, the emphasis on interpreting trauma narratives is a new angle that the literature regarding this setting validates.

We have seen how words are essential in the mental health setting, not just for communication, but for diagnosis and even treatment. The interpreter is even more valued in this context than many others because the mental health professionals would have no way of working with speakers of other languages without them. The literature has highlighted the value of language in this setting, but most of the challenges of the renditions have thus far only focused on psychotic patients. Interpreting Studies has not yet considered how trauma narratives from non-psychotic patients are distinct from regular language and can present challenges for interpreter accuracy. This study will seek to highlight this issue in particular while forwarding the research in this setting. Before doing so, we will look at the literature from psychology that discusses therapists working with interpreters.

4. Mental Health Perspective on Interpreters

In this final section of the literature review, I will present a brief overview of publications from psychology that refer to mental health professionals working with interpreters. The amount of publications on this topic from within this discipline stands in stark contrast to the paucity of scholarship from interpreting studies on working in mental health settings. Whereas the first publication on this topic I could find from Interpreting Studies was from 2001 (Wadensjö "Interpreting"), there are studies dating back to 1975 from the mental health perspective (Price). Most of the earlier studies dealt with problems and challenges in working with interpreters (Price; Raval; Cornes and Napier). This is not surprising considering that interpreting was an even younger, less established profession

at the time of those publications, and the interpreters may not have even been qualified or received prior training. They may have had no prior exposure to mental health training, which would pose even greater challenges for the counselors.

Some of these studies focus specifically on language and translation. In some cases, interpreter language competence was questioned by the author (Price). The oldest published study I found provides some interesting insights into the research questions presented in this paper. In this study, it was discovered that interpreters committed the most omission errors when interpreting for psychotic patients, since their language was more challenging for the interpreters to process (Price 266). There is little modern research on interpreting with these types of patients, and it is unlikely that there will be more given the ethical considerations of working with this population (Bot "Interpreting" 262). Other studies that focus more on language have examined the concerns mental health professionals have about establishing empathy through translated messages, since the way they word their communications with their patients is very intentional (Pugh and Vetere 316). One study even considered the use of interpreters in research, noting that using them to help conduct survey research in mental health may not produce accurate results because of the limitations of language transfer and difference in cultural concepts (Ingvarsdotter et al.).

Another focus of mental health professionals working with interpreters has been on the therapeutic alliance and the change from a dyadic, two-way communication to a triadic, or three-way, one (Boss-Prieto "Differences", "The Dyadic"). The therapist's connection to clients, through words but also through "the unconscious stimulation of feelings towards a person" is impacted with a third person in the room (Costa "When" 3).

While in Interpreting Studies pre-sessions are often mentioned to help the interpreter prepare to understand the language and use the appropriate terminology, mental health professionals talk about how this time can be beneficial to contribute to a working alliance between the interpreter and counselor that will help when the client is in the room (3). This alliance was of major concern in another study, and was found to be challenging but rewarding for those who participated in it (Fidan ii). Sometimes the mental health professionals find it difficult to grow in this therapeutic alliance because the patient is naturally more drawn to a trusting relationship with the interpreter, who speaks the same language. This tension is escalated when interpreters do not remain neutral towards the patient (Raval 34).

One study is particularly notable because it puts the responsibility of specialized mental health interpreter training on the mental health professionals instead of trainers from within Interpreting Studies. It highlights how using interpreters to administer tests and mediate during certain types of therapy has its limitations. Pre- and post-sessions are encouraged as a way to prepare the interpreter for the interpreting assignment. According to the authors, federal law and psychological codes of ethics place the responsibility to find and subsequently ensure the competence of interpreters on the mental health providers (Searight and Searight 444).

Coming from the perspective of the interpreter, it is surprising to read this, because so often interpreters are the ones asking these things of the service providers they work with in public services. However, if the counselors are the ones who must rely on interpreters to carry out the functions of their job in a multilingual context, they feel a greater pressure and responsibility to provide high quality services. I think this is part of

the reason why there is more work done on interpreting in mental health from the mental health providers' perspective. Interpreters often have the freedom to choose the settings they work in and could avoid mental health interpreting if they wanted. Psychologists who want to communicate with their patients through a language barrier inevitably have to use interpreters, a reality that has fueled significant research in the discipline.

Lastly, there are many practical resources available to mental health professionals on best practices and trainings for working with interpreters. One such resource covers topics such as their collaborative relationship, the triadic communication, and how to delineate responsibilities (Costa "Team"). The author is a strong advocate for providing supervision with interpreters and counselors together, so they can learn more about the other's role and increase their working relationship (66). Research from the mental health perspective on working with interpreters has grown in recent years, and it is likely that this trend will continue to cover more questions that arise from the interpreted therapeutic encounters. It is also likely that more trainings and models for collaboration will be developed. Before revealing what the counselor I interviewed said about working with interpreters, I will outline the methodology used in my study.

CHAPTER III
METHODOLOGY

Now that the basic concepts and theoretical framework have been introduced, the methodology will be described. As previously mentioned, this thesis is being written in the context of a broader study, Trauma-Informed Mental Health Interpreting Services (TIMIS). In this section, different aspects of the TIMIS project will be outlined, along with the methods used to collect and analyze the data most relevant to the research questions highlighted in this thesis.

1. TIMIS Project Creation and Development

Before explaining the emphasis on interpreted trauma narratives, I will describe the creation of the TIMIS project to provide a better understanding of the context and parties involved. The first stage of the project design happened in the Spring 2018 semester and involved discussions with university and community partners. Since the research is interdisciplinary in nature, it was designed with the input of different experts in their respective fields. Dr. Lluís Baixauli Olmos, Assistant Professor of Translation and Interpreting from the Department of Classical and Modern Languages at the University of Louisville collaborated with Dr. Katie Hopkins, then Assistant Clinical Professor and director of the Cardinal Success Program to design the project. Their respective expertise allowed them to consider the linguistic and clinical needs of the project. Involvement from a community partner, the Center for Women and Families, a

local organization that provides advocacy and support from trauma victims, was also involved in these initial conversations about the project design.

The study, although created with the intention of providing the direct benefit of counseling services to users through the mediation of an interpreter, also intended to answer specific research questions. These questions were centered around interpreter interventions, trauma-informed care shaping protocols, communicative adjustments from interpreters and counselors working together, and interpreter visibility, all within the mental health setting. These questions continued to be the driving emphases of the research, but as I became involved in the project, other questions of a more linguistic nature arose. Other factors, such as feasibility, personnel changes, and securing research approval from the university's Institutional Review Board (IRB), caused the project to change its shape over time.

Although I was not involved in the initial phases of the project design, I was made aware of the project through a class I was taking in Spring 2018, Interpreting in Educational and Social Service Settings. In Fall 2018, I did an Independent Study with Dr. Baixauli-Olmos entitled Introduction to Interpreting Studies. Since this class emphasized research methods in the discipline, I was able to learn which ones were applied to the TIMIS project while observing and assisting with some stages of the project development. In Spring 2019, I was officially hired as an interpreter and research assistant for the project, which will be discussed in further detail below. As I developed my thesis proposal, it became clear that this project would align well with my research interests if the research questions could be expanded to include trauma narratives. This adjustment was made and I also requested and secured permission to be considered a co-

investigator on the study. Currently, along with conducting the research and analyzing the data most applicable to this thesis, I am involved in nearly all aspects of managing the TIMIS project.

2. Funding

The second step of the project development centered around securing funding for the research. A grant proposal was written and submitted to the University of Louisville's Cooperative Consortium for Transdisciplinary Social Justice Research in Fall 2017. The Consortium "exists to incubate, support, and promote faculty-led, community-driven research teams across many disciplines" and "funds projects dedicated to understanding and finding new, innovative solutions to complex, intransigent social justice problems with a special emphasis on structural inequalities" ("Cooperative"). Since this project aligned with the Consortium's goals, specifically in addressing the structural inequality of linguistic barriers in access to mental health, funding was awarded. These funds provided for a research team for the 2018-2019 academic year: two interpreters concurrently working as graduate-level research assistants and one undergraduate research assistant. A small amount was also set aside as honoraria for community partners. No additional funding was needed to conduct the research presented in this thesis.

3. Project Development and Feasibility

The interpreting sessions were initially expected to start in Fall 2018, but several complications caused a delay. Our initial partner, Katie Hopkins, the supervisor of the counselors in training, left the university and was replaced by Dr. Patrick Pössel. He was still interested in continuing the partnership and invited us to an interest meeting at the Shawnee Academy, where one of the counseling offices belonging to the Cardinal

Success Program is located, in September 2018. Unfortunately, two factors prevented the counseling sessions from beginning right away: (1) the counselors were just beginning their practicums and did not yet feel comfortable adding a third party to the meetings and (2) there were no Spanish-speaking clients immediately in need of counseling services. We continued to work to develop other aspects of the project while looking for solutions to those two problems.

By Spring 2019, there were counselors willing to work with the interpreters on the project, but there have still been many challenges in recruiting service users for the study. The Cardinal Success Program has limited office hours so coordinating multiple schedules is a challenge. Additionally, there is a stigma towards mental health in many of the Spanish-speaking populations we are trying to serve, which can prevent them from seeking out the services. Another barrier is that many undocumented immigrants are afraid of what information could be shared with the governing authorities. Also, because of the vulnerable and personal nature of what is shared in counseling sessions, potential clients may be hesitant to allow us to access that content for a research study.

Some referrals of potential Spanish-speaking clients have been made to the Cardinal Success Program, but at the time of writing no service users have consented to participate in our study. Another obstacle was that some of the referrals were minors, so adjustments had to be made to secure ethical permissions to work with them, which will be discussed in the following section. In the midst of these obstacles, it was clear by the midpoint of the semester that my initial plan to use discourse analysis on interpreted trauma narratives for this thesis was not going to be feasible given the time limitations. I chose instead to interview interpreters and counselors who had worked in mental health

to gather information about their experiences and perceptions of trauma narratives. Information about the subjects and interview method will be described later, but I will first comment on the way ethical research approval was obtained.

4. Ethical Research

This research works with human subjects and therefore permission must be secured from the University of Louisville's Institutional Review Board (IRB) to be able to conduct the study. A protocol which outlined the goals and steps of the study was written and submitted. The study was granted approval by the IRB office on December 13, 2018. However, once potential clients were identified, modifications had to be made in the IRB application to include minors in the study. Final approval including these modifications was received on March 1, 2019.

The study was considered for Expedited Review by the IRB since there is a minimal risk to the human subjects participating in the study. Most of the risks to the clients have to do with the nature of the therapeutic process itself, which requires them to speak about difficult experiences, and are not a result of the interpretations. However, one additional risk of including an interpreter in this process is that the interpreter could unintentionally say something that provokes re-traumatization of the client. To try to prevent this, there is an interpreter training built into the study design. No foreseeable risks are identified for the counselors. The interpreters are potentially exposing themselves to vicarious traumatization and burnout, but measures have been set up to help prevent or mitigate these possible consequences of the work. These risks are outlined in the consent forms that each of the subjects must sign. Minors who may

participate in the study in the future will sign an assent form in the presence of their parent(s) or legal guardian(s), who will also sign a consent form.

5. Personnel and Subjects in the TIMIS Study

There are five members of the TIMIS research team. Dr. Lluís Baixauli-Olmos is the Principal Investigator, and Dr. Patrick Pössel and Miranda Hale (myself) are co-investigators. There is a graduate level research assistant who helps with data collection and a bilingual undergraduate research assistant who helps transcribe and de-identify the data. All members of the research team have received training in ethical research practice with human subjects. The research assistants have bi-weekly meetings with the Principal Investigator to discuss their role in data collection and the general progression of the project.

The interpreters and counselors are also considered subjects in the TIMIS study. The interpreters were chosen by a committee formed to hire two graduate-level interpreters who would also serve as research assistants. The qualifications for these positions included having taken previous graduate-level courses in interpreting and being familiar with trauma-informed interpreting principles. Both have had previous experience volunteering as interpreters in the community in mental health and other settings.

At the time of writing, for the TIMIS project, two counselors have enrolled in the study to provide counseling sessions mediated through the project's interpreters. The counselors who expressed interest in working with the project came from a pool of graduate-level clinical psychology students conducting their practicum through the Cardinal Success Program at the NIA Center. They were recommended by their supervisor and chosen based on their interest in working with an interpreter and

availability. They are both new in their counseling practice and have not worked with interpreters previously.

Training both interpreters and counselors in trauma-informed interpreter mediated counseling is an essential component of the project due to the sensitive nature of the sessions taking place. The interpreters had received previous exposure to trauma-informed interpreting in their graduate level courses, including an introduction to the basics of trauma and how it can manifest itself in an interpreting session. They had practiced with roleplay materials specifically designed for interpreters working with people who had experienced trauma. However, additional training is also provided as part of the study, and weekly meetings with the research staff allowed the interpreting techniques to be continually discussed. Since interpreters typically do not have as much training in traumatization prevention techniques, supervision is provided by Dr. Pössel to allow them to discuss how the difficult nature of the sessions is affecting them while still maintaining confidentiality.

Given that the counselors had not worked previously with interpreters, it was necessarily to orient them to interpreting practices and protocol. This was accomplished through an initial training session with the counselors and interpreters present led by Dr. Baixauli-Olmos, in a discussion-based format. They were introduced to the role of the interpreter in communication and the standard interpreter protocol, and were given space to mention any questions or concerns they might have in terms of working with the interpreters. They were also invited to help shape any trauma-informed protocol for the interpreter based on their expertise in the area of trauma-informed care and counseling. After this meeting, communication was encouraged to remain open throughout the

duration of the study. Counselors and interpreters could also discuss areas of misunderstanding or problems that arose in the counseling sessions during the pre-sessions and debriefing which took place before and after the counseling sessions, respectively.

The inclusion criteria for the clients are as follows: Spanish-speakers who have suffered some sort of trauma. In the original stages of the project, the inclusion criteria were limited to adult women who had experienced domestic violence, but this was found to be too narrow. The new criteria only excludes those who have not experienced trauma, based on the definition given in Chapter 1. Originally, we only expected to work with adults, but because of a need in the community, this has been expanded to include minors age seven and up. These clients are referred to the Cardinal Success Program through their normal referral channels, through social workers or organizations in the community familiar with their work. The Center for Women and Families also has the option of referring clients to the study, but they have not yet done so.

6. Sampling Methods

Since I was unable to rely on recordings from the counseling sessions to answer my research questions in the allotted timeframe, I decided to modify my original strategy. I had to use indirect observation, a qualitative interview method in this case, to collect data. In order to choose relevant subjects, I used purposeful sampling, a process in which participants are chosen based on predetermined criteria. As an inclusion criterion, I chose people who had been working in mental health settings for at least one year. The underlying assumption was that people who met these criteria would have had multiple exposures to trauma narratives. It was not required that the interpreters have a certain

level of qualification since there is not a standardized certification process for mental health interpreting in the United States, but I was made aware of their training and experience beforehand and this information was later confirmed in the interviews.

I will now detail how the subjects were recruited to participate in the interviews for this thesis. Since the other interpreter working for the TIMIS project had volunteered in mental health settings for around a year, she fit the inclusion criteria and agreed to be interviewed. The biggest constraints to securing more subjects were accessibility and time. Thus, I had to think through which of my acquaintances could fit into this category. I was referred to another interpreter who has been practicing professionally in mental health settings in another state, and she consented to be interviewed. As part of my work identifying potential partners in the community for the TIMIS project, I had been in contact with a counselor who regularly conducted her therapy sessions using interpreters. She also agreed to be interviewed. Having her perspective along with the interpreters' perspectives was an advantage in terms of having a triangulation of sources, and these subjects provided helpful information in addressing the research questions. Although the TIMIS project had more than three subjects, in this thesis I will primarily refer to these three who were interviewed, the two interpreters and the counselor.

No other subjects were interviewed due to the constraints previously mentioned. Since the research question is exploratory in nature, and since I am studying a phenomenon that interpreters and counselors may not even be aware of, I hoped to bolster my findings by also using expert sampling. I requested an interview with a sociolinguist who has done substantial work on trauma narratives in the past and also has experience working with interpreters. We were unable to set up a time for this interview,

so the data is limited to the perspective of two interpreters and a counselor. Now that the subjects have been introduced, I will explain the process of data collection in detail.

7. Data Collection

The process of data collection for this thesis varied slightly for each individual interview. The Principal Investigator had already scheduled an interview with me and the other interpreter hired by the TIMIS project. This was intended to shed light on our prior experiences and perceptions about interpreting in mental health settings, before we began interpreting for the project. Instead of conducting two separate interviews, one addressing general TIMIS research questions and another about trauma narratives, we consolidated the questions into one interview. I helped design some of the interview questions, but the Principal Investigator edited them and conducted this first interview. I participated both as a subject in this interview and an observer. I had never conducted a semi-structured interview before, and this gave me the opportunity to experience one before using this interview method myself to collect more data.

I conducted the second and third interviews myself. The second interview was with the counselor. I was able to use the general format of the first interview, but adapted the questions so they were more appropriate for her role as a mental health professional. I also focused more on the questions most relevant to trauma narratives and did not emphasize the broader questions from the TIMIS study, although the content shared occasionally overlapped. I followed the same pattern with the second interpreter, adapting the questions further because I entered the interview with the knowledge that she had more experience working with children. The semi-structured nature of these interviews made these adaptations easy and also allowed for more flexibility as different

topics arose during our conversations. These interviews were recorded with their permission and then transcribed using automatic transcription software so they could be used for data analysis.

8. Data Analysis

The transcripts from the three interviews were analyzed using thematic analysis, which allowed for the creation of a network of conceptual relations. I first reviewed the data set extensively, which allowed me to better understand the content of the interviews. This was followed by an initial coding stage where I selected relevant utterances and labeled them using concepts from the literature review and of my own creation. In the second coding stage, I edited these initial labels and connected similar ideas to create codes of broader concept categories. In the last stage of coding, I consolidated the previously grouped information, leaving a reduced and more manageable number of codes. Throughout this process, I tried to ensure consistency and logical connections between the overlying themes. Although these steps were followed, the process was not always linear, as some themes were easier to connect in earlier steps.

9. Methodological Strengths and Limitations

The study's qualitative nature lends itself to certain strengths and limitations. The semi-structured interviews that were conducted allowed the participants to go into detail about the questions asked and any other information they found relevant. Instead of answering yes or no to close-ended questions about trauma narratives, they were able to provide details and examples about their observations and perceptions. The interviews were designed with the research questions in mind, but I tried to leave room for the participants to share new insights by first asking open-ended questions about trauma

narratives and then prompting for more specific details. Practically, this looked like asking the subjects if they noticed anything different about people's language when they share trauma narratives, and then giving specific examples if they could not initially respond with specific details.

Another limitation of this study is the small sample size; only three people were interviewed in total. Given the small number of participants, the data collected cannot be used to make generalizations about trauma narratives or interpreting in mental health. However, it can help confirm if what has been discussed in the literature has also been observed by people practicing in these professions. Although the sample was small, the study includes multiple perspectives, that of two interpreters and one counselor. Due to the limited time frame, a purposeful sample was used. However, all of the participants had worked extensively in the mental health setting, so they had a range of experiences to comment from.

10. Methodological Principles

There are a few underlying principles driving this research, both through the TIMIS project and this thesis. One of these principles is social justice. Beyond obtaining data solely for the sake of scientific knowledge, the project is intentionally designed to address structural inequalities, specifically in helping overcome the language barrier that prevents Spanish-speakers from accessing mental health services. While the interpreting will address this need for a short period of time, the duration of the funding, we are also helping make structural changes that will facilitate language access in the future. This is accomplished in part through the training that the organization and individual counselors are receiving in how to work with interpreters. It was also provided through the

translation of documents used in counseling, not directly related to the data collection needs of our study.

Complementing the focus on social justice, this project has also been influenced by the spirit behind an action research approach. Instead of approaching the questions in a linear way, starting with a problem and aiming for a direct solution, we are aware that new questions may arise throughout the duration of the study. This is especially true with trauma-informed protocols, as we seek to work with counselors and clients to determine which protocols are most effective. We may try new solutions and find that they work in some cases, but not in others. This thesis has a narrow focus of looking at trauma narratives, and it is currently in an early stage of learning about them. The overarching goal is to understand them with more clarity so that interpreters can be trained to interpret them more appropriately, ultimately giving counselors less hindered access to their clients' voices. However, it is possible that as we learn more about trauma narratives and shed light on alternative ways to interpret them, further questions will arise. This approach gives us the flexibility to work with interpreters and counselors to address these issues as they appear and adapt our solutions to meet the needs at hand. In the following section, the contents from the interviews will be analyzed to give us a better understanding of these issues.

CHAPTER IV

RESULTS

1. Background Information

Before delving into an analysis of the data, I will briefly provide some context about the informants, which will inform an understanding of the experiences and examples they gave. As previously mentioned, all three informants had worked in a mental health setting for at least one year. At the time of the interview, Interpreter 1 had volunteered weekly as an interpreter at a community health clinic for a little over a year. The clinic offered mental health services one to two times a month, and she estimated that she had interpreted in over 50 individual therapy sessions. She typically used the simultaneous interpreting mode, whereas the other informants used or worked with other interpreters who used the consecutive mode. Interpreter 2 had been working as a professional freelance interpreter for a child advocacy center since 2013. Although she sometimes worked with law enforcement and other professionals, she also had extensive experience working with therapists there. The counselor had been practicing since 1974 and first worked with professional interpreters in 2010 at an inpatient unit of a hospital. In her current position, she provides mental health services weekly at a center that also offers other medical services. She regularly works with volunteer Spanish-speaking interpreters.

The informants were asked a series of questions about their experience either interpreting or working with interpreters and what kind of content they had heard in the

sessions. All of them had exposure hearing about trauma in mental health, the types of trauma ranging from physical and sexual abuse, violence and death, to challenging life circumstances that deeply affected the clients. After conducting a thematic analysis of the interviews, the data has been divided into four categories. I will present the findings in terms of what the informants said about the mental health setting, the importance of trauma awareness, the work environment, and the language of trauma narratives.

2. Mental Health Setting

One of the common themes in all the interviews was how the mental health setting is unique in comparison to others. Oftentimes these comparisons were made in direct contrast to interpreting in medical settings, because that was the other setting the informants were most familiar with. In some cases, these observations were elicited from direct questions asking them about the setting, but many of them were shared with no prompting from the interviewer. Reflections were made about the purpose of the therapeutic sessions, the types of activities done in the sessions, and the unique linguistic nature of the setting.

All the informants made observations about the purpose of the counseling sessions and how their roles contributed to that purpose. Interpreter 1 highlighted recovery as the objective and specified that her role in that process was helping the clients "get one step closer to recovery." Both interpreters mentioned being the voice of the victims. Interpreter 2 also spoke multiple times about "helping people" and specified that she did so by connecting the clients with the mental health professionals who were qualified to assist them. While the interpreters emphasized the communicative aspects of the sessions, along with general references to help and recovery, the counselor went a

step beyond those elements. As the mental health professional, it was of more value to her to be able to "do something useful" with the information that was shared as opposed to simply providing a safe place for the client to talk. Some examples she gave were checking to see if a person was suicidal, conducting other psychological evaluations, and determining the need for further care or hospitalization. Everyone described their role in relation to the overall good of the client seeking these services. While the reflections about helping the client and promoting recovery are abstract, all of the informants reported specific activities conducted in the counseling sessions to help promote this end.

Besides the typical talk that is a fundamental part of therapy, counselors also lead their clients in other types of activities. Interpreter 1 and the counselor both referenced deep breathing exercises used to relax the clients. Interpreter 1 commented that she didn't quite know what to do as the interpreter in those situations, but she interpreted the instructions and also participated in the breathing exercises herself. The counselor said that during this activity, since it is intended to be relaxing, it can be counterproductive to have two voices giving instructions, especially when the client does not understand one of the languages. Her solution was to have the interpreter pre-record the instructions in Spanish. That way, clients would listen only in a language they understood, and they even had access to it at home, so it was a tool they could take with them beyond the session. In contrast, Interpreter 2 did not mention any activities intended for relaxation, but she did mention some techniques used with children to help explain concepts using images. The example she gave was when the therapist would draw a male or female body and ask the child where the private parts were. This was used as an instructive tool for the

children but would also serve to help them open up about their experience, a technique which will be explored in the following paragraph.

Two of the informants referenced intentional pragmatic moves unique to mental health settings that the counselors would make to instill trust in the clients, one being proactive and the other preventative. Interpreter 2 stated that the therapists would often begin talking to the adolescent clients about something simple such as their day at school, to help make them feel more comfortable, before encouraging them to speak about the trauma they had experienced. The counselor said that she was very cautious to ask clients about their physical symptoms before diving into the psychological symptoms they were experiencing. Interpreter 1 did not go into much detail about the specific contents of the conversation between the counselor and her clients. All of them did, however, go into great detail about the terminology needed for the sessions.

There seemed to be a discrepancy in the informants' opinions of the level of difficulty of the terminology used in the mental health setting. Interpreter 1 said it was easy on a semantic level. In contrast to medical settings, she did not have to study to acquire specialized terminology for the sessions. Most of the content was about what people were going through, "what was affecting them and their lives." She reported that she found herself intervening less working with counselors as opposed to doctors, because the terminology was less complex. However, later, she shared that the emotional and violent nature of the words often affected her. Having to interpret things such as "he pushed me" and "he shoved me", although easy on a semantic level, affected her personally, even to the point of causing her to lose sleep. She interpreted these statements in first person, which is typical interpreting protocol, but wishes she would have done so

in third person to protect herself from some of the emotional weight of the words themselves.

Interpreter 2 similarly categorized the terminology in mental health as easy, but later mentioned other linguistic challenges. When asked what the easiest part of interpreting in mental health was, she reported that it was the terminology because it's "more or less the same" in each session. She qualified that statement by pointing out that conversations are always unpredictable. Later in the interview, she gave examples of some of the challenges of interpreting the terminology common to this setting. These challenges can be categorized into two groups. The first has to do with the sexual nature of the words and their impact on the hearer. In the context of sexual abuse, often with children, she has to interpret words like 'penetration,' 'semen,' and names for sexual organs. Although at the beginning of the interview she expressed that the terminology used in mental health was easy, she seemed to have struggled with these words earlier in her practice. She said, "After all these years I've become much more comfortable with the terminology they use," indicating some prior discomfort. Part of this discomfort seemed to be because the children often struggle to talk about these concepts. She used phrases like "uncomfortable," "awkward," and "tension in the atmosphere" to describe the interpersonal dynamics during these parts of the conversation.

The second group of words she found difficult to interpret were ones that she was unfamiliar with because they are used in different varieties of Spanish. Interpreter 2 states that parents, especially when talking about sexual abuse of their children, will use euphemisms instead of common names for concepts. For example, instead of using the biological names for genitalia, they will often use colloquialisms that are not mutually

intelligible between different varieties of Spanish. If these words are completely unknown to her, she has to stop and ask the client what they mean. She recounted a time when she distorted the meaning of what someone had said because she thought one of these colloquialisms was referring to a different body part than what the speaker intended. This was not an isolated experience; it has happened many times and caused confusion during the sessions.

While the interpreters viewed the terminology as easy in the sense that it was less technical than in other settings, the counselor interviewed said the opposite. In her opinion, the interpreters who work with mental health professionals in direct contrast to those working with primary care physicians need a higher level of "fluency" in both languages "because you hear more words and more nuance." She mentioned that words such as 'depression,' 'mood,' and other similar language were words the interpreters "might not have heard in other places." She illustrated a time when not understanding this nuance let to confusion.

At the medical practice where the counselor also works, the doctors were referring patients to receive her mental health services because these patients were determined to be at risk for suicide. However, when they came to see her, she realized they were only experiencing physical exhaustion as a side effect of a new medication. It turns out that the interpreters' rendition of the Spanish word 'desesperación' was being interpreted as a feeling of hopelessness, one possible translation of the word, when they were really just talking about a change in their mood. Reflecting on this situation, she said that words can have different meanings in psychiatry than in other contexts, and these are important both in referrals for services and diagnoses.

The interpreters seemed to agree that the pace of the conversations in the mental health setting tends to be slower, and they viewed this positively. Interpreter 1 felt that in medical settings, physicians "just want to hurry up and see the next patient," but the counselors are not in a rush. Interpreter 2 made the same observation, comparing doctors' treatment of their patients to mechanics repairing cars, as though they were machines. But in mental health, she thinks treatment is more profound and personalized.

Throughout the interview, the counselor mentioned wanting to listen to and understand her clients, and did not talk about them in any way that could fit into Interpreter 2's machine analogy that referred to physicians, in spite of her busy schedule. However, she did perceive the pace of the conversations to be fast at times. Sometimes her clients will start talking and not want to stop; the words just tumble out of them. She has a hypothesis that the three-way communication between the client, interpreter and herself can actually benefit clients because it forces them to slow down the pace. This could make the act of opening up "less frightening," but the counselor is still formulating her opinion about this. She attributed the fast pace of the mental health setting to the clients speaking quickly; she did not give any indication of trying to rush them so she could move on to her next client.

3. Work Environment

Above we saw how the informants described the mental health setting in general, and now we will see how they described their work environments. Beyond the distinctive features of interpreting in mental health settings, another common theme mentioned in all the interviews was the work environment more specific to their experiences. This can be broken into two categories. The first category will center around the stress factors which

make the interpreting task more difficult. The second will explore the interpersonal relationship between the counselors and interpreters.

The emotional content in these sessions made interpreting difficult, as previously mentioned, but there were other factors which also contributed to the challenge of performing the task at hand. When initially describing what made interpreting in this setting so difficult, Interpreter 1 mentioned that she barely had any time for a break. This seemed to be one of the most recurring and prominent challenges for her, as she alluded to it four times throughout the duration of the interview. The counselor did not mention this in terms of challenges for the interpreter, but did say that her schedule is also very booked, with clients coming in every half-hour. She sometimes tries to fit other clients in between her previously scheduled sessions. Interpreter 2 did not give any indications of having to interpret for back-to-back sessions but did comment on the length of some of them. If there were multiple family members involved in a case, each of them would have to be interviewed separately. This often caused the sessions to go on for a very long time.

The interpreters also commented on what the space was like and how the facilities presented unique challenges for them. Interpreter 1 worked in a very small clinic and would often have to stand behind the client while interpreting. Although she perceived this had a positive outcome of preventing the clients from directing their gaze at her, it was not the most comfortable working environment. Interpreter 2 also worked in a small space, and this meant she often found herself in the same waiting room as the clients, a problem she hasn't encountered in other settings. Interpreters are trained to avoid these interactions with the clients when the service provider is not present, and this has led to an ethical dilemma for her as clients often talk to her in the waiting room. While she was

facing ethical problems from the space, Interpreter 1 has felt unsafe at her facility. Her most shocking experience was when a woman's abuser made his way to the back of the clinic and knocked on the door where the counseling session was taking place, demanding that the client leave the room. The counselor did not make mention of any limitations regarding the space.

The other common theme throughout the interviews was the work dynamic between the interpreter and the counselor. This often centered around establishing trust between the two professionals. From the interviews, it did not seem as though the interpreters entered the sessions already lacking trust in the counselors or questioning their professional judgment. There seemed to be much more hesitancy from the counselor regarding interpreters, and that trust had to be established. When asked if she had ever had a negative experience with an interpreter, she told of a time when the client spoke for a long time and the interpreter rendered the message in one word. Because of this negative experience and some others she shared, when she works with a new interpreter, she questions their linguistic abilities. Her organization interviews the interpreters that work with her to try to measure this beforehand, but they rely on volunteers and are limited in their options. The ideal for her is when she gets to work with the same interpreter consistently and can build that professional trust over time.

An occasion for gauging the presence of this trust is when conflicts or misunderstandings arise between the interpreter and counselor. When these situations are handled well, potential points of tension can resolve in a sense of trust. When Interpreter 2 had her first session working with children, she was following the standard interpreter protocol of repeating everything that was said in first person. The counselor perceived

that this was not working well, so stopped the session, pulled her aside, and asked the interpreter to be more engaged with the child. This could have caused a great deal of tension, but because the counselor handled it professionally, they were able to continue working together. One of the reasons that Interpreter 2 continues interpreting in mental health despite the challenges is because she feels respected. She reported that the therapists understand her job, consistently thank her for her work, and make her feel important.

Interpreter 1 shared a similar experience of being questioned by the counselor for following standard interpreter protocol. The first time she worked with this counselor, she brought a notepad to help write down terms and interpret accurately. The counselor was suspicious of this and concerned for the client's confidentiality but waited until after the session was over to address it with Interpreter 1. The counselor asked to see her notes and reminded her that confidentiality is important. However, she seemed reassured once she saw that there was no personal information written about the client in the interpreter's notes. This trust seems to have developed over time because the interpreter now values the chance to talk to the counselor after the sessions and discuss how she is being affected by the traumatic content. This exposure to traumatic content will be discussed in the next section.

4. Trauma Awareness

Everyone expressed a desire for interpreters to be better prepared for the traumatic content they are exposed to in the counseling sessions. Despite Interpreter 2's academic training in interpreting, she commented: "I wish there was more training, more workshops." She has found it extremely challenging to be exposed to the traumatic

narratives, especially when the victims are children. She shared that after each session, she replays these conversations in her head for the following 24 hours, and wonders what it would be like for her or her child in the same situation. Even with her many years working in this field, this has not gotten easier over time. She wishes there were more resources to help prepare interpreters for the type of work she does.

Interpreter 1 was caught even more off guard by the traumatic narratives she was exposed to. She showed up at the clinic one day expecting to interpret for medical appointments and was asked instead to work with the counselor. She had no clue what to expect and had never been exposed to anything like it before, so much so that it affected her sleep for the first month. She strongly recommends that interpreters who are considering working in this setting do a lot of research beforehand, know their limitations, and take advantage of the resources available to them, especially the mental health professionals they are working with.

The counselor also commented on how unprepared some of her interpreters were for the contents of the sessions. When asked for an example of when an interpreting session went poorly, she recounted a time when she worked with a new interpreter. "The interpreting went fine" but the interpreter was visibly impacted by the violent content shared in the session. The problem was that the interpreter was not prepared for the type of information that would be discussed in a counseling session. While the counselor does feel a professional duty to help interpreters discuss their emotional responses to these sessions, she thinks interpreters working in mental health need to have a certain level of maturity before taking on these assignments.

When listing the most important qualities a mental health interpreter should have, she rated maturity right after a high level of "fluency." In her words, this person should be responsible, "a little bit older and have some life experience." This life experience will help the interpreters cope with the traumatic stories they are hearing in the sessions. In the past, she's been assigned interpreters who are there to fulfill a requirement for an undergraduate program, and she does not believe that those students, if they do not have a certain level of maturity, should expose themselves to what her clients are sharing. This comment corresponds with her third requirement for interpreters: that they have some sort of interest in the psychiatric field. Interpreters who meet these qualifications will be prepared to respond appropriately, both professionally and emotionally, to mental health interpreting.

Even though all the informants mentioned the importance of interpreters being aware of trauma prior to working in mental health settings for their own sakes, only the counselor mentioned how the lack of this awareness could also negatively impact the client. "Why would you want to re-traumatize people?" she asks. Interpreters who are unaware of trauma and its impacts could act in such a way that it causes re-traumatization of the clients. This is not unique to mental health settings; she believes all interpreters should be trauma-informed. This is because, regardless of the setting, interpreters are going to find themselves in contact with trauma survivors. In many cases, the interpreters will be unaware of the trauma the service users have experienced because "so many people who've experienced trauma don't talk about it." In summary, understanding trauma is important both for the emotional and psychological protection of the interpreter

and the client. Lastly, I will look at how this trauma manifests itself when trauma narratives are shared.

5. Language of Trauma Narratives

After describing their general experience interpreting in mental health, the informants were asked specifically if they noticed anything different about the language people use when sharing trauma narratives. They were all able to point out different aspects of speech that come out during these narratives, some in more detail than others. These included pace, tone, and emotion. The counselor made a general observation that, when sharing these narratives, "sometimes the way people sound just sounds different… it's sort of like they're caught up in something." Interpreters had different solutions for trying to understand and interpret these narratives, and the counselor also gave recommendations.

When asked if she perceived differences in the language of trauma narratives, Interpreter 1 had to think about it before answering. One of the first things that came to her mind was the pace of speech. She stated that when sharing trauma narratives, clients would often speak with a slower pace. Interpreter 2 stated that she had not observed a pattern in regard to pace; it differed for each individual. The counselor commented that she has seen both extremes of the spectrum: sometimes people speak slower, but other times it is as though someone has stuck a pin in them. In the latter instance, they also tend to speak faster and louder.

The counselor was the only one of the informants who mentioned a louder tone of voice, but all of them said a lower tone was common, often to such an extreme that the client was mumbling. Interpreter 1 gave an example of someone simultaneously speaking

low, mumbling, and crying. Although Interpreter 2 was unable to recognize a pattern for the pace, she said that the clients "absolutely" mumbled and spoke in a lower tone of voice when sharing their trauma narratives. The counselor resonated with this experience. Oftentimes in English, she struggles to hear what her clients are saying. Sometimes she is only able to pick up on certain words. In Spanish, this is even more challenging with the presence of an interpreter.

A third element pointed out in the trauma narrative language was emotion, present both in the words themselves and in the act of crying. The counselor mentioned that there can be a lot of affect in the narratives, which is important for her to pick up on. Interpreter 1 said that crying was a common occurrence, although not so for every client. Interpreter 2 also mentioned frequent crying on the part of the clients. However, this was often from the parents as they talked about the details of their child's abuse, and not necessarily from the trauma victims themselves.

Aside from the pace, tone, and the emotional nature of these narratives, Interpreter 2 also highlighted the fact that that the sheer amount of detail can cause these stories to be confusing. This was mentioned in the context of the parents of the abused children. When they are going through all the details of what happened, they tend to use a lot of pronouns ("she said this" and then "she did that," etc.) and it can be difficult to follow. She noted that the details of what happened get more confusing when they get into "more touchy issues." She wasn't sure if this was out of nervousness, a reluctance to talk about what happened, or simply a cultural difference in narrating stories. None of the other informants made a similar observation.

Various suggestions were given about how interpreters handled this language or how they should do so. In the example of the crying, mumbling woman, Interpreter 1 said there was a segment that she did not understand, and she told the counselor "the interpreter doesn't know what she said." Interpreter 2, when faced with mumbling, said "I just say what I hear because I'm not understanding anything," although it is unclear if this means she also explained to the counselor that she could not understand or if she only interpreted the segments she did understand clearly. Looking at the client when they were mumbling or speaking in a lowered voice was a technique she used in those moments to improve her understanding. This, in her opinion, was not ideal, and often caused the clients to direct their speech towards her instead of the therapist.

In the case of confusing speech, when the narratives were about many people and the pronouns were occasionally ambiguous, Interpreter 2 tried to produce a rendition that sounded just as confusing as in the source language. In these cases, the therapist was often confused by this and looked at the interpreter for clarification. During a break or after the session, the interpreter would remind the therapist that she was only interpreting what she heard. In her opinion, "it's the therapist's job" to clarify any misunderstandings and ask for further explanation. This is how she handles interpreting language that is challenging in the sense that the narrative flow is hard to follow. However, when the language is challenging on a semantic level, and the clients use terminology or euphemisms that she does not understand, she does see it as her responsibility to ask for clarification before continuing with her interpretation.

The counselor expressed a similar sentiment about wanting to maintain control over communication in the session. Hypothetically, if the interpreter could not understand

something that was said, the counselor would want to take the lead in clearing up any confusion. “It sort of needs to be my session, it needs to be my responsibility to sort out what’s going on.” As the mental health professional, it can be difficult to have an interpreter present because “they’re the person who’s having the reaction, they’re the person who’s listening.” She explains the reason why this can be so difficult: “it makes me feel like I’m not sort of involved in a way that might be important for me to be involved in.” She views it as essential that interpreters repeat everything they hear and do not pick and choose what might be important for her to hear.

The counselor was asked what the ideal response would be if a client opens up for the first time and shares a traumatic narrative, but the interpreter cannot understand it, or it goes on too long for the interpreter to interpret it accurately. She first said that she would tell the client to pause or ask the interpreter to do so, to determine what was just said. She was asked whether this interruption could negatively affect the client or cause them to close up, and in her response, she reflected on her role. She as the counselor needs to know the actual words that are being said so that she can determine the appropriate next step in their treatment: “…if there is a lot of affect and I don’t understand what’s going on then I’m worried about, you know, if this is somebody who might need hospitalization or some sort of emergency room evaluation or who might need medications…” If the most important part is simply giving the client the opportunity to talk, “you could say, ‘Well, let’s not have an interpreter and just let the person talk if the talking is what’s important.’” From the mental health professional’s point of view, talking in and of itself it not the ultimate end, but rather using those words to determine the next action steps to provide the help they need.

Although everyone gave examples of how speech was changed during trauma narratives, the interpreters had to think about the question for longer and were more hesitant to make general observations. Interpreter 1 gave very short descriptions and, when asked if she had ever encountered incoherent speech, responded that she did not know. Interpreter 2, although she did give many examples after thinking through the question, hesitated to make generalizations. After listing some characteristics of the trauma narratives she had heard and elaborating on examples, she explained why it was hard for her to answer:

> …I cannot remember, you know since sometimes it gets very intense, and sometimes where they're talking for hours, like I tend to forget the whole session. You know like there is so much concentration involved that right after the session I just get the main 'what was this about' and 'what happened' but I don't really know all the specifics, they're gone. I don't know why, they just disappeared from your mind because I was so concentrated saying the right thing and seeing what's going on.

This reflection by the interpreter about the language used in these sessions is useful in approaching the research questions presented at the beginning of the study. In summary, the interviews provided a wealth of interesting information about different aspects of interpreting in mental health and trauma narratives. In the following chapter, I will draw some conclusions from the data and highlight where it shows the need for further research.

CHAPTER V

DISCUSSION

The principal motive for conducting this study was to learn more about the trauma narratives that are shared in a mental health setting and discover how interpreters process and subsequently interpret them. The interviews have shed light on a counselor's and interpreters' perspectives on the characteristics of the mental health interpreting setting, the work environment, the importance of trauma awareness, and the language of the trauma narratives themselves. Although much of this information was not a direct answer to the research questions presented in the introduction, this new body of knowledges gives us a clearer framework for looking at the topic of interpreted trauma narratives. This is because, although we want to consider the final translations of the narratives, they are happening in an interaction with real people in a specific context. Approaching the question from the perspective of a dialogical model, "which treats interpreting as interaction between participants in a social event" (Wadensjö *Interpreting* 275), gives a more complete view of the question at hand.

Before moving into an extended discussion of the data, I want to point out one of the most unexpected results of the study: the counselor's willingness to interrupt a client during a traumatic narrative. To her, hearing the details are vital in determining her next steps. This was surprising to me because I have spent the past year pondering what it looks like to implement trauma-informed interpreting protocol in therapy, and assumed that it could be counterproductive to interrupt someone who may be opening up for the

very first time about their traumatic experience. In my mind, it could tear down the initial trust that allowed them to share in the first place. Training manuals even warn that asking victims to repeat segments of these narratives can be traumatizing (Bancroft et al. 211). The interpreters interviewed were concerned with "giving voice," a concept also mentioned in the literature (Bancroft 201), so the thought of doing something that could potentially hinder a person from speaking would be shocking to them, and likely to other interpreters around the world.

Although the act of sharing a trauma narrative with another can be beneficial to the client, it is not always an end in and of itself. The mental health providers need the information that is being shared in order to help their clients holistically, beyond the initial step of providing a safe place where they can share their story. Trauma-informed interpreting is moving the interpreting profession in a positive direction and providing new insights, namely in that it encourages interpreters to focus on the emotions and wellbeing of the people involved in the interaction instead of just the language. However, adhering too strictly to a people-centered model could cause interpreters to lose sight of the purpose of the interpreted encounter. Just as words from witness testimonies in legal settings are used to convict or acquit, words in counseling sessions in the mental health setting serve as a roadmap for the counselor to diagnose and treat. Care should still be given to protect trauma survivors, but the solutions may be more complex than initially thought.

It is exactly this kind of insight which motivated this research. Since trauma-informed interpreting is a new specialization that has developed in recent years, many aspects of it have not yet been explored in depth. Trauma-informed interpreting can take

place in a variety of contexts, but may look different in a mental health setting. This setting, unlike many others in interpreting, has also received little scholarly attention. Looking specifically at trauma narratives and how they are interpreted is a new focus in Interpreting Studies. That is why the interviews were conducted with interpreters and a counselor with experience in mental health. Through their descriptions, we can get a better understanding of what this setting is like, how these narratives are interpreted, and make recommendations for the future.

1. Mental Health Setting

Not only were the informants in agreement that the mental health setting was unique, but they all contrasted it directly with the broader field of medical interpreting, which supports the distinction that was highlighted in the literature review. Their answers coincided with literature pointing out the difference in the goals of doctor's interviews versus mental health professional's interviews (Roat and Crezee 250). They also seemed to support the specialization of interpreters in mental health, as evidenced by the different selection process for the counselor's interpreters. At the very minimum, with this specialization, interpreters showing up expecting to interpret for standard healthcare procedures wouldn't be thrown into a counseling situation without any mental or emotional preparation as Interpreter 1 experienced.

The interpreters had negative experiences interpreting with physicians and expressed a preference for working with counselors. A possible explanation for this preference could be that the more rushed nature of the medical appointments made the task of interpreting more difficult. This could also be based on their relationship between the medical providers they were working with. However, the counselor spoke positively

of the collaboration at her workplace and the continuum of care she was able to offer by working at a place that provided general health services along with her specialized mental healthcare services.

This care gets at the heart of what healthcare and mental health services have in common. “In healthcare, the interactions are collaborative, meaning that all the participants want the same outcome; they want the patient to get well and stay well” (Roat and Crezee 243). This statement was made comparing healthcare encounters to adversarial legal proceedings in an attempt to answer the question of whether healthcare interpreting is different from interpreting in other settings. In their answer, they continue to describe healthcare settings. One of characteristics they discuss in arguing that healthcare settings are different is the relationship between the providers and their patients. They believe that healthcare providers have more power and preparation than their patients, which can cause the patients to feel disempowered (243).

I do not think this relationship could equally be ascribed to counselors. While mental health providers do want patients to “get well and stay well,” similar to physicians, the process of going about this looks very different from other medical treatments. Although there is a great diversity of techniques used with clients, counselors typically recognize that this healing will take time. Instead of writing a prescription and asking the person to come back in six months, counselors are typically slower to diagnose and more willing to see their clients frequently. Additionally, though they do often hold the power and preparation, they are intentional about yielding these things in a way that empowers their clients. This was exemplified in the breathing exercises two of the

informants mentioned; this is an activity the clients can continue doing independently at home, equipping them to take ownership of their recovery.

Counselors are also different in that they rely almost solely on language to diagnose. Doctors ask questions about symptoms and medical histories, but they rely on the use of other medical instruments to determine the diagnosis and subsequent treatment plan. Counselors, on the other hand, do not have stethoscopes or x-ray machines to tell them what their clients are going through. They listen to what their clients are saying to figure out how to best help them. They may refer to some outside testing, but words are their most powerful tool. With such distinctions in the goals and the means of these types of care, it would seem that interpreting in mental health is vastly different from interpreting in broader healthcare settings.

In this setting, since language holds such a diagnostic and therapeutic power, interpreters should still work hard to seek training to help with the linguistic challenges they will encounter. The fact that the terminology in these sessions can be perceived as easy, as expressed in the interviews with the interpreters, could draw newer interpreters to this specialization because the amount of specialized terminology is not as overwhelming as in legal or medical settings. However, the nuance of the language is extremely important, as the counselor pointed out, and interpreters must train themselves to listen for and convey this nuance in their interpretations. With that said, regardless of their amount of experience in this setting and how much they may have learned about what language indicates certain conditions, interpreters should not be the ones to determine what is or is not important diagnostically. Instead, they should seek to do their

best to convey the messages accurately so that the provider can have all the information needed to make those determinations.

2. Work Environment

Interpreting requires a great deal of concentration; "virtually no other profession undergoes a similar cognitive load" (Riccardi et al. 97). The interpreters in my study highlighted how their physical surroundings such as space limitations contributed to the already difficult task of interpreting in these settings. Although they did not point out any perceived decline in their performance due to these stress factors, it is something that could be explored in further studies on this setting. If interpreters are forced to stand while the other parties are seated or if they feel that their safety is in jeopardy because they are forced to directly confront an abusive person, this stress could hinder the interpreter's ability to concentrate and interpret well. It is worth studying this phenomenon further and seeing what impact these conditions might have on interpreter performance.

The other major feature of the work environment that came to the surface in the interviews was the relationship between the counselor and interpreters. Since interpreting is a more newly established profession, those from other sectors who work with them often do not understand their purpose or significance, and this can create a lack of trust. Other professionals' limited knowledge of what interpreters are supposed to do was a concern raised by interpreters in previous studies (Crezee et al "Issues" 266). Counselors, even if they recognize the value of interpreters, may not have a clear understanding of their role. In the data presented here, the counselor who was interviewed seemed to be distrusting of interpreters because of some negative past experiences with them. While

any professional could have a negative experience working with an interpreter, it is worth pointing out that she has been working with volunteers. Although these people are screened by the organization before working with her, it is unclear whether they had any previous interpreting training, or whether they possessed the skills required to interpret well. Perhaps some of the mishaps she shared could have been prevented if she were working with more qualified interpreters.

When the interpreters reported the initial mistrust towards them that they detected in the counselors, it seemed to indicate ignorance about how interpreters typically carry out their job functions. It also hints that they felt a potential loss of control in the session. Counselors are typically "very mindful of the dynamics of power" and "may feel wrong-footed by having an interpreter in the room" (Costa "Working" 61). Whereas they typically have a great deal of control in managing communication with their clients and in developing a therapeutic alliance, they are now relying on a third party to help them do so. It is understandable that they would feel uneasy about this. As the counselor who was interviewed shared, she is aware that when she works with an interpreter, she is no longer the first one hearing her client's stories, and she needs that information to do her job. Having to rely on an interpreter for something that is typically within her power is challenging.

While this finding coincided with the literature, the interpreters interviewed did not express any mistrust towards the counselors they were working with, something that has also been previously documented. This could be because, unlike with interpreters, society is typically aware of the role and importance of counselors, at least on a superficial level. It is also likely that the counselors' intentional efforts towards

establishing trust with the clients during the sessions also fostered a sense of trust in the interpreters. Most of the incidents of mistrust that have been documented in the literature have to do with interpreters not understanding specific therapeutic strategies that are being used in the sessions (Bancroft et al. 172), a situation these interpreters had not experienced yet.

This working relationship between counselors and interpreters is vital for the success of the sessions. When it is not there, both parties may compensate in a way that can negatively affect the clients, who are already vulnerable and seeking help (Costa "Working" 64). To prevent this and foster a positive working relationship, the author recommends hosting supervision with both professionals. "Where possible clinicians and interpreters should be trained together so that they can understand the extent and limits of each other's roles and responsibilities" (68). Regardless of how this is ultimately implemented, we can see from the informants' stories how valuable their communication and understanding of each other's profession is in making the partnership work.

The above quote mentioned that counselors should learn the interpreter's role, but role is a complex idea in Interpreting Studies, and is debated in each setting. There are not many opposing views on the interpreter's role specifically within the mental health setting because few authors have explored this topic. The most prominent model for the interpreter's role in this setting is a restrictive version of the interactive model of interpreting, where the interpreter is valued as a person in the interaction and seen as more than simply a translation machine, but still prioritizes the therapist's control over the session (Bot *Dialogue* 88-91, 254-255). The comments the counselor made in the interview align with that view, but she was not asked extensively about this topic.

Interpreter 2's decisions to only intervene for semantic clarifications, but to defer other types of clarifications to the counselor also seem to fit within this model.

While this model of role seems to work for the interpreting encounters, the mental health setting allows for flexibility in its application. Because of the unique characteristics of each encounter, "interpreters have to adapt their role according to the type of patient and type of session, and also to the idiosyncratic preferences of each individual mental health provider" (Bot "Interpreting" 254). If the communicative needs of this setting mean that the counselor is to take the lead, then interpreters should be more flexible in their application of their training and understanding of their role, without doing anything they consider to be unethical. Although Interpreter 2 is "breaking protocol" in interacting more with the children than she would with a typical client, this is a justifiable communicative adjustment that can be made in agreement with the counselor. Navigating these complexities with the counselors is further argument for pre-sessions and debriefings to occur regularly in this setting. If these adjustments are agreed upon but turn out poorly, they can be discussed in these set-aside times. This also points further to the need for further research to be conducted in this setting.

3. Trauma Awareness

The emotional reaction the interpreters had to the traumatic narratives they were being exposed to is consistent with the studies cited in the Literature Review. They did not show current signs of burnout, but the mention of symptoms such as replaying the stories consistently in their minds after the sessions and losing sleep thinking about these narratives are vivid examples of the strong potential this work has to wear interpreters

down. Without the proper training and coping strategies, it is easy to see how interpreters in similar situations would be tempted to despair and leave the profession.

The interpreters' desire to prepare for the assignments, both through personal research and more structured trainings, seem to agree with the recommendations of other scholarly articles (Bancroft et al.; Valero-Garcés "The Impact"; Crezee et al. "Teaching") and existing resources (Bancroft et al.; Toledano Buendía and del Pozo Triviño). However, providing even more resources and trainings would be helpful to continue equipping interpreters to face these situations.

The literature encourages interpreters to use their debriefing time with the counselors to not just discuss the case and the interpreting, but also any reactions they are having to the content of the sessions (Bancroft et al. 94-95). It was an interesting finding that the counselor I interviewed instinctively perceived a need for this. She felt an ethical responsibility to provide that kind of help to her interpreter, and it is likely that other mental health providers will be open to this. Given the confidential nature of the sessions, these debriefing times may be the only opportunity the interpreter has to discuss what they've just heard. If the interpreter respectfully requests this from the counselor, and is mindful of the provider's time and other pressing work duties, I think many would be open to dedicating some time to this. One study found that counselors were the most likely practitioners in the healthcare field to debrief with interpreters (Crezee "Health").

While it is true that interpreters can grow in resilience after being exposed to these stories, it is also important for them to recognize their limitations. The counselor suggested imposing an age limit on interpreting in mental health settings or allowing only interpreters with certain life experiences to do so. While it would not be feasible to

strictly implement these restrictions, the spirit behind her comment points to a principle most interpreters already follow: saying no to assignments they know they are unprepared for. Just as interpreters are trained to do this when they aren't prepared linguistically for an assignment, they could also be trained to consider which cases they are not emotionally prepared for. The challenge in that, however, is that many interpreters are not briefed about the assignments beforehand. Counselors could help provide some of this information so that the interpreter can make an informed decision about their level of preparedness for a session.

Just as the majority of studies related to interpreting traumatic content have focused more on its impact on the interpreters, this was a prevalent theme in the interviews. When Interpreter 1 reflected that she perhaps should have interpreted traumatic narratives in the third person, modifying typical interpreting protocol, she was demonstrating an awareness of how not doing so could provoke vicarious trauma. However, as we have seen from the literature, the other side of trauma-informed interpreting is also avoiding re-traumatization of the client (Bancroft 210-11). The counselor was likely the only one who understood that because she has received far more training in trauma and trauma-informed care. It is highly unlikely that the interpreters are apathetic about client re-traumatization; rather, they were probably just unaware of how easily it can happen.

Awareness of potential re-traumatization is not intuitive. Even though both interpreters had received extensive interpreting training and had worked with trauma victims, this was not on the forefront of their minds. In fact, re-traumatization can be counterintuitive to interpreters who are used to practicing their craft in a certain way and

then are asked to modify their protocols taking trauma into account. In one of the trauma-informed interpreting training programs, it took a series of roleplays, discussions, film clips, and hands-on practice to get interpreters to finally grasp how their behaviors could trigger re-traumatization and how negatively that would impact the survivors (Bancroft 212). Their natural instincts of what seemed helpful in the communication actually had the power to harm the people they were seeking to help. More training in trauma-informed interpreting is needed to help interpreters realize how their actions can impact clients.

Despite these challenges, interpreters working in this setting find it very rewarding; the interpreters who were interviewed in this study found great satisfaction in their work. They sacrificially expose themselves to content that can negatively impact their wellbeing in order to help the survivors have their voice heard. As more research is done on trauma-informed interpreting, and interpreters receive more training in recommended practices, they will be able to perform their job in a way that promotes healing to trauma victims. They can experience firsthand the "compassion satisfaction" that has been spoken of by others (Bancroft 2018).

4. Language of Trauma Narratives

In the literature review, it was noted that the vast majority of scholarly work on language and trauma has come from psychology. The practitioners and researchers in this field are the ones working most closely with trauma victims as they seek to work through what has happened to them. Thus, it was not surprising that of the three informants the counselor provided some of the most insightful comments about trauma narratives. Her decades of experience working in this capacity have given her the opportunity to hear

many such stories from her clients. Her reflections confirm the presupposition that these narratives are significant moments in the counseling sessions, both to shape the provider's understanding of the situation and to provide insight into possible routes for treatment.

An interesting finding was that the interpreters had observed a change in language during trauma narratives. It was unclear at the start of the study if interpreters would be able to reflect on their experiences hearing these stories and pinpoint characteristics of how the language differed from ordinary speech. They were able to make observations about pace, tone, and emotion. While I have not been able to find extensive explanations of these topics in regard to trauma narratives, their examples of trauma impacting speech in these ways are supported in the literature. In some of the earlier studies on trauma and language, a change in tone was mentioned (van der Kolk 241). Interpreters have reported that a difficult aspect of interpreting for refugees, many of whom have experienced trauma, is that they speak in a low voice or mumble (Crezee et al. "Issues" 260). In a therapeutic setting, trauma narratives that engage the emotion of the speaker are more effective clinically because they allow "the client to more directly relive the traumatic event" and address it more effectively with therapeutic interventions (Briere and Scott 127). One scholar has explored crying during trauma narratives as a way in which victims transcend the traumatic gap of the horrific event they have experienced (Ladegaard "Coping" 191).

It would seem as though some of the language of trauma narratives that scholars write about is observable even by those who are not researchers in the area. Based on the results, we cannot infer that pace is always faster or slower in trauma narratives, that tone

is always higher or lower, or that emotion always manifests itself in a specific way such as crying. Even if all the informants had been in agreement on these aspects of language, the study design with its small sample would not lead to these conclusions. What can be confirmed, however, is that it seems that trauma narratives do differ from ordinary speech. As the counselor stated, "Sometimes the way people sound just sounds different."

Although the informants spoke of the speaking style clients utilized while sharing trauma narratives, little mention was made of the structure of the narratives. There were no findings in this study to support the literature about incoherent speech. One possible explanation for this is that the average person is not typically attentive to analyzing the language they hear. If they hear something that sounds odd, they may try to make sense of it and move on. Trauma narratives have been documented to be different from ordinary speech, but this difference may not strike the listener as so strange that they remember it. An exception to the rule might be the speaking style of a psychotic person, which can also be incoherent, but these incoherencies are coupled with associative speech and utilizing uncommon words or expressions that may not even exist (Bot "Interpreting" 262). It would seem that trauma narratives are less extreme on the continuum of affected speech and thus not as noticeable to the listener, but this hypothesis would need to be explored in further research.

I have just stated that there were no findings which unquestionably support the incoherent speech, but there is one finding that could potentially fit in that category. Interpreter 2 described how stories could be fraught with so much detail that they caused confusion to her and the counselor. The interpreter herself stated that this could have been due to a cultural difference in narrative styles. Culture is not an issue that has been

taken up extensively in this study, but could be relevant in further research on this topic, especially given that narrative styles can differ drastically across cultures and languages (Blommaert; Grazia Guido).

The other reason I am hesitant to categorize Interpreter 2's example as incoherent speech is because it came from parents, not from the children who had experienced the abuse. Although the parents were telling narratives about trauma, this trauma was not necessarily personally experienced by the narrators. This distinction matters because when traumatic memory is recalled, it provokes the physical sensations and emotions of the initial traumatic event (van der Kolk 219). If the parents did not experience trauma personally, then this example may not qualify as a trauma narrative. However, finding out about or witnessing the abuse of their children could have been a personally traumatic experience for them, so this interpretation cannot be completely discarded. There is not enough information from the data to make a conclusion. Future studies that continue to pursue this line of investigation will perhaps need to have an even clearer criterion for trauma narratives to help work through these problems. The involved selection process behind determining what types of data can be labeled as trauma narratives has been addressed in other studies (Ladegaard "Coping" 194); there is not an easy solution.

While this confusing language cannot definitively be considered a trauma narrative, we can learn from how the interpreter handled it. She produced an equally confusing rendition and relied on the counselor to seek clarification from the client. This is an example of following the "golden rule" in mental health interpreting: "To interpret whatever the patient says, no matter how odd this may sound to the interpreter" (Crezee et al. *Introduction* 159-160). Despite the interpreter's confusion and heightened

concentration, she made an effort to produce an accurate rendition of the original message. Interpreters should also seek to do this as they are being exposed to trauma narratives which may sound different from ordinary speech. This would the counselors to hear the nuances of what their clients are saying and still maintain control of the session.

Perhaps one of the greatest limitations of this study, and of others that rely on interpreters reflecting on past experiences instead of analyzing the actual text from the interpreted event, is that it relies heavily on the interpreter's memory. As Interpreter 2 stated, interpreting is such a mentally demanding task that it is hard to call to mind what was said in the session. Remembering specifics about how they interpreted trauma narratives and other utterances may prove to be even more challenging. Consequently, there is no clear answer to the research question of how interpreters modify the trauma narratives in their renditions. This study was not able to answer whether these renditions maintain some of the same characteristics as the original. It is unknown at this time if these renditions have made a difference in counselors' understanding and diagnosing clients.

We do know, however, that interpreters are faced with a host of psychological and emotional pressures in this setting, along with the cognitive load interpreting places on them. One way to ensure that interpreters are appropriately rendering trauma narratives is by educating them about the features of these narratives. If they are aware that the narratives may utilize a different type of language than interpreters are used to hearing, and that this language can be diagnostically relevant for the counselors, they could be trained to interpret them more accurately. One way to do this is by training them to better monitor their speech and renditions in this setting (Dimitrova and Tiselius 204). With that

said, although the accuracy of the renditions is important, perfection is not expected. An exact equivalence would be impossible, as "investigations of naturally occurring interpreting show that renditions in practice never are unambiguously equivalent with the preceding originals" (Wadensjö "Dialogue" 113).

CHAPTER VI

CONCLUSION

Throughout this paper, I have provided information as to the background of this study and how the research questions regarding trauma narratives were investigated in the context of the broader TIMIS project. Since trauma narratives are different from other types of communication, I sought to explore how interpreters handle these narratives in the mental health setting, and if their renderings can make a diagnostic difference when working with counselors. To do so, I first outlined some basic concepts within Interpreting Studies and psychology to give context to the research. Then, I examined four different topics within the literature: language and trauma, trauma-informed interpreting, interpreting in mental health, and the mental health perspective on working with interpreters. This literature review revealed that more research is needed on interpreting in the mental health setting with trauma survivors, especially from a linguistic perspective as it relates to trauma narratives.

After introducing the project and summarizing relevant points in the literature, I gave a detailed explanation of the methodology. I explained how these particular research questions were examined in light of the TIMIS project, and as such, how funding and ethical research approval were obtained. After discussing the project development in a broader sense, I detailed the methodology used to address the research questions highlighted in this thesis. This involved including information such as how the subjects, two interpreters and a counselor, were chosen for semi-structured interviews, and then

how the data from those interviews was analyzed qualitatively using thematic analysis. I have reflected on the strengths and weaknesses of this methodological approach.

The strength of this approach gave me exposure to a vast set of reflections on interpreting within the mental health setting. I categorized this information in the Results section into four overarching groups, summarizing what the informants shared about the mental health setting, the work environment, trauma awareness, and the language of trauma narratives. After reporting on these interviews, I tied what the informants shared back to the literature review in the Discussion, mentioning points of agreement and variations from what has been previously documented, then giving some possible explanations as to why.

To return to what was stated in Chapter 1, this study set out to respond to a social and scientific problem in Interpreting Studies by looking at trauma narratives in the mental health setting. The data collected provided rich points of consideration, and particularly helped shed light on the context of the interactions in which these trauma narratives are interpreted. The findings about the unique nature of mental health interpreting with its elevation of language, the challenging physical and interpersonal aspects of the work environment, and the importance of a trauma awareness which considers the client and the trauma survivor are all useful considerations when approaching trauma narratives. Interpreters are already able to distinguish some differences in the language used to report these experiences. As further research gives us a clearer understanding of this phenomenon, interpreters can be trained to have a heightened awareness of it and carefully consider how to interpret it in a way that will produce accurate linguistic renderings of diagnostic relevance to the counselors.

This study has also served to help fill a gap in the literature. There are few studies on interpreting in mental health, and there are very few on language and trauma outside of psychology. This study has been able to contribute to both. It has taken a topic that is slowly growing as an area of research interest (trauma narratives) and shown its value with a different angle in a new context: interpreter-mediated counseling sessions.

Although the data did not provide a thorough answer to all the research questions, it has laid the foundation for further studies. In the interviews, the interpreters were able to reflect on the language of trauma narratives and share some strategies they have used to handle them in the past. However, the methodological approach of this study in and of itself prevented a comprehensive understanding of the way interpreters render trauma narratives. To continue to find answers to this question, more research must be done. One advantage is that, after finishing this thesis, I will still be involved in an active research project seeking to do just that. These interviews have shed light on the significance of trauma narratives; hopefully the data we eventually obtain from the counseling sessions offered through the TIMIS project will give further insight.

As I mentioned in the introduction, Interpreting Studies has the potential to immediately take what has been learned from the body of research and apply it to real people in need. The insights from this study will help our team as we make decisions about trauma-informed interpreting care throughout the duration of our study. In addition, this information has been valuable to me. Conducting this research has been a rewarding experience, and I will be able to take what I have learned from the literature and the interviews and put it into my own practice as an interpreter. This will help me as I seek to

give voice to those who are hindered by a language barrier when accessing mental health services.

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