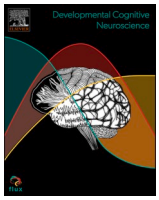
Developmental Cognitive Neuroscience 72 (2025) 101531

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn



Maternal depressive symptoms in childhood and offspring brain cortical and subcortical volumetric change: A repeated imaging study from age 4–10 years

Yuna Koyama [a,b,c,*], Ai Peng Tan [b,d,e], Ekaterina Sadikova [a], Peipei Setoh [f], Birit Broekman [d,g,h], Juan Helen Zhou [i,j,k], Peter Gluckman [l,m], Helen Chen [n,o], Henning Tiemeier [a,p]

[a] Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
[b] Department of Diagnostic Imaging, National University Hospital Singapore, Singapore 119074, Singapore
[c] Department of Public Health, Institute of Science Tokyo, Tokyo 113-8510, Japan
[d] Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), Singapore 138632, Singapore
[e] Department of Diagnostic Radiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore
[f] Psychology Division, School of Social Sciences, Nanyang Technological University, Singapore 639818, Singapore
[g] Department of Psychiatry, Amsterdam UMC, location VUmc, VU University, Amsterdam 1076, the Netherlands
[h] Department of Psychiatry, Onze Lieve Vrouwe Gasthuis, Amsterdam 1061, the Netherlands
[i] Centre for Sleep and Cognition, Centre for Translational Magnetic Resonance Research, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117549, Singapore
[j] Human Potential Translational Research Program, Department of Medicine, National University of Singapore, Singapore 117597, Singapore
[k] Department of Electrical and Computer Engineering, Integrative Science and Engineering Programme (ISEP), NUS Graduate School, National University of Singapore, Singapore 119077, Singapore
[l] International Science Council, Paris 75116, France
[m] Koi Tu: The Centre for Informed Futures, University of Auckland, Auckland 1010, New Zealand
[n] Department of Psychological Medicine, KK Women's and Children's Hospital, Singapore 229899, Singapore
[o] Duke-National University of Singapore, Singapore 118420, Singapore
[p] Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

ARTICLE INFO

Keywords:
Maternal depression
Brain volumetric development
Structural MRI
Deprivation
Delayed development
Repeated brain imaging

ABSTRACT

Maternal depressive symptoms have been associated with offspring's brain structural differences. However, previous studies were limited by cross-sectional designs, brain region-of-interest analyses, or clinical samples. Importantly, few studies assessed the early childhood brain. This study analyzed data from a Singaporean cohort of 217 children with 589 repeated structural neuroimaging from 4.5 to 10.5 years (2–4 assessments) in relation to maternal depressive symptoms. Maternal depressive symptoms were measured by questionnaire at child age 4.5 years. Mixed models explored within-sample change accounting for non-linear brain development. Multiple testing was corrected, and a stringent threshold was applied. Maternal depressive symptoms were associated with persistently smaller precentral gyral volume over time ($\beta = -0.162$ [-0.238; −0.086], $p_{adj} < 0.001$). In analysis with time interaction, maternal symptoms were associated with curvilinear changes in the volumes of supramarginal ($\beta = -0.019$ [-0.027; −0.010], $p_{adj} < 0.001$) and precuneus gyrus ($\beta = -0.016$ [-0.025; −0.007], $p_{adj} = 0.007$); this suggests delayed volumetric development in brain areas governing attention, memory, and language among children exposed to severe maternal symptoms. The findings implicate that childhood maternal depressive symptoms are associated with persistent differences in precentral volume and affect the brain volumetric development of complex sensory information processing regions, rather than in emotion regulation areas implicated in the depression experience. Our findings emphasize repeated childhood imaging to understand child brain development risk factors.

Abbreviations: MRI, Magnetic resonance imaging.

* Correspondence to: Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA 02115, USA.
E-mail address: ykoyama@hsph.harvard.edu (Y. Koyama).

https://doi.org/10.1016/j.dcn.2025.101531
Received 9 October 2024; Received in revised form 8 February 2025; Accepted 11 February 2025
Available online 14 February 2025

1. Introduction

Maternal depression is a leading public health challenge globally. Approximately 10–15 % of mothers experienced depression perinatally in high-income countries such as the US (Ertel et al., 2011; Pineros-Leano et al., 2021). Mothers with depression are involved less often and more negatively with children (Lovejoy et al., 2000), speak toward children with fewer words and less sensitively (Scheiber et al., 2022), and respond to their children's actions in less age-appropriate ways (Brummelte and Galea, 2016). Moreover, marital conflict is more likely (Cummings et al., 2005). These circumstances are characteristic of reduced capacity for care – a type of adversity that encompasses the absence of expected cognitive, social, and emotional stimulation necessary for normative development and can also impact mother-child attachment (McLaughlin et al., 2019). As a consequence, the children's growth and development can be impacted. Offspring of mothers with depression have been reported to show more internalizing and externalizing psychopathological problems (Goodman et al., 2011).

The experiences of being exposed to caregivers with chronic or severe depression are often considered deprivation (McLaughlin et al., 2019). Deprivation is any form of parental absence and under-stimulation, including neglect and institutional rearing (McLaughlin et al., 2019). A body of evidence supported the relationships between experiences of deprivation and brain development. The recent model of 'change of pace' posits that exposure to deprivation is related to delay in brain development, in contrast to exposure to threat, which is related to accelerated development (McLaughlin et al., 2019; Rakesh et al., 2023; Tooley et al., 2021). For instance, emotional neglect has been consistently associated with thinner and smaller cortices, especially in frontoparietal regions (McLaughlin et al., 2019). However, whether these findings truly reflect a delayed pattern of brain development is questionable. Most empirical research is based on cross-sectional studies and speculates about developmental changes based on a single child's assessment compared to the normative developmental pattern (McLaughlin et al., 2019; Rakesh et al., 2023). Changes in brain developmental patterns can be captured only with repeated brain imaging. Moreover, it is not clear if depressive symptoms in the general population can be mapped on the continuum of deprivation. Investigating possible changes in brain developmental patterns among children being exposed to caregivers with depressive symptoms in the general population gives insights into the nature of this experience. Deprivation entails many negative experiences, such as familial poverty, ethnic minority status, or disabilities, which make mothers more likely to experience depression and cope with depression (Belle and Doucet, 2003). In addition, less supportive communities, neighborhoods, or other social environments, which are strongly tied to cultures make mothers more vulnerable to depression (Halbreich and Karkun, 2006). Therefore, when examining the associations between exposure to mothers with depression and brain development, it is essential to consider the background factors that may shape maternal experiences of depression.

Maternal depression has been associated with offspring brain structural differences (Cattarinussi et al., 2021), but the associations between maternal depressive symptoms and any variability in offspring brain morphology (Cattarinussi et al., 2021) have not been consistent across studies. Some research reports no associations, and, importantly, the directionality is mixed. This inconsistency is likely not explained by the timing of exposure only, i.e., antenatal, perinatal, and postpartum periods (Cattarinussi et al., 2021). Not only are symptoms of depression often modestly persistent, but studies of specific exposure periods also showed no clear association pattern. For instance, maternal history of depression was not associated with offspring's gray matter volumes at age 3 years in a cross-sectional study (Vandermeer et al., 2020). Other studies exploring the associations of postpartum depressive symptoms found thinner offspring cortices in the right superior frontal regions including caudal middle frontal and precentral areas at age 3.5 years (Lebel et al., 2016) and in the bilateral frontal and the left temporal lobes at age 10 years (Zou et al., 2019), and smaller volumes in the fusiform gyrus at 10 years of age (Koc et al., 2023; Zou et al., 2019). Studies of the subcortical regions predominantly took a region-of-interest (ROI) approach, focusing on limbic regions, such as the amygdala. Maternal depressive symptoms throughout postpartum to early childhood were not associated with the amygdala volume in several studies (Donnici et al., 2023; Guma et al., 2023; Vandermeer et al., 2020; Wen et al., 2017; Zou et al., 2019), although one study reported smaller amygdala volumes in 2–3-year-old children of mothers who had postpartum depressive symptoms (Pellowski et al., 2023).

This line of research is suggestive of associations between maternal depressive symptoms and offspring brain morphology, but existing studies have major limitations and reveal knowledge gaps. First, most studies investigated regions of interest only (Donnici et al., 2023; Guma et al., 2023; Koc et al., 2023; Pellowski et al., 2023; Vandermeer et al., 2020; Wen et al., 2017; Zou et al., 2019). Focal regions were often determined based on the findings in clinically depressed samples due to a lack of understanding of which brain regions are impacted by maternal depressive symptoms (Vandermeer et al., 2020). However, exposure to an attachment figure with depression likely has different biological implications than experiencing depressive symptoms. Second, while brain structures undergo changes during early childhood, few studies have captured this important period with repeated assessments. Gray matter volumes increase rapidly in the perinatal period with the peak velocity at 0.5 years postnatally, reaching volumes equivalent to that of adults at 5 years old, peaking at approximately 6 years old, and continuing to decline throughout life (Bethlehem et al., 2022). This may be indicative of a sensitive period when the brain is susceptible to environmental stressors (Shonkoff and Phillips, 2000), and the best timing to explore the impact of environmental factors. Third, most studies utilize single-time assessments of brain structures, yet such an approach has two major disadvantages. Capturing brain development with single-time assessments is challenging, especially at younger ages, and cross-sectional neuroimaging studies cannot examine within-person changes (Bethlehem et al., 2022; Di Biase et al., 2023; Vidal-Pineiro et al., 2021). Recently, the impact of adversities, including maternal depression, was discussed by not only focusing on volumetric differences but also the differences in the pace of brain morphological development, although we lacked evidence from repeated measures of brain development (Rakesh et al., 2023; Tooley et al., 2021). If maternal depression, an experience of reduced capacity of care and, in an extreme case, emotional neglect and deprivation, is expected to be linked to delayed developmental pace, this can only be determined with multiple brain assessments in a relevant developmental period. Snapshot assessments of smaller or larger volumes do not inform how the developmental pace is altered. Similarly, within-person variability or change over time at the individual level, a main focus in developmental theory (Berry and Willoughby, 2017), can be obtained only from repeated measurements. Fourth, most previous studies were set in North American and European countries (Donnici et al., 2023; Guma et al., 2023; Koc et al., 2023; Lebel et al., 2016; Vandermeer et al., 2020; Zou et al., 2019), and little research has been conducted in other countries, limiting the generalizability of results (Pellowski et al., 2023; Wen et al., 2017).

The current study tries to fill these gaps and exploits state-of-the-art developmental neuroimaging data and a unique approach to explore the associations between maternal depressive symptoms and offspring's cortical and subcortical gray matter volumetric development throughout childhood. By leveraging a whole-brain approach and repeated brain imaging that covers early childhood to preadolescence, we can associate the variations in maternal depressive symptoms with the within-subject variations in offspring brain structure. To this end, we used the data from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort (Soh et al., 2014), a birth cohort with structural brain imaging at child ages 4.5, 6, 7.5, and 10.5 years. First, we examined the overall associations between maternal depressive

symptoms at baseline and persistent child cortical and subcortical regional gray matter volumetric differences over time. Second, we conducted a longitudinal analysis to explore the associations between maternal depressive symptoms and changes in regional gray matter volumes over time. We hypothesized that children of mothers with severe depressive symptoms in early childhood showed smaller cortical as well as subcortical gray matter volumes across time points, especially in frontal regions. Further, we expected that some fronto-temporal regions showed delayed developmental trajectories according to the levels of maternal depressive symptoms. Yet, in this hypothesis, we did not posit any regional specificity, given the limited evidence from prior studies.

2. Methods and materials

2.1. Participants

The current study analyzed data from the Growing Up in Singapore Towards healthy Outcomes (GUSTO), a longitudinal birth cohort study in Singapore. Originally, 1450 pregnant women aged 18 years and above were recruited at their first-trimester clinic visit at two major public maternity units between June 2009 and September 2010 and approximately half of them underwent neurodevelopmental assessments. A total of 436 mothers reported depressive symptoms at a child age of 4.5 years. Among these child-mother dyads, 318 children underwent brain scans and provided usable images at least once. We excluded those who only had one-time points to better estimate the change within subjects, ending up with 217 children (43 for 4 scans, 69 for 3 scans, and 105 for 2 scans; a total of 589 scans) as the analytical sample. Half of the participants were girls (n = 111, 51.2 %) and had ethnically Chinese mothers (n = 113, 52.1 %). The remainder were Malay (n = 75, 34.6 %) and Indian (n = 29, 13.4 %). In our analytical sample, we observed more Malay and Indian populations compared to the general Singaporean population. Further sample characteristics are shown in Table 1. The GUSTO study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the SingHealth Centralized Institutional Review Board (CIRB). Written informed consent was obtained from all caregivers on behalf of the children.

Table 1
Sample demographics (n = 217).

Child sex, N (%)	Girls	111 (51.2)
	Boys	106 (48.8)
Marital status, N (%)	Living with partner	207 (98.1)
	Not living with partner	4 (1.9)
	Missing	6
Maternal ethnicity, N (%)	Chinese	113 (52.1)
	Malay	75 (34.6)
	Indian	29 (13.4)
Maternal education level, N (%)	Primary or secondary	73 (34.1)
	ITE/MITEC	27 (12.6)
	GCE A levels/Polytechnic/ Diploma	59 (27.6)
	University (Bachelor, Master, PhD)	55 (25.7)
	Missing	3
Household monthly income, N (%)	SGD 0–1999	35 (17.6)
	SGD 2000–3999	68 (34.2)
	SGD 4000–5999	51 (25.6)
	SGD 6000 +	45 (22.6)
	Missing	18
Maternal depressive symptoms, mean (SD)		6.4 (7.7)
Age at MRI measurement, mean (SD)	Wave 1	4.6 (0.09)
	Wave 2	6.0 (0.12)
	Wave 3	7.5 (0.14)
	Wave 4	10.7 (0.18)
Number of usable scans, N (%)	4	43 (19.8)
	3 only	69 (31.8)
	2 only	105 (48.4)

2.2. Maternal depressive symptoms

The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) was used to measure maternal depressive symptoms at 4.5 years postpartum, the most proximal measure to the first brain imaging. The BDI-II is a 21-item self-report questionnaire that assesses the presence and severity of depressive symptoms, using a 4-point Likert scale. The BDI-II is widely used, including in Singapore (Soe et al., 2018), where cross-cultural measurement invariance was shown (Van Doren et al., 2024). The BDI-II has been shown to predict clinical outcomes (Arnau et al., 2001). The prorated score was calculated for responses with 1 or 2 missing and standardized within the GUSTO sample.

2.3. Brain magnetic resonance imaging (MRI) data acquisition

Children underwent neuroimaging at ages 4.5, 6, 7.5, and 10.5 years using a 3.0 Tesla MRI scanner (4.5 & 6 years: Siemens Magnetom Skyra, 7.5 & 10.5 years: Siemens Magnetom Prisma) and T1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE) images were measured. We could not include the structural MRI in the neonatal period in the analyses as these images were acquired with a 1.5 Tesla scanner, no T1 image was obtained, and the infant FreeSurfer pipeline worked poorly.

The imaging protocols were as follows: repetition time = 2000 ms, echo time = 2.08 ms, inversion time = 877 ms, flip angle = 9°, acquisition matrix = 192 × 192, field of view = 192 mm × 192 mm, slices thickness = 1.0 mm, number of slices = 160 for scans at 4.5 & 6.0 years and 192 for 7.5 & 10.5 years, scanning time = 3.5 min. T1 images were preprocessed under the standard recon-all pipeline of FreeSurfer version 7.1.1. The whole brain was segmented using a Desikan-Killiany atlas in FreeSurfer and total intracranial volume and volumes of each area (cortex: 34 regions, subcortex: 7 regions, in each hemisphere) were calculated. The output was manually inspected and unusable images due to severe blurs or poor registration were excluded.

Volumetric data was further processed (details are in Text S1) by standardizing brain regional volumes at each time point to have a mean of 0 and a standard deviation of 1 in order to minimize the influence of changes in scanners. Outliers were detected and excluded if necessary. Outliers were defined as values lying outside of the population mean ± 3 SD at each time point and the difference values between adjacent time points lying outside of the population mean ± 3 SD. Missing brain volumes and covariates were imputed, and brain volumes were harmonized using the R package "longCOMBAT (Beer et al., 2020)". For the main analyses, the regional gray matter volumes of the left and right hemispheres are combined to obtain the average regional gray matter volumes. We retained only those with two or more usable repeated imaging measures for the analysis.

2.4. Covariates and missing imputation

Data including child sex, maternal ethnicity, household income, and maternal educational attainment were obtained via self-report questionnaires.

Missing covariates and outcome measures were imputed using multiple imputations by chained equations with the R package "mice" (van Buuren and Groothuis-Oudshoorn, 2010) assuming the data are missing at random (MAR). The imputation models included the exposure, outcomes, confounders (child sex, maternal ethnicity, maternal education level, household income, estimated total intracranial volume, and age at brain scans), and auxiliary variables (marital status, paternal education level, and CBCL internalizing and externalizing scale scores). Missing proportion ranged from 0 (child's sex, maternal ethnicity, age at brain scans) to 47.8 % (regional brain volumes). The outcome measures were imputed with the method "norm". This method implements the

Gibbs sampler (Kasim and Raudenbush, 1998), which can recover the intra-class correlation quite well and predict values even in situations of severe MAR, high amounts of missing data in the outcome or the predictor, and heteroscedastic errors. Predictive mean matching was applied for the other missing variables. A total of 30 datasets were obtained with a maximum of 25 iterations.

2.5. Statistical analysis

We applied linear mixed models to examine the overall associations with average regional brain volumes and the longitudinal associations with changes in regional brain volumes over time. Overall associations were obtained by regressing the regional brain volumes on maternal depressive symptom scores, child age at scans (varying by individuals; see the mean and SD in Table 1), quadratic term of age at scan (age^2),

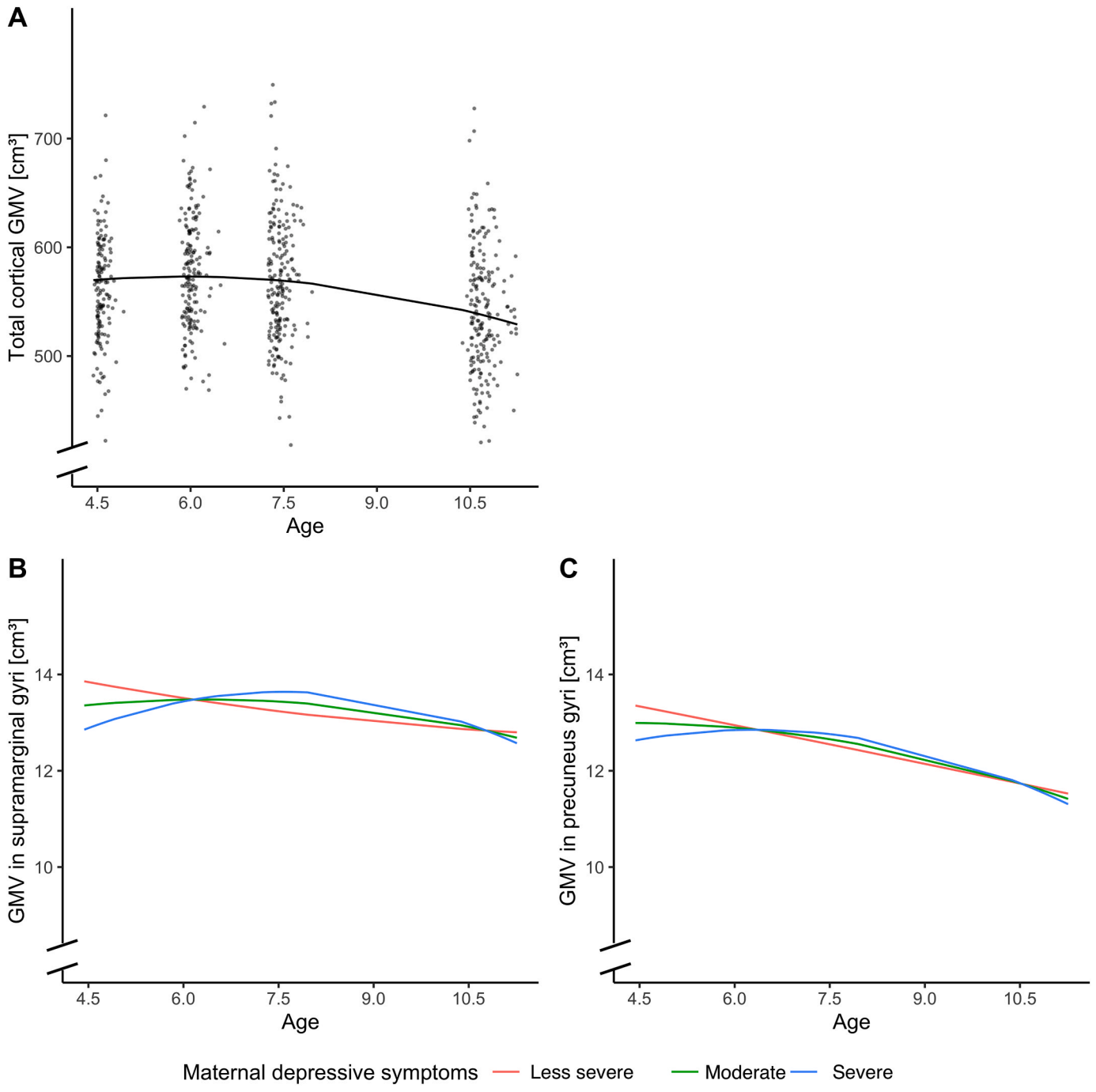


Fig. 1. Cortical volumetric trajectory by maternal depressive symptoms. The predicted cortical gray matter volumetric trajectories taken from linear mixed models with random intercept and slope for age and age^2 terms are shown. A) Total cortical gray matter volume, B) supramarginal gyrus, and C) precuneus. The coefficients for the interaction between maternal depressive symptoms and age^2 were β = -0.012, p = 0.625 for total gray matter volume, β = -0.019, $p_{adj} < 0.001$ for supramarginal gyrus volume, and β = -0.016, $p_{adj} = 0.007$ for precuneus volume. To increase the interpretability, we depicted the raw values of cortical volumes by converting the standardized coefficients obtained from linear mixed models. Please see the method for further explanation. The red lines indicate a −1 SD score of maternal depressive symptoms (labeled as "less severe"). The green lines indicate the mean of maternal depressive symptom score (labeled as "moderate"). The blue lines indicate a + 1 SD score of maternal depressive symptoms (labeled as "severe"). Dots indicate the observed values.

and covariates mentioned below. To consider the within-subject variability and individual non-linear developmental trajectories, random intercepts and slopes for age and age^2 were included. This was followed up with multivariate linear regression to estimate the associations between maternal depressive symptoms at 4.5 years and cortical and subcortical regional volumes at 4.5, 6, 7.5, and 10.5 years respectively. P-values were adjusted for cortical and subcortical regions separately.

As for longitudinal associations, the interaction terms between maternal depressive symptoms and age and between maternal depressive symptoms and age^2 were further incorporated in the above linear mixed models. We first examined the association of interaction between maternal depressive symptoms and age^2, and if significant, it was interpreted together with the interaction between maternal depressive symptoms and linear age. Otherwise, the linear interaction was examined alone (see note in Table 3). Associations were graphically depicted to aid the interpretations. Fig. 1 shows the raw cortical volumes calculated based on standardized estimates. We carefully considered the scanner differences across time points by standardization, harmonization, and statistical adjustment. However, as scanners and child age at assessment were correlated, changes in brain metrics over time might be an artifact of scanners; therefore, the interpretation of the figure needs some caution. With the caveat of possible effects of attrition bias, variations in maternal depressive symptoms in early childhood were not associated with brain imaging availability across time points; this makes differences in developmental trajectories related to maternal depressive symptoms interpretable. To confirm the robustness of the findings, we ran several sensitivity analyses of the significant associations between maternal depressive symptoms and the volume changes in specific brain regions. First, we included only children with three- or four-time brain imaging assessments (n = 112). Second, we included children with only one brain imaging assessment in the main analytical sample (n = 318). Third, we analyzed with unimputed data (n = 216). Fourth, we provide the unadjusted estimates (n = 216).

All the models adjusted for the following covariates: child sex, maternal ethnicity, maternal education level, household income, estimated intracranial volume, and scanner difference. Child sex and scanner differences are binary variables, and maternal ethnicity, maternal education level, and household income are categorical variables. Before being entered into the models, ages at scans were mean-centered, and depressive symptom scores were standardized with a mean of 0 and a standard deviation of 1. Our choice of quadratic models is based on the following reasons. First, our sample size does not allow the inclusion of a cubic term for age-random effects (thus, we could only test age-fixed effects) in the models. Second, we compared the polynomial models for age effects (linear fixed effect only, linear mixed effect, quadratic fixed effect only, quadratic mixed effect, and cubic fixed effect only) on cortical and subcortical gray matter volumes. Based on the likelihood ratio test, quadratic models provide the best fit across regions, with the exceptions of transverse temporal gyrus, thalamus, nucleus accumbens, and amygdala, for which linear models demonstrated the best fit. Third, given our analytical sample's age range, a quadratic model might be more appropriate to predict developmental trajectories than a cubic model (Lenroot et al., 2007; Sussman et al., 2016). Therefore, we fit the quadratic age models using the R package "lme4" (Bates et al., 2015) with restricted maximum likelihood estimation. Each analysis was repeated for 30 imputed datasets and each estimate was aggregated to produce final estimates using Rubin's rule (Rubin, 1987). P-values were adjusted (p_{adj}) using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995) considering the false discovery rate in the multiple hypothesis testing. As we combined the measures of the left and right hemispheres in the absence of a strong hypothesis regarding laterality, we considered a total of 34 tests for cortical and 7 tests for subcortical regions. In secondary analyses, we followed up with separate analyses for the left and right hemispheres. Further, acknowledging the number of hypothesis tests throughout the current study, we used a stringent cut-off of significant level $\alpha < 0.01$ (two-sided) to encourage the interpretation of the results. All analyses were conducted with R version 4.2.3 (R core Team, 2023). The R code used for the main analyses is shown in Text S2.

3. Results

3.1. Maternal depressive symptoms and child cortical and subcortical volume differences aggregated over time

First, the total gray matter volumetric trajectory from 4.5 to 10.5 years was explored to detect the population mean of age of peak gray matter volume (Fig. 1A). The peak volume was reached at age 5.79 years on average.

Next, we examined whether the gray matter volume throughout the observation period differed by maternal depressive symptoms (Table 2). Children of mothers with severe depressive symptoms had persistently smaller gray matter volumes in the precentral gyrus, which survived the multiple comparison corrections ($\beta = -0.162$ [-0.238; −0.086], $p_{adj} < 0.001$) (Fig. 2A; Table S1). Our secondary analysis confirmed that the smaller precentral gyrus volume was evident in early childhood (4.5 years: $\beta = -0.191$ [-0.327; −0.056], nominal (unadjusted) $p = 0.007$; 6 years: β = -0.193 [-0.302; −0.085], nominal $p = 0.001$). Subcortical regional gray matter volumes did not differ by maternal symptoms (Table S2).

3.2. Maternal depressive symptoms and brain volumetric change over time

The associations between maternal depressive symptoms and changes in regional gray matter volumes were analyzed including interaction terms with quadratic and linear terms of age (Table 3, Table S3). Children whose mothers reported higher levels of depressive symptoms showed different curvilinear changes in gray matter volumes in the supramarginal gyrus (quadratic: $\beta = -0.019$ [-0.027; −0.010], $p_{adj} < 0.001$; linear: $\beta = 0.150$ [0.084; 0.216], $p_{adj} < 0.001$) and in the precuneus (quadratic: $\beta = -0.016$ [-0.025; −0.007], $p_{adj} = 0.007$; linear: $\beta = 0.130$ [0.056; 0.205], $p_{adj} = 0.005$).

Trajectories of these two parietal regions (Fig. 1B & C) illustrate a very similar pattern: children of mothers with less severe depressive symptoms (depressive symptoms score < −1 SD) showed greater volumes in early childhood and followed a steeper decline. In contrast, those with more severe depressive symptoms (depressive symptoms score > +1 SD) showed more curved trajectories that reached a clear peak volume during the observational period. The interpretation of the

Table 2
Overall associations between maternal depressive symptoms and cortical and subcortical regional volumes aggregated over time.

	β 95 %CI	P-values	P_{adj}
Cortical regional volumes [SD]			
Precentral	−0.162 (−0.238; −0.086)	< 0.001	< 0.001 *
Postcentral	−0.129 (−0.216; −0.042)	0.004	0.06
Rostral middle frontal	0.102 (0.022; 0.181)	0.012	0.14
Temporal pole	0.105 (0.014; 0.196)	0.024	0.19
Frontal pole	0.099 (0.008; 0.190)	0.032	0.19
Fusiform	0.098 (0.006; 0.189)	0.036	0.19
Superior parietal	−0.092 (−0.179; −0.005)	0.039	0.19
Pericalcarine	0.113 (0.001; 0.225)	0.049	0.21
Subcortical regional volumes [SD]			
Nucleus Accumbens	0.091 (0.001; 0.180)	0.048	0.34

Models adjusted for child sex, child age, maternal ethnicity, total intracranial volume, scanner, maternal education level, and household income.
Random slope and random intercept were included.
This table only depicts the associations with nominal significance (8 associations from a total of 34 tests of cortical regions and 1 association from a total of 7 tests of subcortical regions). P-values were adjusted using the Benjamini-Hochberg method for false discovery rates.

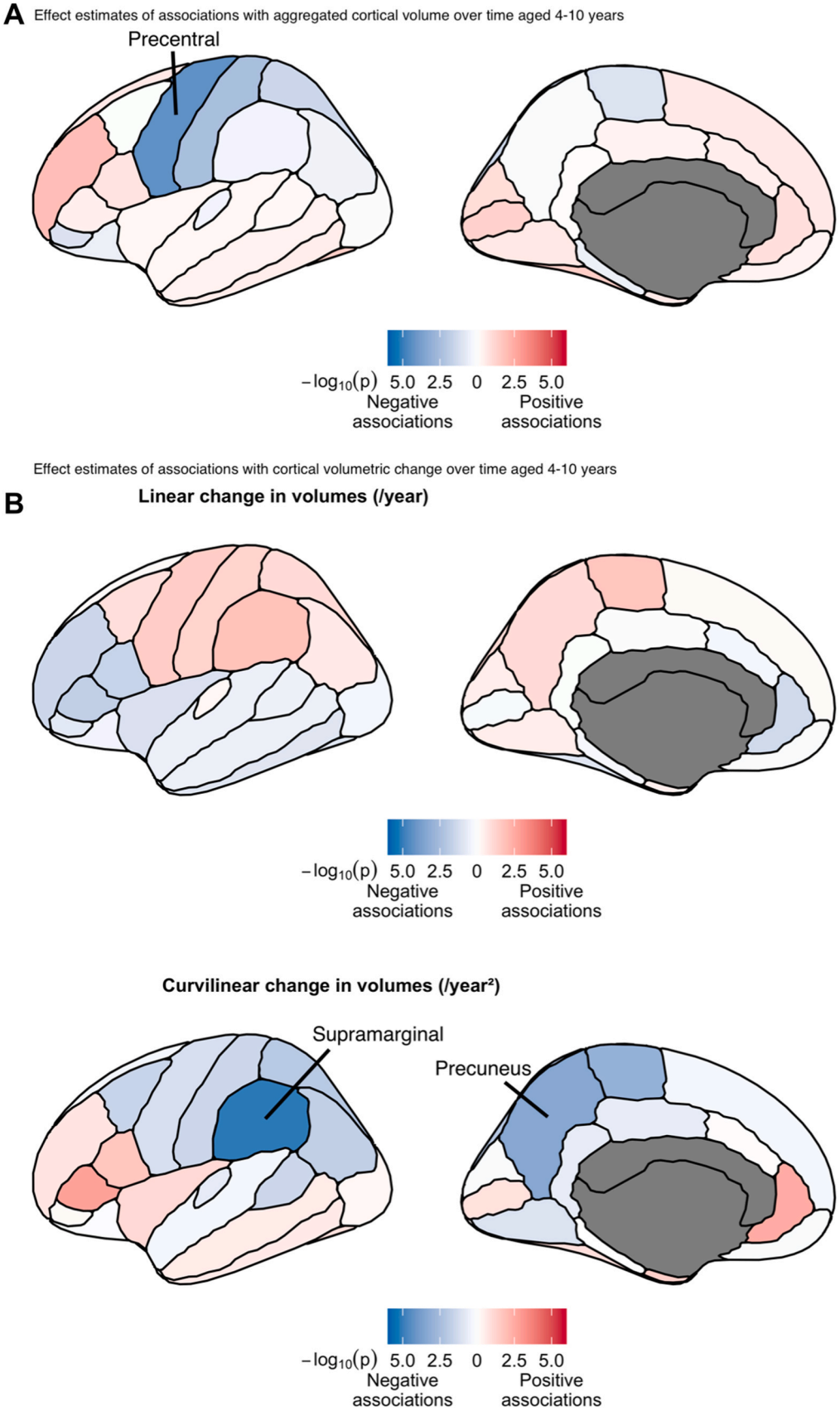


Fig. 2. Cortical regional volumetric linear and curvilinear changes by age in response to maternal depressive symptoms. The heat map on the brain shows the -$\log_{10}$(p) and directionality of the associations obtained from linear mixed models for the combined volumes. A) overall aggregated associations, B) longitudinal associations over time. The blue indicates the negative associations, and the red indicates the positive associations. The brighter colors indicate associations with smaller p-values. To interpret the p-values for lower-order linear terms, they are obtained using the orthogonal polynomials (for details, see Text S3).

Table 3
Longitudinal associations between maternal depressive symptoms and change in cortical regional volumes throughout childhood.

Exposure	Outcome: Cortical regional volumes	Change in volume by age [SD/year]			Change in volume by age^2 [SD/year^2]			
		β 95 %CI	P-values	P_{adj}	β	95 %CI	P-values	P_{adj}
Maternal depressive symptoms [SD]	Supramarginal	0.150 (0.084; 0.216)	< 0.001	< 0.001	−0.019	(−0.027; −0.010)	< 0.001	< 0.001*
	Precuneus	0.130 (0.056; 0.205)	0.001	0.005	−0.016	(−0.025; −0.007)	< 0.001	0.007*
	Paracentral	0.119 (0.054; 0.184)	< 0.001	0.003	−0.014	(−0.022; −0.006)	0.001	0.011
	Pars triangularis	−0.091 (−0.141; −0.041)	< 0.001	0.003	0.010	(0.004; 0.017)	0.002	0.015
	Rostral anterior cingulate	−0.075 (−0.121; −0.030)	0.001	0.008	0.009	(0.003; 0.015)	0.004	0.024
	Superior parietal	0.120 (0.031; 0.210)	0.009	0.042	−0.014	(−0.025; −0.003)	0.010	0.058
	Inferior parietal	0.054 (0.010; 0.099)	0.017	0.071	−0.007	(−0.012; −0.001)	0.018	0.086
	Pars opercularis	−0.075 (−0.126; −0.024)	0.004	0.024	0.008	(0.001; 0.015)	0.021	0.088
	Caudal middle frontal	0.073 (0.011; 0.134)	0.020	0.073	−0.008	(−0.016; −0.001)	0.030	0.114
	Superior temporal sulcus and its banks	0.027 (−0.008; 0.063)	0.131	0.235	−0.005	(−0.010; −0.0003)	0.038	0.115
	Postcentral	0.071 (0.011; 0.132)	0.022	0.073	−0.008	(−0.015; −0.0004)	0.039	0.115
	Entorhinal	−0.045 (−0.101; 0.010)	0.106	0.212	0.008	(0.0003; 0.015)	0.041	0.115

Models adjusted for child sex, child age, maternal ethnicity, total intracranial volume, scanner, maternal education level, and household income. Random slope and random intercept were included.
This table only depicts the associations of maternal depressive symptoms × age^2 with nominal significance (12 associations from a total of 34 tests of cortical regions). P-values were adjusted using the Benjamini-Hochberg method for false discovery rates.
None of the associations reached nominal significance when interaction with age was modeled as a linear term only.
* represents regions whose adjusted p-values for interaction terms between maternal depressive symptoms and age^2 are below 0.01, thus chosen to depict the graphs (Fig. 1).
Complete results for the above analysis and separated analysis for left and right regions are shown in Supplementary materials.

coefficients in these polynomial models is shown in Text S3. Curvilinear and linear associations with maternal symptoms are delineated on the brain map (Fig. 2B). A series of sensitivity analyses confirmed the robustness of results with similar effect sizes and direction of associations (Table S4-7).

Maternal depressive symptoms were not related to subcortical volumetric changes (Tables S8). Analyses for the left and right hemispheres separately (Table S9) showed the associations with curvilinear changes in volumes of the left pars triangularis, supramarginal, precentral, and pars opercularis. This suggested that the left hemisphere might mainly drive the associations with curvilinear changes in supramarginal gyrus volume. Further, no sex interactions survived the multiple comparison correction, indicating that associations were consistent across child sex (Tables S10 & S11).

4. Discussion

This population-based study examined the associations between childhood maternal depressive symptoms and offspring brain volumetric development from 4.5 to 10.5 years. Children whose mothers reported more depressive symptoms showed smaller precentral gyral volume throughout the observation period, suggesting that the association of maternal symptoms with a smaller precentral gyrus volume is persistent across childhood and likely arises early in life. Further, maternal depressive symptoms were associated with curvilinear changes in cortical gray matter volumes in two parietal regions, the supramarginal and precuneus gyrus, indicating delayed brain structural development among children exposed to maternal depressive symptoms.

The smaller volume in the precentral gyrus was in line with studies reporting associations of exposure to maternal depressive symptoms predominantly with frontal regions (Cattarinussi et al., 2021). While not using volume measurements, previous studies pointed to morphological differences in the precentral gyrus. Maternal depressive symptoms during pregnancy were associated with thinner precentral gyrus in 7-year-old offspring (Davis et al., 2020; Sandman et al., 2015). Children of mothers with postpartum depressive symptoms had thinner precentral gyrus in early childhood (Lebel et al., 2016). Less precentral gyrification was found in 8-year-old children exposed to maternal depressive symptoms at age 3 years (El Marroun et al., 2016). Our finding extends these studies by suggesting that maternal depressive symptoms might have a lasting impact on the frontal gray matter, specifically the precentral structure if occurring early in childhood or even prenatally. Our secondary repeated measures analyses showed the most pronounced differences in precentral gyral volumes in early childhood (4.5 and 6 years). The precentral gyrus is the primary motor cortex central to executing voluntary movement (Banker and Tadi, 2023). When integrated with other brain regions, its function extends to inhibitory control, sensorimotor integration, and language processing, of which developmental delays in response to maternal depressive symptoms were reported in the meta-analysis (Fan et al., 2024). We speculated that a reduction in cognitive, social, and emotional stimulation due to maternal depression, i.e., some degree of neglect or deprivation, hinders synaptogenesis and myelination or even triggers synaptic pruning, representing experience-dependent plasticity (McLaughlin et al., 2019; Tooley et al., 2021).

Our approach using repeated measures from early childhood to preadolescence showed different volumetric trajectories by the severity of maternal depressive symptoms in two parietal regions: supramarginal and precuneus gyrus. Associations of maternal depressive symptoms with offspring supramarginal and precuneus structural and functional differences have been shown in previous studies. Prenatal maternal

depressive symptoms were associated with thinner supramarginal cortex in offspring at age 7 years (Sandman et al., 2015). In another study, children exposed to severe postpartum maternal depressive symptoms showed lower amygdala functional connectivity with the parietal region including supramarginal and precuneus gyrus at age 5 (Donnici et al., 2021). Maternal anxiety symptoms during pregnancy, which are often comorbid with depressive symptoms, were associated with a smaller precuneus volume at 4 years old (Acosta et al., 2019). Our finding extends this previous literature by demonstrating possible delayed development characterized by differences in the shape of trajectory and a possible late peak age in children exposed to more severe maternal symptoms. An interesting difference in trajectories highlighted a faster decline in regional brain volumes among children exposed to more maternal symptoms compared to a protracted decrease in those exposed to no or less severe maternal symptoms. We speculated that this steeper decline leads to smaller volumes in later childhood/adolescence, increasing the risk of internalizing and externalizing problems among the offspring of mothers with depression (Durham et al., 2021; Goodman et al., 2011). However, we could not find an association between delayed brain developmental trajectories and internalizing and externalizing problems at age 10.5 years in our sample. Possibly, our sample size is too small or any effects of maternal depression on offspring's behavioral problems mediated by brain morphological changes become evident only later. Further, the volumes among children exposed to no or less severe maternal symptoms continued to decline with no peak in the observation period. Given that gray matter regional volumes follow expansion-to-contraction trajectories peaking between ages 2–10 years (Bethlehem et al., 2022), children with very limited or no exposure to maternal depressive symptoms must reach peak parietal cortical volume prior to or around age 4.5 years. To detect, future studies with earlier imaging assessments are necessary.

Two aspects warrant further discussion. First, the developmental timing of these cortical areas is notable. The gray matter of supramarginal and precuneus gyrus reaches peak volumes earlier than the overall gray matter volumetric age at peak (5.9 years) and typically follows a declining trajectory throughout mid-childhood (Bethlehem et al., 2022). Exposure to maternal depressive symptoms during early childhood delays the peak of parietal brain volumetric development possibly due to the unmet need for an attachment figure's physiological and emotional care (Roubinov et al., 2021). Exposure to maternal depression can disrupt the development of white matter due to alterations in myelination, axonal growth, or connectivity patterns, leading to impaired communication between brain regions, ultimately impacting gray matter development and maintenance (Smith and Pollak, 2020). Second, the findings may reflect brain regional functions. The supramarginal gyrus has a role in phonological processing during language and verbal working tasks and the precuneus is involved in visuospatial imagery, episodic memory retrieval, and self-processing operations. Additionally, both structures are involved in integrative associations beyond the simple sensory or motor processing. Exposure to maternal depressive symptoms might delay the development of this highly complex function. The lack of a difference in developmental changes in brain regions often implicated in individuals with depressive symptoms such as prefrontal and limbic regions is an important negative finding in this study of childhood exposure to maternal depressive symptoms. It implies that candidate ROIs derived from studies of depressed adults may be less likely to be implicated in the brain development of children exposed to an attachment figure with depressive symptoms.

We emphasized several important implications for future research. First, the periods when the brain morphological changes are significant, especially from infancy to childhood, must be included. We included brain scans from age 4.5 years, while most studies started follow-ups during preadolescence. This allows for capturing environmental impacts on the brain morphological development more sensitively. Second, whole-brain approaches with stringent multiple comparisons control are arguably preferable to hypothesis-driven approaches if the biological understanding is limited. We examined the whole brain of a total of 34 cortical and 7 subcortical regions using p-values adjusted for false discovery rate and a stringent statistical significance threshold, while the previous research predominantly used an ROI approach. An ROI approach based on clinical findings of depressed persons may poorly guide child studies of exposure to a caregiver with depression. Third, brain structures should be repeatedly measured, and appropriate models should be applied to account for within-person effects and non-linear trajectories. We applied linear mixed modeling, including quadratic age terms, to data comprising four repeated brain imaging measures. Focusing on within-person effects rather than group differences allows the modeling of individual developmental trajectories and mitigates the impact of time-invariant confounders such as genetic factors. Fourth, future research should include ethnically diverse populations. Our target sample is multi-ethnic Asian children in Singapore, while so far, most imaging studies have been conducted in populations of European descent. Our approach makes it difficult to situate our findings in the context of previous research. The study design differences could provide some explanations for our findings partially inconsistent with prior literature, especially the lack of evidence of subcortical regions.

The present study had some limitations. First, maternal depressive symptoms were self-reported. Although most previous observational studies utilized self-report questionnaires and their clinical relevance was established, measurement error due to negative attentional bias is likely in persons with depressive symptoms. Second, we included 2–4 repeated brain measures, but the total sample size was modest. To make the most of the available data, we employed outcome imputation in children with 2–3 imaging assessments. Third, we acknowledge the potential residual confounding by social and genetic factors. Particularly, social and genetic factors contribute to intergenerational transmission of neurocognitive effects; therefore, the observed associations are not deterministic.

Confounding is a fundamental problem in every observational study, and our study of maternal depressive symptoms is not exempt from this potential bias. However, our approach to focus on within-individual changes mitigates the impact of time-invariant confounders such as genetic factors. In contrast, time-varying social and environmental background factors could confound the associations, such as factors related to fathers' behavior and characteristics of external caregivers, which were not assessed in the present study. Several (quasi-)experimental designs, such as clinical trials (Weissman et al., 2015) or twin studies (Hannigan et al., 2018), may help disentangle confounding and causal associations and can be incorporated into future studies. However, in studies of depressive symptoms, background risk factors such as poverty are not only confounders of associations with child outcomes but are also possible effect modifiers or mediators. Therefore, future child brain imaging studies should consider this complex relationship of maternal depression with environmental variables, clarifying their temporality and assessing possible effect heterogeneity and mediation paths.

In conclusion, children exposed to more severe maternal depressive symptoms in early childhood had persistently smaller precentral gyral volumes from early childhood to preadolescence. Further, children exposed to mothers with severe depressive symptoms showed differential gray matter volumetric trajectories in two parietal regions, the supramarginal and precuneus gyrus, suggesting a region-specific delay in brain structural development from early childhood to preadolescence. Although the associations are not deterministic given the possibility of residual confounding and individual-level variabilities in susceptibility, this novel finding shows that exposure to an attachment figure with depressive symptoms is associated with delayed development of brain regions involved in processing and integrating complex sensory information rather than with developmental differences in regions involved in emotional regulation that were implicated in experiencing depression. To better understand the associations between maternal depressive

symptoms and child brain development, we emphasize the importance of multiple brain imaging starting from early childhood and suggest a focus on within-subject variability.

CRediT authorship contribution statement

Sadikova Ekaterina: Writing – review & editing, Methodology. **Setoh Peipei:** Writing – review & editing. **Broekman Birit:** Writing – review & editing, Project administration. **Zhou Juan Helen:** Writing – review & editing, Project administration. **Gluckman Peter:** Writing – review & editing, Project administration. **Chen Helen:** Writing – review & editing, Project administration. **Tiemeier Henning:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Koyama Yuna:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Tan Ai Peng:** Writing – review & editing, Project administration, Methodology, Data curation.

Declaration of Competing Interest

There is no financial disclosure or conflict of interest to declare.

Acknowledgments

The GUSTO research program was established through grants NMRC/TCR/004-NUS/2008 and NMRC/TCR/012-NUHS/2014 from the Singapore National Research Foundation under the Translational and Clinical Research Flagship and grant OFLCG/MOH-000504 from the Open Fund Large Collaborative Grant Programs and administered by the Singapore Ministry of Health's National Medical Research Council, Singapore. Current funding is provided by the Singapore Institute for Clinical Sciences and the Brain-Body Initiative Strategic Research Program, Agency for Science Technology and Research, Singapore. YK is supported by funding from the JSPS Overseas Research Fellowship. APT is supported by funding from the NMRC Transition Award (MOH-001273–00). ES is supported by funding from the National Institutes of Health's Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant Number T32 HD104612). PS is supported by funding from Yong Lin School of Medicine, National University of Singapore, NUHSRO/2021/093/NUSMed/13/LOA, and Singapore Ministry of Education Academic Research Fund Tier 1 RG39/22. The relevant work was presented at the 2024 SER conference.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2025.101531.

Data availability

The authors do not have permission to share data.

References

Acosta, H., Tuulari, J.J., Scheinin, N.M., Hashempour, N., Rajasilta, O., Lavonius, T.I., Pelto, J., Saunavaara, V., Parkkola, R., Lähdesmäki, T., Karlsson, L., Karlsson, H., 2019. Maternal pregnancy-related anxiety is associated with sexually dimorphic alterations in amygdala volume in 4-year-old children. Front. Behav. Neurosci. 13, 175.

Arnau, R.C., Meagher, M.W., Norris, M.P., Bramson, R., 2001. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychol. 20, 112–119.

Banker, L., Tadi, P., 2023. Neuroanatomy, Precentral Gyrus. StatPearls Publishing.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models Usinglme4. J. Stat. Softw. 67. https://doi.org/10.18637/jss.v067.i01.

Beck, A.T., Steer, R.A., Brown, G., 1996. Beck depression inventory–II. Psychol. Assess. https://doi.org/10.1037/t00742-000.

Beer, J.C., Tustison, N.J., Cook, P.A., Davatzikos, C., Sheline, Y.I., Shinohara, R.T., Linn, K.A., Alzheimer's Disease Neuroimaging Initiative, 2020. Longitudinal ComBat: a method for harmonizing longitudinal multi-scanner imaging data. Neuroimage 220, 117129.

Belle, D., Doucet, J., 2003. Poverty, inequality, and discrimination as sources of depression among U.s. women. Psychol. Women Q. 27, 101–113.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B Stat. Methodol. 57, 289–300.

Berry, D., Willoughby, M.T., 2017. On the practical interpretability of cross-lagged panel models: rethinking a developmental workhorse. Child Dev. 88, 1186–1206.

Bethlehem, R.A.I., Seidlitz, J., White, S.R., Vogel, J.W., Anderson, K.M., Adamson, C., Adler, S., Alexopoulos, G.S., Anagnostou, E., Areces-Gonzalez, A., Astle, D.E., Auyeung, B., Ayub, M., Bae, J., Ball, G., Baron-Cohen, S., Beare, R., Bedford, S.A., Benegal, V., Beyer, F., Blangero, J., Blesa Cábez, M., Boardman, J.P., Borzage, M., Bosch-Bayard, J.F., Bourke, N., Calhoun, V.D., Chakravarty, M.M., Chen, C., Chertavian, C., Chetelat, G., Chong, Y.S., Cole, J.H., Corvin, A., Costantino, M., Courchesne, E., Crivello, F., Cropley, V.L., Crosbie, J., Crossley, N., Delarue, M., Delorme, R., Desrivieres, S., Devenyi, G.A., Di Biase, M.A., Dolan, R., Donald, K.A., Donohoe, G., Dunlop, K., Edwards, A.D., Elison, J.T., Ellis, C.T., Elman, J.A., Eyler, L., Fair, D.A., Feczko, E., Fletcher, P.C., Fonagy, P., Franz, C.E., Galan-Garcia, L., Gholipour, A., Giedd, J., Gilmore, J.H., Glahn, D.C., Goodyer, I.M., Grant, P.E., Groenewold, N.A., Gunning, F.M., Gur, R.E., Gur, R.C., Hammill, C.F., Hansson, O., Hedden, T., Heinz, A., Henson, R.N., Heuer, K., Hoare, J., Holla, B., Holmes, A.J., Holt, R., Huang, H., Im, K., Ipser, J., Jack, C.R., Jr, Jackowski, A.P., Jia, T., Johnson, K.A., Jones, P.B., Jones, D.T., Kahn, R.S., Karlsson, H., Karlsson, L., Kawashima, R., Kelley, E.A., Kern, S., Kim, K.W., Kitzbichler, M.G., Kremen, W.S., Lalonde, F., Landeau, B., Lee, S., Lerch, J., Lewis, J.D., Li, J., Liao, W., Liston, C., Lombardo, M.V., Lv, J., Lynch, C., Mallard, T.T., Marcelis, M., Markello, R.D., Mathias, S.R., Mazoyer, B., McGuire, P., Meaney, M.J., Mechelli, A., Medic, N., Misic, B., Morgan, S.E., Mothersill, D., Nigg, J., Ong, M.Q.W., Ortinau, C., Ossenkoppele, R., Ouyang, M., Palaniyappan, L., Paly, L., Pan, P.M., Pantelis, C., Park, M.M., Paus, T., Pausova, Z., Paz-Linares, D., Pichet Binette, A., Pierce, K., Qian, X., Qiu, J., Qiu, A., Raznahan, A., Rittman, T., Rodrigue, A., Rollins, C.K., Romero-Garcia, R., Ronan, L., Rosenberg, M.D., Rowitch, D.H., Salum, G.A., Satterthwaite, T.D., Schaare, H.L., Schachar, R.J., Schultz, A.P., Schumann, G., Schöll, M., Sharp, D., Shinohara, R.T., Skoog, I., Smyser, C.D., Sperling, R.A., Stein, D.J., Stolicyn, A., Suckling, J., Sullivan, G., Taki, Y., Thyreau, B., Toro, R., Traut, N., Tsvetanov, K.A., Turk-Browne, N.B., Tuulari, J.J., Tzourio, C., Vachon-Presseau, É., Valdes-Sosa, M.J., Valdes-Sosa, P.A., Valk, S.L., van Amelsvoort, T., Vandekar, S.N., Vasung, L., Victoria, L.W., Villeneuve, S., Villringer, A., Vértes, P.E., Wagstyl, K., Wang, Y.S., Warfield, S.K., Warrier, V., Westman, E., Westwater, M.L., Whalley, H.C., Witte, A.V., Yang, N., Yeo, B., Yun, H., Zalesky, A., Zar, H.J., Zettergren, A., Zhou, J.H., Ziauddeen, H., Zugman, A., Zuo, X.N., Bullmore, E.T., Alexander-Bloch, A.F., 2022. Brain charts for the human lifespan. Nature 604, 525–533.

Brummelte, S., Galea, L.A.M., 2016. Postpartum depression: etiology, treatment and consequences for maternal care. Horm. Behav. 77, 153–166.

van Buuren, S., Groothuis-Oudshoorn, K., 2010. mice: multivariate imputation by chained equations in R. J. Stat. Softw. 1–68.

Cattarinussi, G., Aarabi, M.H., Sanjari Moghaddam, H., Homayoun, M., Ashrafi, M., Soltanian-Zadeh, H., Sambataro, F., 2021. Effect of parental depressive symptoms on offspring's brain structure and function: a systematic review of neuroimaging studies. Neurosci. Biobehav. Rev. 131, 451–465.

Cummings, E.M., Keller, P.S., Davies, P.T., 2005. Towards a family process model of maternal and paternal depressive symptoms: exploring multiple relations with child and family functioning. J. Child Psychol. Psychiatry 46, 479–489.

Davis, E.P., Hankin, B.L., Glynn, L.M., Head, K., Kim, D.J., Sandman, C.A., 2020. Prenatal maternal stress, child cortical thickness, and adolescent depressive symptoms. Child Dev. 91, e432–e450.

Di Biase, M.A., Tian, Y.E., Bethlehem, R.A.I., Seidlitz, J., Alexander-Bloch, A.F., Yeo, B.T. T., Zalesky, A., 2023. Mapping human brain charts cross-sectionally and longitudinally. Proc. Natl. Acad. Sci. USA 120, e2216798120.

Donnici, C., Long, X., Dewey, D., Letourneau, N., Landman, B., Huo, Y., Lebel, C., 2021. Prenatal and postnatal maternal anxiety and amygdala structure and function in young children. Sci. Rep. 11, 4019.

Donnici, C., Long, X., Reynolds, J., Giesbrecht, G.F., Dewey, D., Letourneau, N., Huo, Y., Landman, B., Lebel, C., 2023. Prenatal depressive symptoms and childhood development of brain limbic and default mode network structure. Hum. Brain Mapp. 44, 2380–2394.

Durham, E.L., Jeong, H.J., Moore, T.M., Dupont, R.M., Cardenas-Iniguez, C., Cui, Z., Stone, F.E., Berman, M.G., Lahey, B.B., Kaczkurkin, A.N., 2021. Association of gray matter volumes with general and specific dimensions of psychopathology in children. Neuropsychopharmacology 46, 1333–1339.

El Marroun, H., Tiemeier, H., Muetzel, R.L., Thijssen, S., van der Knaap, N.J.F., Jaddoe, V.W.V., Fernández, G., Verhulst, F.C., White, T.J.H., 2016. Prenatal exposure to maternal and paternal depressive symptoms and brain morphology: a population-based prospective neuroimaging study in young children. Depress Anxiety 33, 658–666.

Ertel, K.A., Rich-Edwards, J.W., Koenen, K.C., 2011. Maternal depression in the United States: nationally representative rates and risks. J. Women's. Health 20, 1609–1617.

Fan, X., Wu, N., Tu, Y., Zang, T., Bai, J., Peng, G., Liu, Y., 2024. Perinatal depression and infant and toddler neurodevelopment: a systematic review and meta-analysis. Neurosci. Biobehav. Rev., 105579

Goodman, S.H., Rouse, M.H., Connell, A.M., Broth, M.R., Hall, C.M., Heyward, D., 2011. Maternal depression and child psychopathology: a meta-analytic review. Clin. Child Fam. Psychol. Rev. 14, 1–27.

Guma, E., Andrýsková, L., Brázdil, M., Chakravarty, M.M., Marečková, K., 2023. Perinatal maternal mental health and amygdala morphology in young adulthood. Prog. Neuropsychopharmacol. Biol. Psychiatry 122, 110676.

Halbreich, U., Karkun, S., 2006. Cross-cultural and social diversity of prevalence of postpartum depression and depressive symptoms. J. Affect. Disord. 91, 97–111.
Hannigan, L.J., Eilertsen, E.M., Gjerde, L.C., Reichborn-Kjennerud, T., Eley, T.C., Rijsdijk, F.V., Ystrom, E., McAdams, T.A., 2018. Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: genetic analyses in the Norwegian Mother and Child Birth Cohort Study. Lancet Psychiatry 5, 808–815.
Kasim, R.M., Raudenbush, S.W., 1998. Application of Gibbs sampling to nested variance components models with heterogeneous within-group variance. J. Educ. Behav. Stat. 23, 93–116.
Koc, D., Tiemeier, H., Stricker, B.H., Muetzel, R.L., Hillegers, M., El Marroun, H., 2023. Prenatal antidepressant exposure and offspring brain morphologic trajectory. JAMA Psychiatry.
Lebel, C., Walton, M., Letourneau, N., Giesbrecht, G.F., Kaplan, B.J., Dewey, D., 2016. Prepartum and postpartum maternal depressive symptoms are related to children's brain structure in preschool. Biol. Psychiatry 80, 859–868.
Lenroot, R.K., Gogtay, N., Greenstein, D.K., Wells, E.M., Wallace, G.L., Clasen, L.S., Blumenthal, J.D., Lerch, J., Zijdenbos, A.P., Evans, A.C., Thompson, P.M., Giedd, J. N., 2007. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36, 1065–1073.
Lovejoy, M.C., Graczyk, P.A., O'Hare, E., Neuman, G., 2000. Maternal depression and parenting behavior. Clin. Psychol. Rev. 20, 561–592.
McLaughlin, K.A., Weissman, D., Bitrán, D., 2019. Childhood adversity and neural development: a systematic review. Annu. Rev. Dev. Psychol. 1, 277–312.
Pellowski, J.A., Wedderburn, C.J., Groenewold, N.A., Roos, A., Subramoney, S., Hoffman, N., Fouche, J.-P., Joshi, S.H., Woods, R.P., Narr, K.L., Zar, H.J., Donald, K. A., Stein, D.J., 2023. Maternal perinatal depression and child brain structure at 2-3 years in a South African birth cohort study. Transl. Psychiatry 13, 96.
Pineros-Leano, M., Saran, I., Parchment, T.M., Grafft, N., 2021. Prevalence and predictors of parental depressive episodes: results from a 15-year longitudinal study. J. Affect. Disord. 295, 255–263.
R core Team, 2023. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.
Rakesh, D., Whittle, S., Sheridan, M.A., McLaughlin, K.A., 2023. Childhood socioeconomic status and the pace of structural neurodevelopment: accelerated, delayed, or simply different? Trends Cogn. Sci. 27, 833–851.
Roubinov, D., Meaney, M.J., Boyce, W.T., 2021. Change of pace: how developmental tempo varies to accommodate failed provision of early needs. Neurosci. Biobehav. Rev. 131, 120–134.
Rubin, D.B., 1987. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons.
Sandman, C.A., Buss, C., Head, K., Davis, E.P., 2015. Fetal exposure to maternal depressive symptoms is associated with cortical thickness in late childhood. Biol. Psychiatry 77, 324–334.
Scheiber, F.A., Ryckman, K.K., Demir-Lira, Ö.E., 2022. Maternal depressive symptoms and maternal child-directed speech: a systematic review. J. Affect. Disord. 297, 194–207.
Shonkoff, J.P., Phillips, D.A. (Eds.), 2000. From Neurons to Neighborhoods: The Science of Early Childhood Development.
Smith, K.E., Pollak, S.D., 2020. Early life stress and development: potential mechanisms for adverse outcomes. J. Neurodev. Disord. 12, 34.
Soe, N.N., Wen, D.J., Poh, J.S., Chong, Y.-S., Broekman, B.F., Chen, H., Shek, L.P., Tan, K. H., Gluckman, P.D., Fortier, M.V., Meaney, M.J., Qiu, A., 2018. Perinatal maternal depressive symptoms alter amygdala functional connectivity in girls. Hum. Brain Mapp. 39, 680–690.
Soh, S.-E., Tint, M.T., Gluckman, P.D., Godfrey, K.M., Rifkin-Graboi, A., Chan, Y.H., Stünkel, W., Holbrook, J.D., Kwek, K., Chong, Y.-S., Saw, S.M., 2014. Cohort profile: growing up in singapore towards healthy outcomes (GUSTO) birth cohort study. Int. J. Epidemiol. 43, 1401–1409.
Sussman, D., Leung, R.C., Chakravarty, M.M., Lerch, J.P., Taylor, M.J., 2016. The developing human brain: age-related changes in cortical, subcortical, and cerebellar anatomy. Brain Behav. 6, e00457.
Tooley, U.A., Bassett, D.S., Mackey, A.P., 2021. Environmental influences on the pace of brain development. Nat. Rev. Neurosci. 22, 372–384.
Van Doren, N., Zainal, N.H., Hong, R.Y., Newman, M.G., 2024. Examining cross-cultural invariance of common mental disorder symptom measures in the United States and Singapore. Cogn. Ther. Res. https://doi.org/10.1007/s10608-024-10519-4.
Vandermeer, M.R.J., Liu, P., Mohamed Ali, O., Daoust, A.R., Joanisse, M.F., Barch, D.M., Hayden, E.P., 2020. Orbitofrontal cortex grey matter volume is related to children's depressive symptoms. NeuroImage Clin. 28, 102395.
Vidal-Pineiro, D., Wang, Y., Krogsrud, S.K., Amlien, I.K., Baaré, W.F.C., Bartres-Faz, D., Bertram, L., Brandmaier, A.M., Drevon, C.A., Düzel, S., Ebmeier, K., Henson, R.N., Junqué, C., Kievit, R.A., Kühn, S., Leonardsen, E., Lindenberger, U., Madsen, K.S., Magnussen, F., Mowinckel, A.M., Nyberg, L., Roe, J.M., Segura, B., Smith, S.M., Sørensen, Ø., Suri, S., Westerhausen, R., Zalesky, A., Zsoldos, E., Walhovd, K.B., Fjell, A., 2021. Individual variations in "brain age" relate to early-life factors more than to longitudinal brain change. Elife 10. https://doi.org/10.7554/eLife.69995.
Weissman, M.M., Wickramaratne, P., Pilowsky, D.J., Poh, E., Batten, L.A., Hernandez, M., Flament, M.F., Stewart, J.A., McGrath, P., Blier, P., Stewart, J.W., 2015. Treatment of maternal depression in a medication clinical trial and its effect on children. Am. J. Psychiatry 172, 450–459.
Wen, D.J., Poh, J.S., Ni, S.N., Chong, Y.-S., Chen, H., Kwek, K., Shek, L.P., Gluckman, P. D., Fortier, M.V., Meaney, M.J., Qiu, A., 2017. Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. Transl. Psychiatry 7, e1103.
Zou, R., Tiemeier, H., van der Ende, J., Verhulst, F.C., Muetzel, R.L., White, T., Hillegers, M., El Marroun, H., 2019. Exposure to maternal depressive symptoms in fetal life or childhood and offspring brain development: a population-based imaging study. Am. J. Psychiatry 176, 702–710.