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Prenatal and Childhood Adverse Events and Child Brain Morphology: A Population-Based Study

Andrea P. Cortes Hidalgo,[a] Scott W. Delaney,[b] Stavroula A. Kourtalidi,[c] Alexander Neumann,[a] Runyu Zou,[a] Ryan L. Muetzel,[a] Marian J. Bakermans-Kranenburg,[d] Marinus H. van IJzendoorn,[c] Henning Tiemeier,[a,b] and Tonya White[a,e,*]

[a] Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC, Rotterdam, the Netherlands
[b] Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, United States
[c] Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, Rotterdam, the Netherlands
[d] Clinical Child & Family Studies, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[e] Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands

ABSTRACT

Prenatal and childhood adverse events have been shown to be related to children's cognitive and psychological development. However, the influence of early-life adversities on child brain morphology is not well understood, and most studies are based on small samples and often examine only one adversity. Thus, the goal of our study is to examine the relationship between cumulative exposures to prenatal and childhood adversities and brain morphology in a large population-based study. Participants included 2,993 children from the Generation R Study, a cohort of children growing up in Rotterdam, the Netherlands. Recruitment was initiated between 2002 and 2006, and the study is currently performing the 17- to 19-year follow-up wave. Prenatal adversities were reported by mothers at 20–25 weeks of pregnancy, and the child's lifetime exposure to adversities was reported by mothers when the children were 10 years old. The total brain, gray and white matter volumes, and the volume of the cerebellum, amygdala, and hippocampus were assessed with magnetic resonance imaging when children were 10 years old. In total, 36% of children had mothers who were exposed to at least one adversity during pregnancy and 35% of children were exposed to adversities in childhood. In our study sample, the cumulative number of prenatal adversities was not related to any brain outcome. In contrast, per each additional childhood adverse event, the total brain volume was 0.07 standard deviations smaller (SE = 0.02, $p = 0.001$), with differences in both gray and white matter volumes. Childhood adversities were not related to the amygdala or hippocampal volumes. Additionally, the link between childhood events and the preadolescent brain was not modified by prenatal events and was not explained by maternal psychopathology. Our results suggest that childhood adversities, but not prenatal adverse events, are associated with smaller global brain volumes in preadolescence. Notably, this is the first large population-based study to prospectively assess the association between the cumulative number of prenatal adversities and the preadolescent brain morphology. The study findings extend the evidence from high-risk samples, providing support for a link between cumulative childhood adverse events and brain morphology in children from the general population.

Keywords: Adversity; brain; childhood; magnetic resonance imaging; pregnancy; stress

Correspondence: Tonya White, MD, PhD, Child and Adolescent Psychiatry Department, Erasmus MC, Dr. Molewaterplein 60, Kp-2869, 3000 CB Rotterdam, the Netherlands. Email:t.white@erasmusmc.nl

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INTRODUCTION

Adversities, defined as the negative experiences that deviate from the expectable environment, need to be chronic (e.g. parental loss) or sufficiently severe to require a considerable psychobiological adaptation (1). Children whose mothers experienced adversities during pregnancy tend to have more behavioral problems (2), and childhood adversities are associated with poorer intellectual performance (3). Although studies in high-risk samples have addressed the relationship between early-life adversity and child brain morphology (1), the

association of prenatal and childhood adversities with child brain morphology is not well documented in the general population.

Fetal life, when the brain undergoes its greatest relative growth, is a critical period for brain development (4). Starting with differentiation of the ectoderm into neural tissue, there is a complex cascade of events that involve neurulation, neurogenesis and subsequent migration, apoptosis, synaptogenesis, and dendritic arborization (4, 5). This developmental period of incredible growth and change is a sensitive window, in which environmental factors that generate maternal toxic psychological stress may have profound and lasting effects (6). However, few studies have examined the relationship between prenatal adversities and offspring neurodevelopment. As reviewed by Franke, Van den Bergh (7), studies examining head circumference (HC) at birth showed mixed results. For example, prenatal adversities were not related to HC at birth in a population-based sample (N = 4,211) (8), whereas a small *positive* association was found in a larger cohort (N = 78,017) (9). HC metrics are easily accessible and a proxy for total brain volume. However, they might not capture region-specific differences (7). Only one study assessed prenatal adversities and child brain morphology using magnetic resonance imaging (MRI) and found that girls whose mothers were exposed to an adverse event in pregnancy had *larger* amygdala volumes (N = 68) (2). To date, no large population-based study has examined the relationship between cumulative prenatal adversities and child brain morphology.

In contrast, there is substantial research on childhood adversities and offspring neurodevelopment, including case–control studies, where adversities are often severe (e.g. institutionalization), and studies in children exposed to a more graded scale of events. Severe adversities have been related to smaller cerebellar (1) and global brain volumes, with differences in multiple brain regions (10). Evidence for differences in the amygdala and hippocampus is mixed, with both larger (11, 12) and smaller volumes (13) reported. Hanson, Nacewicz (13) examined three samples of children exposed to different adversities (physical abuse, neglect, low socioeconomic status (SES)) and found a smaller amygdala in relation to all adversities.

Studies in children exposed to more common adversities have reported differences in the cerebellum, cortex, and limbic structures. Cumulative early-life adverse experiences were associated with smaller gray matter volumes of the cerebellum, the amygdala, and multiple cortical regions in the frontal, parietal, and temporal lobes in a sample of 58 adolescents (14) and with smaller prefrontal cortex, amygdala, and hippocampal volumes in a study oversampled for child depression (15, 16). Importantly, the adversity definition in the latter study included parental psychopathology. Although having a parent with psychopathology may represent an adversity, shared genetic factors may underlie the association (7), and parental psychopathology may additionally interact with the adversities' effect (17).

There are also other relevant factors that may influence the association between early adverse events and downstream brain morphology. First, SES is related to child brain morphology and function, possibly through factors such as exposure to pollution, and the availability of education, cognitive stimulation, and healthcare (18). Importantly, while adversity occurs more often in individuals experiencing poverty, stress and the consequences thereof may also occur in other socioeconomic strata. The effects of adversity are likely explained by the biological stress response (19), thus suggesting that adversity and SES could have independent pathways underlying their effects on brain morphology. Determining whether early-life adversity is associated with brain morphological differences independent of the already known effect of SES is important to obtain a more precise estimation of the role of adversity on the brain (19). Second, accounting for the potential direct neurobiological effect of maternal smoking and alcohol use during pregnancy (20) can help to elucidate whether childhood adversity is related to the child's brain, independent of these exposures.

Evidence suggests a cumulative relationship between childhood adversities and numerous health-related outcomes, including health-risk behaviors and psychiatric disorders (21). To address a potential cumulative adversity effect on brain morphology, two main approaches have been proposed. First, the "lumping" approach focuses on the cumulative number of adverse events, assuming that different stressful events have similar effects on brain morphology (22). Second, the "dimensional" approach, proposed by McLaughlin and Sheridan (23), distinguishes between threatening events such as community violence and physical abuse, and deprivation-related events, or those related to lack of cognitive and social stimulation such as neglect and poverty. The dimensional approach hypothesizes potentially different psychobiological effects and underlying mechanisms between the two groups (23). However, largely similar brain differences have been described across the exposure to threatening and to deprivation-related events (10, 13, 22), suggesting low specificity across adversity types. We acknowledge that both approaches could offer a complementary perspective on the mechanisms and public health implications of childhood adversity, and the debate on how to assess adversity is still an open question. It is however clear that compared to examining single adversities, the cumulative adversity assessment offers a more naturalistic view of the adversity exposure, because adverse events are often related and tend to co-occur (22). In this study, we assessed the association between early-life adversities and brain morphology based on the broader cumulative adversity approach.

Notably, a randomized-controlled trial in institutionalized children demonstrated that cognitive outcomes improved when children were placed into foster care, especially if this placement occurred at younger ages (3). Sheridan, Fox (24) additionally described white matter volume differences between the children who remained in the institution and those never institutionalized, but not when comparing the foster care group with the never-institutionalized group. Thus, child neurodevelopment can improve, within the available biological reserve, after adversity ceases (25). This has two implications for our study. First, the timing of adversity exposure may influence the association with brain morphology. Children with no childhood adversities, but whose mothers experienced adversities during pregnancy, may show differences due to the pronounced neurodevelopment that occurs during prenatal life (25). Children with adversities in both the prenatal and childhood periods may have the largest brain differences. Thus, we examined adversities in both periods in relation to child brain morphology. Second, when adversity occurs only prenatally, delays in brain development could "catch up" postnatally, approaching the typical growth curve (25). To examine whether postnatal brain changes could have a role in our association of interest, we included fetal HC measures in sensitivity analyses.

Overall, evidence suggests that childhood adversity may be associated with the volume of the amygdala, the hippocampus, and the cerebellum (1, 14, 26). Adversity has also been found to be associated with widespread cortical differences, including the frontal, parietal, temporal, and occipital lobes (10, 14, 26, 27), likely indicating a global cortical effect of adversity. Thus, in this population-based study, we examined the relationship between cumulative prenatal and childhood adversities and preadolescent brain morphology, with a focus on the hippocampus, amygdala, cerebellum, and global brain volumes. We hypothesized that a greater number of adversities would be related to smaller global brain, amygdala, and hippocampal volumes. We additionally hypothesized a stronger association between childhood adversities and brain morphology in children whose mothers were exposed to prenatal adversities.

MATERIALS AND METHODS

Participants

This study is part of the Generation R Study, a population-based prenatal birth cohort in Rotterdam, the Netherlands (28). In total, 9,778 pregnant mothers with a delivery date from April 2002 to January 2006 were enrolled, and information was collected from children and parents by questionnaires, interviews, and research visits. Study protocols for each wave of data collection were approved by the Medical Ethical Committee of the Erasmus Medical Center, and all parents gave written informed consent.

T_1-weighted MRI scans were acquired in 3,966 9- to 11-year-old children (29), of which 3,186 had good image quality data. Among these children, 3,146 had complete information on prenatal and/or childhood adversities. We randomly excluded one sibling (N=153) to avoid nonindependent data. In total, 2,993 children were included in the analyses (2,242 in prenatal adversities analyses and 2,923 in childhood adversities analyses; Figure S1).

Measures

Adversities

Prenatal adversities. Adverse events occurring prenatally and shortly before pregnancy were assessed with a Dutch-adapted version of the Social Readjustment Rating Scale (SRRS) (30). At 20–25 weeks of pregnancy, mothers reported the occurrence of ten stressful events in the preceding 12 months (e.g. serious illnesses of family members, partner's death) (31). As part of the adversity score, we included a measure of substantial financial downturn to assess instability and drastic changes in the preexisting social and economic resources that could have led to a prolonged or severe biological stress response. The occurrence of robbery, theft, physical abuse, or rape was self-reported by the participant as a response to a single question and was additionally included in the prenatal adversities measure, given the relevance of these adverse experiences. Moving to a new home, originally assessed by the SRRS, was excluded as it could also reflect a positive situation. A *prenatal adversities score* was computed as the cumulative number of occurrences of ten adverse events (Table S1).

Childhood adversities. Occurrence of stressful life events from birth to age 10 years was reported by mothers during an interview when children were 10 years old (32). This instrument was based on the TRAILS study questionnaires (33) and the Life Events and Difficulty Schedule (34) and comprised 24 events of varying severity (e.g. high amount of school work, parental conflicts). To better measure *severe* adversities in this population-based sample, specific adverse events were selected using as reference the Adverse Childhood Experiences studies (e.g. Felitti, Anda (21)). *A childhood adversities score* was computed as the cumulative occurrence of these adversities (Table S2).

The measures of prenatal and childhood adversities were defined assuming equal weights of the individual events, following the "cumulative" mainstream approach to adversity, as outlined by Smith and Pollak (22). This approach provides a useful measure of adversity, which is simple and can be replicated across studies independent of sample-specific differences that otherwise affect data-driven approaches (e.g. latent constructs).

Brain Imaging

Brain MRI data were obtained in 9- to 11-year-old children using a 3 Tesla GE 750w Discovery platform (General Electric, Milwaukee, WI) (29). T_1-weighted images were collected with a receive-only 8-channel head coil and an inversion recovery fast spoil gradient recalled sequence (TR = 8.77 ms, TE = 3.4 ms, TI = 600 ms, flip angle = 10°, field of view = 220 × 220, acquisition matrix = 220 × 220, slice thickness = 1 mm, number of slices = 230, ARC acceleration factor = 2).

We processed and conducted the segmentation and reconstruction of the neuroimaging data with the FreeSurfer image analysis suite (v.6.0) (35). Reconstructed images were inspected for quality, and poor-quality reconstructions were excluded from further analyses (Supplemental Information) (36). The total brain volume, the cortical gray and cerebral white matter volumes, the cerebellar volume, and the amygdala and hippocampal volumes were included in the analyses.

Ultrasound Measures

Fetal ultrasound measures were collected at three time points during pregnancy (37), at a median gestational age of 13.1 weeks (95% range = 9.3, 17.5) for the first assessment, 20.5 weeks (95% range = 18.4, 23.3) for the midpregnancy assessment, and 30.4 weeks (95% range = 27.9, 33.0) for the last assessment (38). The HC data collection was described in detail by Verburg, Steegers (39). Briefly, sonographers established the gestational age based on the first ultrasound assessment and measured fetal HC based on the outline of the skull and to the nearest millimeter using standardized techniques. The HC measures collected during the third trimester of pregnancy were included in the sensitivity analyses. These HC metrics have been shown to be predicted by maternal smoking during pregnancy (38) and by maternal education levels (40). Additionally, the HC metrics in our sample had a correlation of 0.55 ($p < 0.001$) with the gestational age at the ultrasound assessment and of 0.38 ($p < 0.001$) with the total brain volume at age 10 years, supporting the validity of our measures. There was high reliability for the HC metrics in early pregnancy, with intra- and interobserver intraclass correlation coefficient (ICC) of 0.995 and 0.988, respectively, and intra- and interobserver coefficient of variation (CV) of 2.2 and 3.8, respectively (41).

Covariates

We included as covariates child sex and age at the MRI scan, total intracranial volume, maternal national origin, highest household education, and maternal prenatal alcohol use and smoking. Child sex was collected from birth records. Maternal national origin was defined based on her parents' birth country and was self-reported during pregnancy. Maternal national origin was categorized as Dutch, non-Dutch Western, and non-Western. Mothers were considered of Dutch origin if both of her parents were born in the Netherlands. When one of her parents was born abroad, the maternal origin was defined based on the country of birth of this parent. We grouped the national origin minorities as non-Dutch Western (including European, Indonesian, Japanese, Oceanian, and North American) and non-Western (including other national origins, e.g. Surinamese and Moroccan) (42) (see also Troe, Raat (43)). The highest household education and prenatal alcohol consumption and smoking were reported through questionnaires during pregnancy (see Supplemental Information).

Maternal psychopathology in pregnancy was assessed with the Brief Symptom Inventory, a validated and widely used questionnaire (44). We used the global severity index score, a measure of the global severity of psychopathology, in additional analyses.

Statistical Analyses

We examined the associations of prenatal and childhood adversities with brain outcomes using multiple linear regression. We first fitted a minimally adjusted model controlling for child sex and age at MRI scan, total intracranial volume (in amygdala and hippocampus analyses), and maternal national origin. Child sex and age at MRI scan were included as precision variables to account for typical differences in brain morphological characteristics (45). Child intracranial volume was included in all analyses of the amygdala and hippocampus to determine whether childhood adversity was associated with the volume of these regions of interest independently of the adversity-related global brain differences. Considering the multiethnic nature of our study sample, the maternal national origin was controlled for to account for differences in the adversity exposure and possible anatomical brain variations across national origins (46). In a second model, we adjusted for the highest household education as an indicator of SES. Although adversity occurs more frequently in families experiencing poverty, it is argued that both factors have an independent effect and potentially different biological mechanisms (19). Therefore, we aimed to determine the association between adversity and brain morphology in children living in any SES. Finally, we also controlled for prenatal alcohol use and smoking in a third, fully adjusted model, since these factors may have a direct neurobiological effect (20) and could be also considered part of the pathway between prenatal adversities and brain morphology.

We subsequently examined the interaction between prenatal and childhood adversities in relation to brain morphology. Additionally, for descriptive purposes, we assessed the relationship between a categorical adversity measure and the brain outcomes, using four groups: children with one or more of the prenatal adversities that we measured (N = 460), children with one or more of the childhood adversities that we measured (N = 433), children with adversities in both periods (N = 321), and children with none of these adversities (N = 958).

Several sensitivity analyses were performed. We first examined whether child sex modified the associations between adversity and brain morphology. Second, we analyzed the associations of adversity and brain morphology in a more homogeneous group, children whose mothers had a Dutch national origin, and we explored the interaction between national origin and adversity on the brain outcomes by adding an interaction term in a model that included participants from all national origin groups. Third, we explored whether associations between adversity and brain morphology were explained by maternal psychopathology, and we examined the interaction between maternal psychopathology and adversity in relation to child brain morphology. Finally, we explored whether postnatal brain growth and volumetric changes in response to environmental factors (25) could influence the association of adversity and brain morphology by assessing whether prenatal adversities were associated with HC at the last pregnancy trimester, as HC is a proxy for an early measure of total brain volume (analyses adjusted for gestational age at ultrasound).

Analyses were performed in R v.3.6.1 (47). Outcomes were standardized. Multiple imputations of missing values (maximum missingness: maternal psychopathology = 23.4%) were performed ("mice" package (48)), and results were pooled across 25 imputed datasets. We found no signs of violation of the regression assumptions (i.e. independence, normal distribution, homoscedasticity). Additionally, the variance inflation factor was <2.5 for all variables in analyses of the interaction between prenatal and childhood adversity, suggesting no multicollinearity. Adjustment for multiple testing was performed using the Bonferroni approach in the analyses with prenatal adversities, childhood adversities, and the interaction between prenatal and childhood adversities (15 tests, including all brain outcomes, except for total brain volume).

Nonresponse and MRI Exclusions Analyses

Children included in the analyses of prenatal adversities and brain morphology (N = 2,242) were compared to children with data on prenatal adversities but with no neuroimaging data available (N = 3,552). Continuous variables were compared with the Mann–Whitney U test and categorical variables with chi-squared tests. Mothers of children without imaging data were more often exposed to prenatal adversities (one or more events: 40.7%) than those of children in analyses (one or more events: 36.1%) and were less often highly educated (22.1% vs 30.5%). Additionally, mothers of children without imaging data were less often from Dutch origins (no imaging data group: 50.6%; study sample: 61.1%) and had more psychiatric symptoms (median (IQR) = 0.19 (0.1, 0.4)) than those in the analyses (median (IQR) = 0.15 (0.1, 0.3)).

Children with prenatal and/or childhood adversity and neuroimaging data available but who were excluded due to nonusable MRI data (N = 760) did not differ from children included in the analyses (N = 2,993) in the exposure to prenatal (p = 0.27) or childhood adversities (p = 0.31), in maternal national origins (p = 0.09), or in maternal psychiatric symptoms (p = 0.26). Excluded children more often had mothers with lower education (54.0%) compared to those in the analyses (47.3%; p = 0.01).

RESULTS

In our study sample, the child age at the MRI scan was between 8.72 and 11.99 years (median: 9.93 years), with 90% of children below the age of 11.19 years. In total, 36% of children had mothers who were exposed to at least one prenatal adversity and 35% of children were exposed to adversities during childhood (Table 1).

Table 1. Baseline characteristics

	Mean (SD) or %*	*N*
Adversity measures		
Prenatal adversities (ten items), % (*N* = 2242)		
0	63.9	1,432
1	20.6	461
2	10.5	236
3	3.8	85
4 or more	1.2	28
Childhood adversities (four items), % (*N* = 2923)		
0	64.9	1,897
1	27.2	795
2	6.3	185
3	1.4	41
4	0.2	5
Child characteristics		
Sex, % girls	50.8	1,521
Age at MRI scan, years	10.1 (0.6)	2,993
Parental characteristics		
Maternal national origin, %		2,993
Dutch	57.6	1,725
Non-Western	30.3	906
Other Western	12.1	362
Highest household education, %		2,993
Low education	41.0	1,227
Medium education	22.4	670
High education	36.6	1,096
Maternal prenatal alcohol use, % never during pregnancy	41.0	1,226
Maternal prenatal smoking, % never during pregnancy	76.9	2,303
Maternal psychiatric symptoms, median (Q1, Q3)	0.15 (0.06, 0.32)	2,993

Characteristics of the sample with information for **prenatal AND/OR childhood adversities** and brain structural MRI data (*N* = 2993). *Otherwise indicated. Based on imputed datasets.

Children with mothers exposed to prenatal adversities were more likely to experience adversities during childhood (41%) compared to those without prenatal adversities (31%). The most commonly reported prenatal event was a substantial financial downturn (14.5%), followed by a serious illness of a family member (11.6%) (Table S1). In childhood, parental separation or divorce was the most prevalent event (21.45%) (Table S2). Distributions and Pearson correlations for all variables of interest are presented in Figure S2 and Table S3, respectively. There was a correlation of 0.13 ($p < 0.001$) between prenatal and childhood adversities. Prenatal and childhood adversities were more common in children of non-Western mothers (any adversity = 51.4%, and 43.7%, respectively) compared to children of Dutch mothers (any adversity = 30.2% and 31.1%, respectively). Prenatal adversities occurred in 37.0% of boys and 35.0% of girls, and childhood adversities in 36.3% of boys and 33.3% of girls.

The cumulative number of prenatal adverse events was not related to any brain outcome (Table 2). In contrast, a consistent association was found between childhood adversities and all global brain metrics (total brain, cortical gray and white matter volumes, and total cerebellar volumes). Children had, on average, a 0.11 standard deviation smaller total brain volume (SE = 0.02, $p < 0.001$) per each additional childhood adverse event, adjusting for child sex, age at the MRI scan, and maternal national origin. The associations between childhood adversities and the total brain, cortical gray and white matter volumes remained after adjustment for parental education, and prenatal alcohol use and smoking (total brain volume: $B = -0.07$, SE = 0.02, $p = 0.001$) (Figure S3). Childhood adversities were not related to the amygdala and hippocampus (Table 2). After adjustment for multiple testing, the associations between childhood adversities and the cortical gray (p-adjusted < 0.05), and cerebral white matter volumes (p-adjusted = 0.03) remained.

No interaction was observed between prenatal and childhood adversities in relation to child brain morphology (Table 3). Also, when using the categorical adversity measure, the exposure to *only* prenatal adversities was not related to the total brain volume, whereas the specific exposure to childhood adversities was associated with a 0.10 standard deviation smaller total brain volume ($p = 0.04$). Additionally, children with adversities in both periods had a 0.10 standard deviation smaller total brain volume than those nonexposed to any of the adversities measured ($p = 0.06$). Altogether, our results suggest that only childhood events are related to brain morphology and that this association is independent of the occurrence of prenatal adversities (Figure 1).

We further examined the specificity and robustness of the association between childhood adversities and brain morphology. No interaction was found between child sex and childhood adversities for any brain outcome. When including only children with Dutch mothers, childhood adversities were related to the total brain, gray and white matter, and cerebellar volumes (Table S4), and there was no evidence of a significant moderating effect of national origin on the association between adversities and brain

Table 2. Associations between cumulative prenatal and childhood adversities and child brain morphology

	Model 1			Model 2			Model 3		
	B	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
Prenatal adversities									
Global brain metrics									
Total brain volume	−0.03	0.02	0.14	−0.02	0.02	0.39	−0.01	0.02	0.52
Cortical grey matter volume	−0.03	0.02	0.20	−0.01	0.02	0.57	−0.01	0.02	0.71
Cerebral white matter volume	−0.02	0.02	0.23	−0.02	0.02	0.41	−0.01	0.02	0.56
Total cerebellar volume	−0.03	0.02	0.10	−0.03	0.02	0.20	−0.02	0.02	0.26
Subcortical brain metrics									
Amygdala, mean volume	0.02	0.02	0.40	0.01	0.02	0.41	0.01	0.02	0.52
Hippocampus, mean volume	0.01	0.02	0.42	0.01	0.02	0.42	0.01	0.02	0.50
Childhood adversities									
Global brain metrics									
Total brain volume	−0.11	0.02	<0.001	−0.08	0.02	<0.001	−0.07	0.02	0.001
Cortical grey matter volume	−0.11	0.02	<0.001	−0.08	0.02	0.001	−0.07	0.02	0.003*
Cerebral white matter volume	−0.10	0.02	<0.001	−0.08	0.02	0.001	−0.07	0.02	0.002*
Total cerebellar volume	−0.07	0.02	0.003	−0.05	0.02	0.03	−0.05	0.02	0.06
Subcortical brain metrics									
Amygdala, mean volume	0	0.02	0.90	0	0.02	0.87	−0.01	0.02	0.70
Hippocampus, mean volume	−0.01	0.02	0.58	−0.01	0.02	0.63	−0.01	0.02	0.59

Model 1 is adjusted for child age at MRI scan, child sex, total intracranial volume (in subcortical metrics), and maternal national origin. Model 2 is additionally adjusted for the highest household education. Model 3 is additionally adjusted for maternal prenatal alcohol use and smoking. All outcomes are standardized. $N = 2{,}242$ in prenatal adversities analyses, $N = 2{,}923$ in childhood adversities analyses. *These p-values survived correction for multiple testing.

Table 3. Interaction between prenatal adversities and adversities in childhood in relation to brain morphology

	Main Effect: Prenatal Adversities			Main Effect: Adversities in Childhood			Interaction Effect		
	B	SE	*p*	*B*	SE	*p*	*B*	SE	*p*
Global metrics									
Total brain volume	−0.02	0.02	0.33	−0.10	0.03	0.002	0.04	0.03	0.15
Cortical grey matter volume	−0.02	0.02	0.33	−0.10	0.03	0.001	0.04	0.03	0.08
Cerebral white matter volume	−0.02	0.03	0.55	−0.09	0.03	0.01	0.02	0.03	0.40
Total cerebellar volume	−0.03	0.03	0.22	−0.06	0.03	0.09	0.03	0.03	0.35
Subcortical metrics									
Amygdala, mean volume	0	0.02	0.96	−0.02	0.03	0.43	0.03	0.02	0.24
Hippocampus, mean volume	0.01	0.02	0.56	0.01	0.03	0.69	0	0.02	0.94

Model is adjusted for child age at MRI scan, child sex, total intracranial volume (in subcortical metrics), maternal national origin, the highest education in the household, maternal prenatal alcohol use, and maternal prenatal smoking. All brain outcomes were standardized. Adversities measures represent the cumulative number of events. *N* = 2,172.

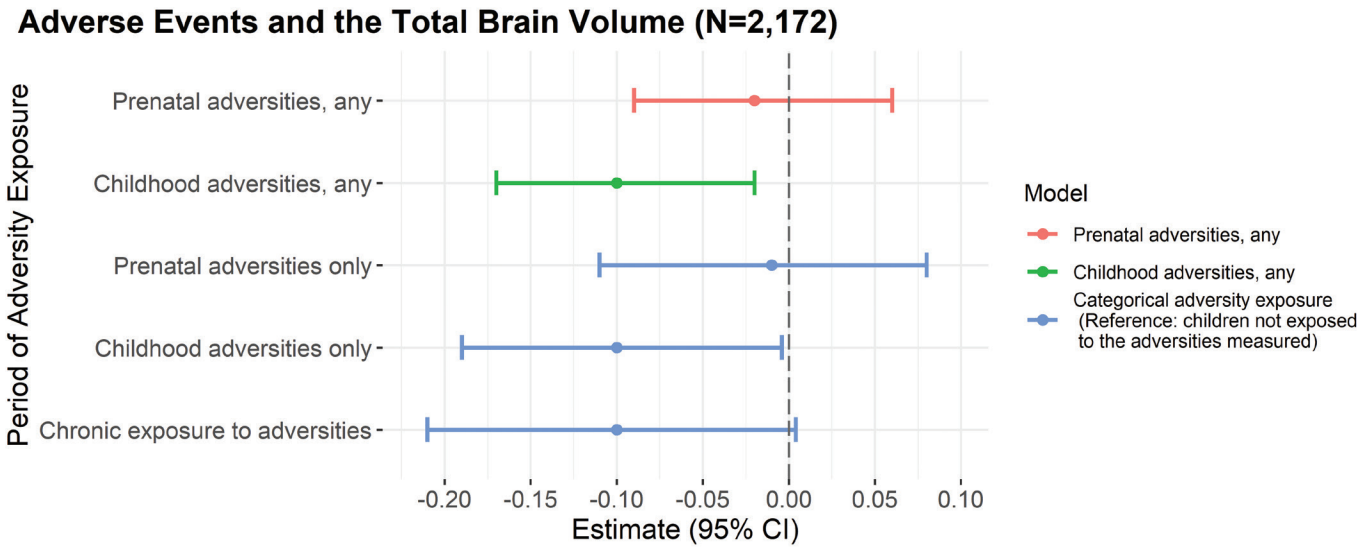

Fig. 1. Associations between prenatal and childhood adversities with the total brain volume.

morphology. Also, the associations between childhood adversities and brain morphology were not explained nor modified by maternal prenatal psychopathology (Table S5). Additionally, the cumulative number of prenatal adversities was not related to variations in the fetal HC (*B* = 0.00, SE = 0.02, *p* = 0.82; *N* = 2,168). Finally, we performed a post hoc analysis to assess whether the global brain differences observed in relation to childhood adversities were driven by a specific adversity. We found that, except for psychological abuse (*B* = 0.00, SE = 0.05, *p* = 0.94), all childhood adversities were similarly related to total brain volume (e.g. parental loss: *B* = −0.11, SE = 0.04, *p* = 0.004), supporting the validity of our cumulative approach.

DISCUSSION

In this population-based study, childhood adversities, but not prenatal adverse events experienced by the mother, were related to global brain volume differences at age 10 years. Our study provides two novel contributions to the literature. This is the first study to examine the association between cumulative prenatal adversities and brain structure in children from the general population. Contrary to our hypothesis, we found no relationship between cumulative prenatal adversities and preadolescent brain morphology using a large population-based sample, an assessment of prenatal adversities while mothers were pregnant, and neuroimaging data. Second, cumulative childhood adversities were related to smaller total brain volumes, and differences were observed across gray and white matter volumes. These findings are consistent with research in some small high-risk samples, supporting a relationship between cumulative childhood adversities and child neurodevelopment.

The absence of associations between prenatal adversities and child brain morphology is surprising, as the brain undergoes dramatic developmental changes during

pregnancy (25). Our study may have lacked sufficient power to observe subtle effects. However, we assessed a considerably larger sample than previous studies (2). The brain can adapt in response to environmental effects (10), which raises the question of whether brain postnatal volumetric changes could have obscured an association between prenatal adversities and brain morphology. Given a rich and positive childhood environment, the brain development of children whose mothers experienced stress in pregnancy could catch up and return to the normative trajectory (25). If this were the case, prenatal adversities would be related to brain differences earlier in life. However, we found no association between prenatal events and HC in the last pregnancy trimester, arguing against the plasticity hypothesis (25) (see also a study from this cohort examining family dysfunction and fetal HC (37)). It is also possible that the adversity type and severity influence the relation with brain morphology. Whereas Jones, Dufoix (2) found a relation between the gestational exposure to a natural disaster and amygdala volumes, the cumulative exposure to a range of more normative adverse events was not associated with the global brain volume nor the amygdala and hippocampus in our study.

Numerous studies have examined *childhood* adversity and brain morphology, but results are difficult to compare due to differences in the events assessed, the age of occurrence of adversities, and the age at the MRI assessment (10). Overall, research suggests that children exposed to early-life adversity have smaller total brain, gray and white matter, and cerebellar volumes (10). Consistently, we observed that childhood adversity was related to smaller total brain volumes, and this finding was robust to the adjustment for confounders. Analyses with the gray and white matter volumes further supported this association. Additionally, maternal psychopathology did not explain nor modify the relationship between childhood adversity and these brain outcomes. Our results might be interpreted as reflecting a causal effect of adversity on child brain morphology, but our analyses are based on an observational study sample and a single MRI assessment, thus precluding the inference of causality (49). Other explanations for our findings are also possible. Importantly, genetic and biological characteristics, such as psychological traits, and genetic influences on hormonal and neural pathways may underlie our findings. These factors are partly heritable and simultaneously related to the exposure to adversity (e.g. emotional abuse (50)), which could explain a noncausal link between early-life adversity and child brain morphology.

Contrary to what we expected, childhood adversities were not related to the limbic volumes. The amygdala and hippocampus are of particular interest because they have a high density of cortisol receptors and cortisol influences the neuronal development (7). Interestingly, both larger and smaller amygdala and hippocampal volumes have been reported (11–13). In addition to the methodological differences across studies, various hypotheses could underlie these mixed findings. The volumetric growth of the amygdala and hippocampus peaks at around age 10 years (51); thus, different findings could be expected between studies assessing brain morphology during childhood, preadolescence, and at later ages. The adversity severity may also influence the results, and the impact of early adversity in some structures may only become apparent later in development (10). Further, the amygdala (52) and hippocampus (53) show continued neurogenesis after fetal life, suggesting that these regions could undergo plastic changes in response to adversity and other environmental factors.

Our adversity measures were selected with a focus on *concrete* environmental events that could generate stress in the pregnant mother or the child and require a substantial psychobiological adaptation (1). The cumulative prenatal adversity measure was based on a major life events inventory (30), similar to those included in other population-based studies (54). Similarly, our childhood adversity measure included events assessed by key childhood adversities studies (21, 55), previously shown to be associated with greater child psychopathology (32). Different items were used in the prenatal and childhood adversity measures, to focus on *maternal* stressful events in the prenatal measure and on *childhood* adverse events in the latter measure. Consistent with previous studies (54), the cumulative exposure to prenatal adversities was related to the number of childhood adversities. Our additive approach to adversity was based on the well-established "lumping" adversity framework (22). Although multiple alternatives have been proposed to assign weights to the specific adverse events, based on factors like the severity, intensity, and the timing of occurrence (22), there is no current consensus. Future studies should examine the role of these factors, and especially focus on the variability among individual perceptions of adversity, which likely has a unique influence in the determination of the adversity effects (22).

Our study has some limitations. First, we did not account for the age of occurrence of childhood adversities. Although events at specific ages could have different effects on brain morphology, it is difficult to determine the exact period of occurrence of adversities that are often chronic and variable (2). Second, mothers reported childhood adversities at age 10 years, and thus, these reports could be affected by recall bias. Nonetheless, other methods to collect information on childhood adversity in the general population, such as adolescent reports, are limited by the accuracy in reporting early-life events (11). Third, mothers of children without imaging data were more often exposed to prenatal adversities and were less often highly educated than mothers in our study. Fourth, we did not examine national origin in detail given the limited sample size for specific groups.

Additionally, we only included maternal national origin, as we expected a potentially differential exposure to prenatal adversities by the national origin of the pregnant mother in contrast to the biological father. Finally, the prenatal adversity measure was based on information collected when mothers were 20–25 weeks pregnant about adverse events that occurred in the preceding 12 months. By including events that occurred before pregnancy, we could have misclassified some women who were not experiencing prenatal stress as exposed. However, cumulative preconception adversities have also been shown to predict poor offspring outcomes (56). Additionally, events occurring after the 20- to 25-week assessment (in the third trimester of pregnancy) were not included, thus leading to a potential under-inclusion of late prenatal adversities.

CONCLUSION

In conclusion, we found that the number of adversities experienced by the mother during pregnancy was not related to brain morphological differences in children from the general population. Childhood adversities were consistently associated with smaller brain volumes, with alterations in both gray and white matter volumes. The association between childhood adversities and the global brain volume was neither modified by maternal psychopathology nor by the number of prenatal adversities. Our results support a cumulative association between childhood adversities and brain morphology, previously described in small high-risk samples. If the adversity and brain morphology relation is replicated in large samples with repeated MRI and adversity assessments, priority should be given to intervention studies that determine whether providing additional support to children following periods of adversities will prevent the emergence of brain differences.

ETHICS STATEMENT

All study protocols and the measurements assessed in each wave of data collection were approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam.

DATA AVAILABILITY

The datasets analyzed in this study are currently not publicly available due to legal and ethical restraints due to the General Data Protection Regulations (GDPR). However, the consent has been altered for the current wave of data collection that will provide the participants the option to determine the extent that they want their data shared. Via data transfer agreements, the data can be made available upon request. Interested researchers can direct their requests to Vincent Jaddoe (v.jaddoe@erasmusmc.nl).

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CONFLICTS OF INTEREST

Tonya White is current Editor-in-Chief of Aperture, and thus, an external review is necessary. All other authors declare no conflicts of interest.

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Supplemental Information for Prenatal and Childhood Adverse Events and Child Brain Morphology: A Population-Based Study

Brain Imaging

Reconstructed FreeSurfer images were visually examined for accuracy as described previously (1, 2). Eight trained and reliable raters compared the white and pial surfaces against the brain image at several slices and in sagittal, coronal, and axial planes and visually inspected for artifacts in the three-dimensional inflated and pial surface representations. All brain images were rated on a three-point scale, and images considered of "poor" quality were excluded from analyses. To ensure inter-rater reliability, training was initially performed with a standardized MRI set, and raters were considered reliable if they rated a training MRI set correctly. The amygdala and hippocampal segmentation was visually inspected by Weeland, White (3) in a subset of 2,551 MRI scans, with less than 1% of the images deemed as poor quality, suggesting a low rate of problematic amygdala and hippocampal segmentations in the present cohort study.

Covariates

Alcohol consumption during pregnancy included four categories: "never during pregnancy," "until pregnancy was known," "continued drinking occasionally in pregnancy," and "continued drinking frequently in pregnancy." Maternal prenatal smoking was categorized into the following: "never during pregnancy," "until pregnancy was known," and "continued in pregnancy." Information on maternal and paternal education was collected by self-report during pregnancy and was classified following the Dutch standard classification of education (4). The highest education in the household was included in the analyses.

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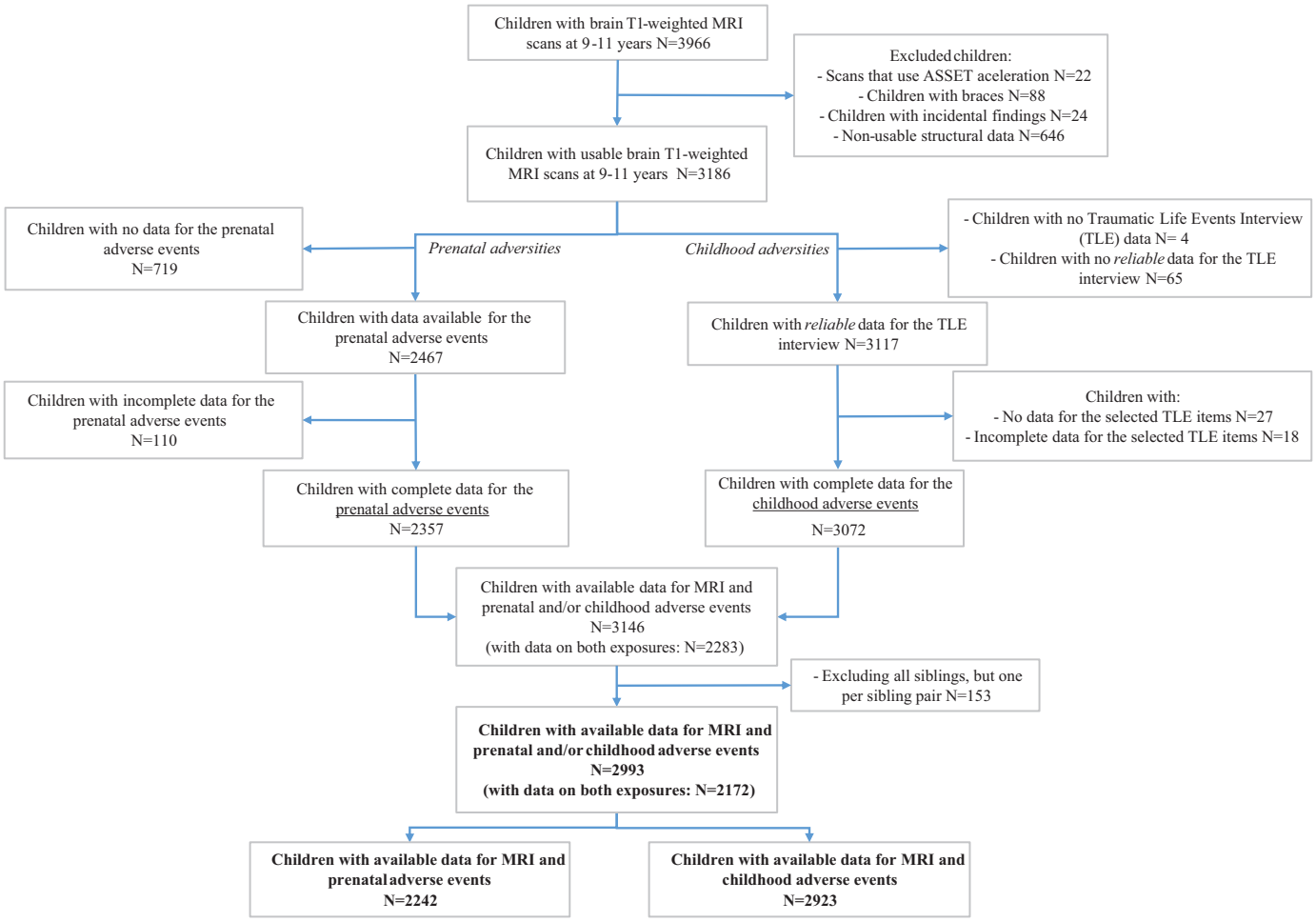

Fig. S1. Flowchart of sample selection.

Table S1. Prevalence of prenatal adverse events

Event	Prevalence, %	*N* Exposed
Have you been a victim of robbery, theft, physical abuse or rape?	3.88	87
Have you suffered a substantial downturn in your financial situation?	14.5	325
Have you become unemployed?	8.97	201
Has your partner or other member of your family become unemployed?	6.51	146
Has one or more of your children been seriously ill?	1.52	34
Has your partner, or other family member, or one of your parents (in-law) been seriously ill?	11.6	260
Has one of your children died?	0.71	16
Has your partner died?	0.04	1
Has your father or mother (in-law), a brother or sister, or good friend died?	7.09	159
Have you had a divorce or broken off the relationship with your partner?	3.57	80
Any category reported	36.13	810

N = 2,242.

Table S2. Prevalence of childhood adverse events

Category of Childhood Exposure	Prevalence per Category, %	*N* Exposed
Psychological abuse		
Has anyone almost used physical violence against your child? So that it did not actually happen, but your child was scared.	11.53	337
Physical abuse		
Has anyone ever used physical violence against your child? For example, beating him/her up.	6.77	198
Sexual abuse	4.41	129
Has anyone made sexual comments or movements towards your child?*	3.42	100
Did your child experience inappropriate sexual behavior?*	1.61	47
Parental loss	22.03	644
Is your child's father / mother or other caregiver still alive? (reversed)*	0.89	26
Are you and your partner divorced or separated?*	21.45	627
Any category reported	35.1	1026

N = 2,923. *Sexual abuse and parental loss categories include two items.

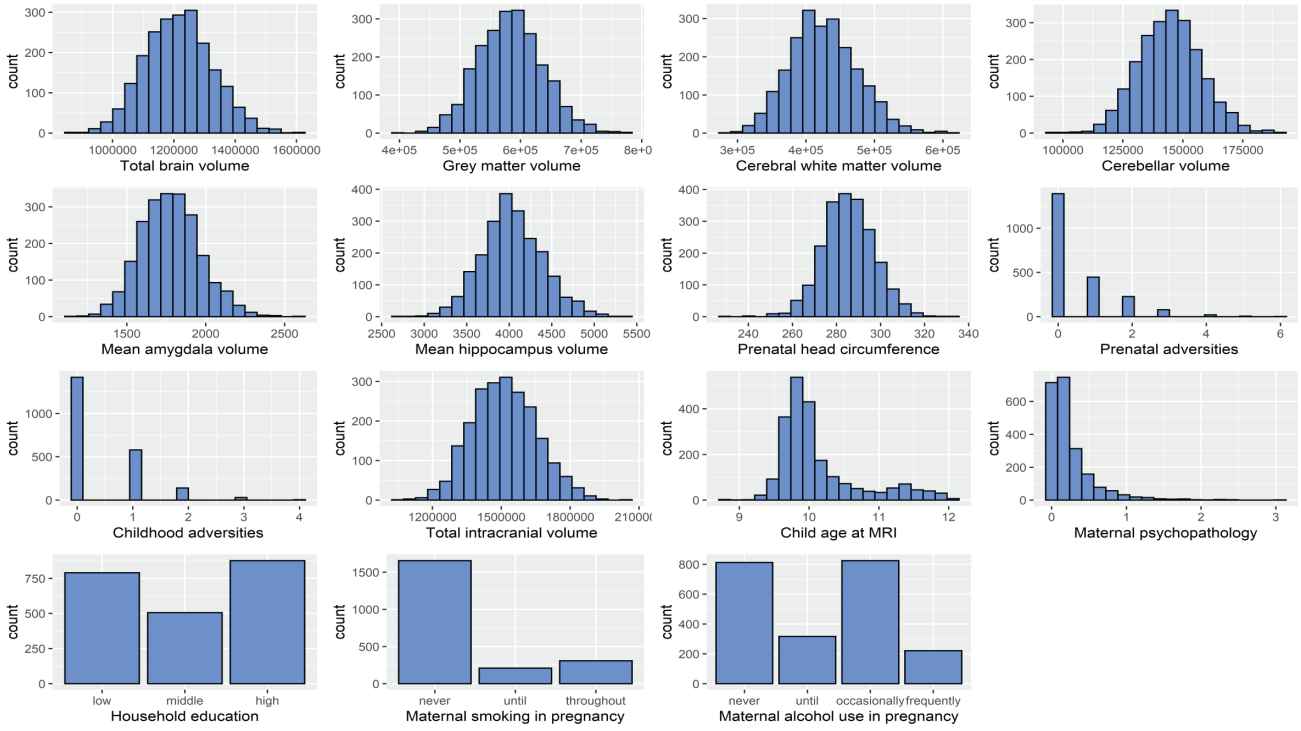

Fig. S2. Histograms of main variables of interest.
Note. **Value labels: "never" = never during pregnancy; "until" = until pregnancy was known; "throughout" = continued during pregnancy; "occasionally" = continued occasionally during pregnancy; "frequently" = continued frequently during pregnancy. Household education classified as: low (secondary, phase 2 or lower education), middle (higher, phase 1) and high (higher, phase 2) education. *N* = 2172.**

Table S3. Correlation matrix for the main variables of interest

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Total brain volume	-															
2	Cortical grey matter volume	0.95***	-														
3	Cerebral white matter volume	0.94***	0.82***	-													
4	Total cerebellar volume	0.66***	0.56***	0.54***	-												
5	Amygdala, mean volume	0.68***	0.66***	0.62***	0.44***	-											
6	Hippocampus, mean volume	0.66***	0.62***	0.60***	0.48***	0.67***	-										
7	Prenatal head circumference	0.38***	0.37***	0.35***	0.27***	0.25***	0.26***	-									
8	Prenatal adversities	−0.06**	−0.07**	−0.05*	−0.07**	−0.02	−0.03	−0.03	–								
9	Adversities in childhood	−0.07***	−0.08***	−0.06**	−0.05*	−0.03	−0.02	−0.04	0.13***	–							
10	Total intracranial volume	0.93***	0.87***	0.89***	0.65***	0.62***	0.62***	0.40***	−0.07***	−0.06**	–						
11	Age at the MRI scan	0.05*	−0.01	0.11***	0.06**	0.05*	0.06**	−0.01	0.01	0.05*	0.08***	–					
12	Child sex	−0.51***	−0.47***	−0.48***	−0.41***	−0.40***	−0.35***	−0.22***	0	−0.04	−0.51***	−0.04*	–				
13	Highest household education	0.19***	0.22***	0.12***	0.14***	0.10***	0.11***	0.10***	−0.17***	−0.20***	0.20***	−0.06**	0	–			
14	Maternal prenatal alcohol use	0.13***	0.15***	0.09***	0.10***	0.09***	0.09***	0.03	−0.01	−0.05*	0.14***	0.01	−0.06**	0.33***	–		
15	Maternal prenatal smoking	−0.06**	−0.07**	−0.04*	−0.02	−0.01	−0.04	−0.09***	0.11***	0.13***	−0.06**	0.05*	−0.02	−0.24***	0.14***	–	
16	Maternal psychopathology	−0.09***	−0.10***	−0.06**	−0.09***	−0.01	0	−0.06*	0.34***	0.19***	−0.10***	0.07**	−0.02	−0.26***	−0.10***	0.15***	–

Correlations in the first imputed dataset. N = 2,172 except for correlations with prenatal head circumference (N = 2,100). Child sex: 1 = boy, 2 = girl. Point-biserial correlations were calculated between child sex and all variables. ***$p < 0.001$. **$p < 0.01$. *$p < 0.05$.

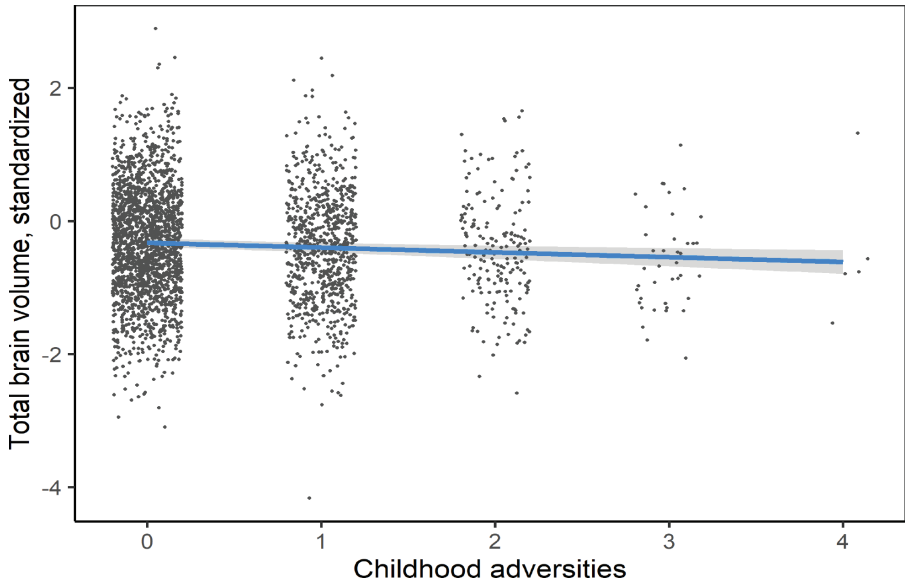

Fig. S3. Association between childhood adversities and the total brain volume.
Note. **Plot of the association between childhood adversities and the total brain volume adjusted for covariates.**

Table S4. Association between childhood adversities and brain morphology in children with Dutch mothers

	B	SE	*p*
Outcome			
Global metrics			
Total brain volume	−0.09	0.03	0.004
Cortical grey matter volume	−0.08	0.03	0.02
Cerebral white matter volume	−0.09	0.03	0.01
Total cerebellar volume	−0.08	0.03	0.02
Subcortical metrics			
Amygdala, mean volume	0	0.03	0.94
Hippocampus, mean volume	−0.03	0.03	0.37

Analyses performed in children with Dutch mothers. Model adjusted for child age at MRI scan, child sex, total intracranial volume (in subcortical metrics), the highest education in the household, maternal prenatal alcohol use and maternal prenatal smoking. All outcomes are standardized. *N* = 1,669.

Table S5. Interaction between maternal psychopathology and childhood adversities in relation to child brain morphology

	Interaction Effect		
	B	SE	*p*
Outcome			
Global metrics			
Total brain volume	0.08	0.06	0.19
Cortical gray matter volume	0.08	0.06	0.23
Cerebral white matter volume	0.09	0.07	0.19
Total cerebellar volume	0.02	0.06	0.78
Subcortical metrics			
Amygdala, mean volume	0.01	0.06	0.91
Hippocampus, mean volume	0.02	0.06	0.74

Model adjusted for child age at MRI scan, child sex, total intracranial volume (in subcortical metrics), maternal national origin, the highest education in the household, maternal prenatal alcohol use, maternal prenatal smoking, maternal psychiatric symptoms, and the interaction term of maternal psychiatric symptoms with childhood adversities. All outcomes are standardized. *N* = 2,923.

