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Full-length Article

Sex-specific associations between maternal prenatal inflammation and offspring cortical morphology in youth: A harmonised study across four birth cohorts

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ABSTRACT

Maternal immune activation (MIA) during pregnancy is implicated in offspring psychiatric disorders. However, it is unknown to what extent MIA affects neurodevelopment, particularly cerebrocortical anatomy, in the general population, and whether effects differ by sex. The current study used vertex-wise statistics to examine the association between maternal prenatal CRP, an archetypal systemic inflammatory marker, and offspring cortical thickness, surface area, and volume, in 2635 mother–child dyads (5.4–26.5 years) from three population-based cohorts, and one clinical cohort enriched for presence of inflammation markers.

Maternal CRP within a normal physiological range (<10 mg/L) exhibited sex-specific quadratic associations with cortical morphological measures in 2 regions in males and 1 region in females at childhood. Elevated (>10 mg/L) CRP was associated with regional cortical morphology in females and in a pooled sample of sexes. Overall,

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MIA is associated with cortical development in a regional and sex-specific manner in studies spanning childhood to adulthood.

1. Introduction

The developmental trajectory of the human brain is highly susceptible to perturbation by various environmental factors (Han et al., 2021; Estes and McAllister, 2016). Maternal immune activation (MIA), the chronic overstimulation of the maternal immune system during pregnancy, has been extensively studied in relation to offspring neurodevelopment and the risk of neurodevelopmental disorders (Brown and Meyer, 2018; Jain et al., 2021; Khandaker et al., 2013; Knuesel et al., 2014). Epidemiological studies have provided converging evidence of MIA increasing the risk of autism spectrum disorder (ASD) and schizophrenia in the offspring (Babulas et al., 2006; Brown et al., 2004; Sørensen et al., 2009). Outcomes associated with MIA are not limited to psychiatric disorders, as children exposed to MIA are more likely to suffer from neurological morbidities and show lower academic performance (Jain et al., 2021; Ramsay et al., 2020). Neurodevelopmental outcomes in the offspring have been linked to maternal pro-inflammatory markers related to high BMI, cigarette smoking, and psychological stress (Bennett et al., 2018; Davies et al., 2020; Hertz-Picciotto et al., 2022; Wang et al., 2016) but also more direct measures of inflammation like C-reactive protein (CRP) (Brown et al., 2014; Canetta et al., 2014; Chudal et al., 2017; Zerbo et al., 2016).

CRP is an acute phase protein secreted in high concentrations by the liver in response to pathogen-non-specific increase in circulating IL-6, with various immune functions including cytokine stimulation and activation of the complement system. It is routinely measured for its diagnostic utility in infectious and other inflammatory diseases and is therefore a useful broad marker of MIA (Ansar and Ghosh, 2013). Animal models of MIA suggest that the brain structural and behavioural alterations in exposed offspring are caused not by the infectious agents themselves, but by maternal immune mechanisms (Shi et al., 2005; Smith et al., 2007; Wu et al., 2017). The levels of inflammatory markers in maternal blood are reflected in foetal circulation, but also in different foetal brain regions, specific to postnatal developmental stage (Garay et al., 2013), where they have been shown to critically contribute to neuron proliferation, differentiation, and axonal and synaptic growth (Boulanger, 2009; Deverman and Patterson, 2009). Non-human primate studies indicate that exposure to MIA alters postnatal brain development, resulting in reduced cortical volume (Vlasova et al., 2021) and altered amygdala growth (Ramirez et al., 2020).

Few human neuroimaging studies have elucidated the neuroanatomical correlates of MIA in offspring. Only one prior large-scale study (n = 2053) has investigated the effect of maternal CRP on brain morphology; Suleri et al. (2022) reported an association between gestational maternal CRP and offspring smaller total cerebellar volume and reported differences in total brain volume in female offspring mediated by gestational age at birth (Suleri et al., 2022). Previous functional and structural studies, mostly conducted in neonates and infants, suggest that higher gestational CRP is associated with alterations in salience network connectivity (Spann et al., 2018). Gestational IL-6 is associated with larger amygdala volume and connectivity (Graham et al., 2018), altered resting state functional connectivity (Rudolph et al., 2018), and less frontolimbic white matter integrity in offspring (Rasmussen et al., 2019). Most earlier studies, however, included only some tens of subjects and focused on restricted *a priori* or total brain measures, leaving regional cerebral morphology across development unexplored. This is a particularly pertinent gap in our knowledge because cortical regions are formed prenatally when most neurogenesis and neuronal migration are completed, making cortical development especially susceptible to *in utero* environmental influences (Gilmore et al., 2018).

While whole-brain mean cortical measures develop according to similar trajectories in males and females (Bethlehem et al., 2022), there are substantial *regional* sex differences in the development of cortical thickness, surface area, and volume. In some areas of the cortex, these parameters follow not just different rates, but entirely different patterns of change between males and females (Gennatas et al., 2017; Sotiras et al., 2017; Sowell et al., 2007). Sex is known to influence foetal sensitivity to prenatal stressors including MIA. Maternal inflammation has been suggested to exert sex-specific effects on the risk of psychosis or depression, and brain function, in adult offspring (Gilman et al., 2016; Goldstein et al., 2014, 2021; Hunter et al., 2021). Whether MIA has sex-specific effects on the development of cortical morphology remains a key outstanding question.

In the current study, we sought to examine whether MIA is a predictor of cortical morphology in non-clinical populations of young individuals at different ages. To this end, we used gestational CRP as a marker of MIA, and performed surface-based vertex-wise analyses to assess its relationship with cortical thickness, surface area, and volume separately in male and female offspring. We used three independent birth cohorts with neuroimaging performed at three different ages spanning early childhood to young adulthood (ages five to twenty-six years). We also tested the generalizability of the findings in a clinical cohort of children. Harmonised independent analyses in each cohort allowed us to test whether MIA is associated with cortical alterations in a specific sample and age range, and in a across-age *meta*-analysis of non-clinical samples. All analyses were stratified by sex to test the hypothesis that maternal CRP exerts sex-specific effects on the offspring cortex at different ages.

2. Materials and methods

2.1. Birth cohorts

The present study consists of participants from three independent European birth cohorts (FinnBrain, Finland; Generation R, the Netherlands; and Northern Finland Birth Cohort 1986, Finland) and one clinical cohort (PREOBE, Spain). All studies are approved by their local Medical Ethics Committee (FinnBrain: VARHA/18203/13.02.02/2023, Generation R: MEC 2015-749 and MEC-2007-413, NFBC1986: EETTMK:53/2011, and PREOBE: 0727-N-16 (2016), n° 888/941571464-71464-45-515, 10933 (2006)).

2.2. FinnBrain

The FinnBrain Birth Cohort Study is a prospective birth cohort, which was established in Turku, Finland, in 2011. A total of N = 3837 children and their parents were recruited in 2011–2015 in the area of Turku and Åland Islands, southwest Finland (Karlsson et al., 2018). At approximately 5 years of age, a number of children were contacted for a follow-up visit, including magnetic resonance imaging (MRI). Exclusion criteria have been described elsewhere (Pulli et al., 2022). A total of 173 scans progressed to image pre-processing, and of these 115 had matching maternal CRP measurements and were included in the current study.

2.3. Generation R

The Generation R Study is a prospective population-based cohort of approximately 10,000 pregnant mothers recruited from 2002 to 2006 in Rotterdam, the Netherlands (Kooijman et al., 2016). The present study consists of participants from the second wave of MRI data collection,

Table 1
Sample characteristics as means (SD) or n (%).

		Population-based cohorts			Clinical sample
		FinnBrain (n = 114)	Generation R (n = 2030)	NFBC1986 (n = 363)	PREOBE (n = 128)
Offspring variables	**Age at MRI**	5.4 (0.13)	9.9 (0.60)	26.5 (0.52)	6.41 (0.32)
	Sex n (%)				
	Male	64 (56.0)	992 (48.9)	152 (41.9)	66 (51.56)
	Female	50 (44.0)	1038 (51.1)	211 (58.1)	62 (48.44)
Maternal variables	**Maternal age**	31.0 (4.6)	30.7 (4.7) *	27.7 (5.4)	31.58 (4.40)
	Gestational week at blood draw	24.0 (0.0)	13.4 (1.9)	11.1 (3.0) *	24.09 (1.02)
	C-Reactive Protein (mg/L)	4.1 (3.1)	6.7 (11.3)	4.0 (6.0)	11.01 (8.17)
	C-Reactive Protein (<10 mg/L)	3.5 (2.4) n = 105	4.0 (2.5) n = 1684	2.5 (2.2) n = 330	5.31 (2.80) n = 63
	Maternal pre-pregnancy BMI	24.5 (4.6)	23.4 (4.1) *	22.6 (4.0) *	27.19 (4.79)
	Maternal smoking n (%)		*		
	No	107 (93.9)	1398 (76.2)	199 (54.8)	108* (84.37)
	Yes, until pregnancy was known	6 (5.2)	180 (9.8)	–	14 (10.94)
	Yes/continued smoking during pregnancy	1 (0.9)	256 (14.0)	164 (45.2)	6 (4.69)
	Maternal alcohol consumption n (%)		*	*	
	No	84 (73.7)	705 (37.2)	305 (84.0)	95* (74.22)
	Yes, until pregnancy was known	21 (18.4)	291 (15.3)	–	31 (24.22)
	Yes/continued drinking during pregnancy	9 (7.9)	901 (47.5)	53 (16.0)	2 (1.56)
	Maternal education n (%)		*		
	Basic education	27 (23.7)	40 (2.2)	125 (34.4)	15 (11.71)
	Secondary education	26 (22.8)	618 (34.6)	228 (62.8)	21* (16.40)
	Higher education	61 (53.5)	1128 (63.2)	10 (2.8)	92* (71.87)

* Variable was imputed using multiple chained equations, missingness of each variable is presented in the Supplement.

performed to children aged between 9 and 12 years (White et al., 2018). Out of the 3992 children scanned, 2030 met the inclusion criteria for the present study, having both usable FreeSurfer reconstruction and maternal serum sample of CRP. Exclusion criteria comprised incidental findings, major image artefacts, and quality of the FreeSurfer reconstruction.

2.4. NFBC1986

The Northern Finland Birth Cohort 1986 (NFBC1986) is a longitudinal birth cohort of an unselected population of 9362 mothers with an estimated date of delivery from July 1985 to June 1986 in Northern Finland. The present study leveraged a sub-sample of 471 participants who took part in a study focusing on the effects of prenatal maternal cigarette smoking. MRI was performed on participants aged between 25 and 28 years. Inclusion and exclusion criteria for the original study are described elsewhere (Lotfipour et al., 2014). From these, a total of 363 participants had overlapping usable FreeSurfer reconstruction and maternal serum CRP.

2.5. PREOBE

PREOBE is a prospective cohort examining the influence of maternal overweight and gestational diabetes on offspring. The present study consists of 331 mothers recruited between 2007 and 2012 in Granada, Spain. MRI was performed on 170 children at 6 years of age. A total of 128 participants met inclusion criteria for the present study.

3. Maternal CRP

Maternal blood was drawn at different gestational weeks in each cohort, and this is shown in Table 1. Gestational blood samples were stored at −80 °C. High sensitivity (hs)-CRP, measured in mg/L, was analysed from stored samples using immunoturbidimetric assay (Generation R), latex immunoassay with Architect Analyser (NFBC1986), turbidimetric assay with Indiko Plus analyser (FinnBrain), or Sandwich enzyme-linked immunosorbent assay with TECAN infinite 200 PRO Analyser (PREOBE). The distributions of CRP were transformed by $\log_{10}$ in each cohort.

4. Image acquisition and pre-processing

Image acquisition parameters from each study are presented in Supplementary materials, Table S1. Participants in FinnBrain, PREOBE and Generation R Study underwent a practice session to familiarise with the imaging environment due to their young age (White et al., 2018).

The image pre-processing procedure was harmonised between cohorts. Cortical surface reconstructions were performed on high resolution T1-weighted MR images using FreeSurfer analysis suite version 6.0 (Fischl, 2012). The main procedure includes motion correction, removal of non-brain tissue, and parcellation of the cortex based on the Desikan-Killiany atlas (Desikan et al., 2006). Quality control was manually performed in the Generation R and NFBC1986 and with a semi-automated protocol in FinnBrain described in detail elsewhere (Pulli et al., 2022). Unsuccessful reconstructions were excluded (Generation R) or corrected (FinnBrain, NFBC1986, PREOBE) when reasonable. Sample sizes reported in Table 1 are successfully reconstructed MR images for whom maternal CRP is available.

5. Confounders

Offspring age and sex were included in all models (except the latter in sex-stratified analyses) because these variables are strongly related to the outcome (cortical morphology) (Gennatas et al., 2017). Maternal confounders were chosen for antecedence of exposure: only those variables which could conceivably have influenced both the independent (maternal CRP), and dependent (offspring cortical morphology) variables, see Supplement. These variables are gestational week of maternal blood draw for CRP analysis; maternal pre-pregnancy BMI; maternal smoking during pregnancy (categorised as “never”, “yes, until pregnancy was identified”, or “yes and continued to smoke after identification of pregnancy”); maternal alcohol consumption during pregnancy (with the same categories as maternal smoking); maternal age; and maternal education as proxy for socioeconomic status (categorised as basic, secondary, or higher education). Maternal smoking, alcohol consumption, and education were assessed by questionnaire given to the mothers, and category definitions were harmonised across all four cohorts if applicable.

Table 2
Associations of quadratic maternal CRP (<10 mg/L) and offspring cortical measures.

	Parameter	Cohort (Age)	N of Subjects	N of Vertices	B	SE	Linear B	Linear SE	Region	Hemi
a) Males	Cortical volume	FinnBrain (5)	59	257	−3.045	0.842	1.942	0.639	Lingual	Right
	Surface area	Generation R (10)	823	721	−0.130	0.036	0.089	0.031	Superior frontal	Left
b) Females	Cortical thickness	Generation R (10)	861	397	0.259	0.067	−0.198	0.057	Paracentral, Superior frontal	Right

B = Beta coefficient, SE = Standard error, Hemi = Hemisphere.

6. Statistical analyses

All analyses were performed using R statistical software. The R package QDECR was used to examine the association between maternal CRP and offspring cortical thickness, surface area, and volume. QDECR applies vertex-wise linear regression and corrects for multiple comparisons using Monte Carlo simulations with a cluster-forming threshold of $p = 0.001$. Since the hemispheres were analysed separately, further cluster-wise Bonferroni correction was applied for a statistical significance threshold of $p = 0.025$ (Lamballais and Muetzel, 2021). All analyses were performed both pooled and sex-stratified to test our hypothesis of sex-specific patterns of cortical development (Gennatas et al., 2017).

Primary analysis included linear regression between logCRP and cortical measures. A nonlinear term $logCRP^2$ was added to test for quadratic associations. Because quadratic models are particularly sensitive to outlier effects, all clusters from these models were subjected to a post-hoc sensitivity analysis, whereby visually assessed highly influential data points were excluded and the model re-run; only clusters that passed this additional test are presented in the main body of this paper. For these models, samples were restricted to those with CRP < 10 mg/L to focus on low-grade inflammation within a normal physiological range and exclude potential confounding by infection.

A secondary analysis assessed the effects of elevated CRP. CRP was coded as a categorical variable to compare "low" (0–3 mg/L) vs. "high" (>10 mg/L) CRP, intermediate levels of CRP (3–10 mg/L) were excluded from the analysis. These cut-off points were selected based on the American Heart Association recommendations and clinical threshold for infection (Pearson et al., 2003).

Analyses were performed independently for each cohort and then meta-analysed using the R package *meta* (Balduzzi et al., 2019). Regression coefficients and standard errors from the individual vertex-wise analyses were pooled using fixed-effects meta-analysis with correction for multiple comparisons across all vertices using False Discovery Rate (FDR) with a p-value threshold of 0.05 (Estévez-López et al., 2023).

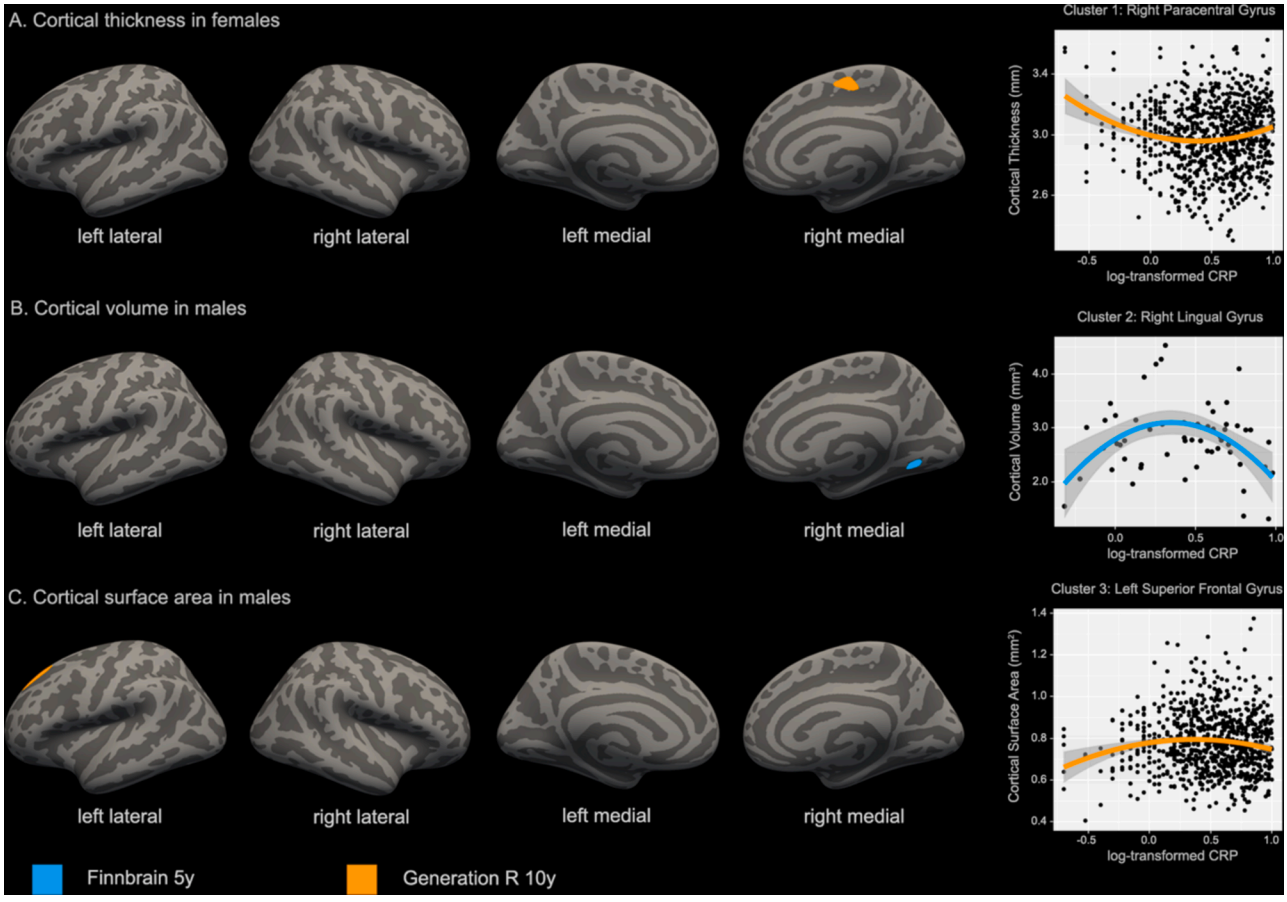

Fig. 1. Cortical clusters associated with physiological prenatal maternal CRP (<10 mg/L) in the population-based cohorts. Associations between offspring cortical morphology (cortical thickness, cortical volume, surface area) and prenatal maternal CRP (<10 mg/L) in vertex-wise quadratic regression in the population-based cohorts. The model was adjusted for participant age at MR imaging, gestational week of CRP measurement, maternal smoking, alcohol use, pre-pregnancy BMI, age, and education. CRP was measured from serum samples collected during the first or second trimester of pregnancy. Panel A represents cortical thickness in females, panel B represents cortical volume in males, and panel C represents cortical surface area in males. Colours represent different cohorts.

Table 3
Associations in categorical analysis of elevated maternal prenatal CRP (>10 mg/L) and cortical measures.

Population-based cohorts		Cohort (Age)	N of Subjects	N of Vertices	B	SE	Region	Hemi
a) Females	Cortical volume	FinnBrain (5)	34	826	0.941	0.214	Medial orbitofrontal	Left
		FinnBrain (5)	34	474	0.391	0.100	Insula, Pars triangularis, Lateral orbitofrontal	Right
		NFBC1986 (26)	151	571	−0.385	0.094	Precuneus, Superior parietal, Cuneus	Left
	Surface area	FinnBrain (5)	34	1413	0.154	0.041	Insula, Pars triangularis, Lateral orbitofrontal	Right
		NFBC1986 (26)	151	1406	−0.137	0.035	Superior parietal, Precuneus, Cuneus	Left
b) Pooled	Cortical volume	FinnBrain (5)	62	653	0.696	0.182	Medial orbitofrontal	Left
Clinical cohort		**Cohort (Age)**	**N of Subjects**	**N of Vertices**	**B**	**SE**	**Region**	**Hemi**
a) Pooled	Cortical volume	PREOBE (6)	81	989	−0.473	0.114	Superior temporal, Banks of the superior temporal sulcus	Left
	Surface area	PREOBE (6)	81	1268	−0.110	0.028	Superior temporal, Banks of the superior temporal sulcus	Left

B = Beta coefficient, SE = Standard error, Hemi = Hemisphere.

For all analyses, a minimally adjusted model included gestational week of CRP measurement, participant age, and sex as covariates. A fully adjusted model included additionally maternal cigarette smoking and alcohol use during pregnancy, pre-pregnancy BMI, age, and education (Table 1). The confounding variables were harmonised across cohorts with the exception of ethnicity in the Generation R cohort. Gestational week of CRP measurement was not adjusted for in the FinnBrain cohort, see Supplement. Missing confounding variables were imputed with chained equations using the *mice* R package (van Buuren and Groothuis-Oudshoorn, 2011) in PREOBE, Generation R, and NFBC1986 samples, Table S2. In all instances, the significant clusters reported are those from the fully-adjusted models that survived post-hoc sensitivity analysis.

To test the generalisability of our findings to a clinical sample enriched for inflammation, all analyses were independently replicated in PREOBE, a clinical cohort with high maternal BMI concomitant with highly elevated serum CRP. In this instance, the primary analysis (linear and quadratic regression) was not restricted to those with CRP < 10 mg/L as this is less than half the sample, and the purpose of this analysis was to study a high-inflammatory setting. Due to the heterogeneity between this sample and the three population-based cohorts, the results from PREOBE are presented separately and were not included in the meta-analysis.

7. Results

1. Sample characteristics

To examine the effects of maternal inflammation on offspring brain structure, we used a total of 2507 participants from three population-based cohorts: n = 114 (mean age 5.4) from FinnBrain, n = 2030 (mean age 9.9) from Generation R, and n = 363 (mean age 26.5) from NFBC1986. Additional analyses were replicated in a clinical sample of n = 128 participants (mean age 6.4) from PREOBE. Sample characteristics are presented in Table 1.

The serum samples of CRP were collected during the first trimester of pregnancy in Generation R (mean gestational week 13.4) and NFBC1986 (mean gestational week 11.1), and in the second trimester of pregnancy in the FinnBrain (mean gestational week 24.0) and PREOBE (mean gestational week 24.1) cohorts. The mean CRP was higher in the clinical sample PREOBE (mean 11.0, SD 8.2) compared to the population-based cohorts FinnBrain (mean 4.1, SD 3.1), Generation R (mean 6.7, SD 11.3), and NFBC1986 (mean 4.0, SD 6.0). Maternal pre-pregnancy BMI was higher in the clinical sample PREOBE (mean 27.2, SD 4.8) compared to FinnBrain (mean 24.5, SD 4.6), Generation R (mean 23.4, SD 4.1), and NFBC1986 (mean 22.6, SD 4.0).

2. Associations between maternal CRP and offspring cortical measures

All findings presented below are those which are statistically significant in fully-adjusted models with correction for multiple vertex testing, and in the case of quadratic models, after exclusion of highly influential data points to eliminate spurious associations, Fig. S1.

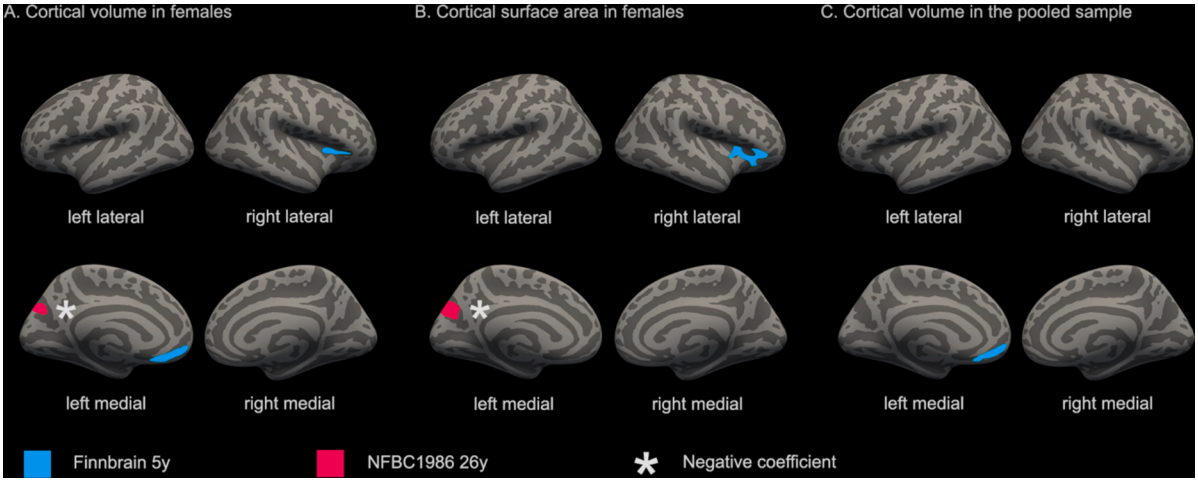

Fig. 2. Cortical clusters associated with elevated prenatal maternal CRP (>10 mg/L) in the population-based cohorts. Associations between offspring cortical morphology (cortical volume and surface area) and categorical prenatal maternal CRP (>10 mg/L compared to <3 mg/L) in the population-based cohorts. Maternal CRP was collected during the first or second trimesters of pregnancy. The model was adjusted for participant age at MR imaging, gestational week of CRP measurement, maternal smoking, alcohol use, pre-pregnancy BMI, age, and education. Panels A, B, and C represent statistically significant clusters for cortical volume in females, cortical surface area in females, and cortical volume in the pooled sample, respectively. Colours represent different cohorts. Asterisk (*) represents negative association, positive associations are not marked separately.

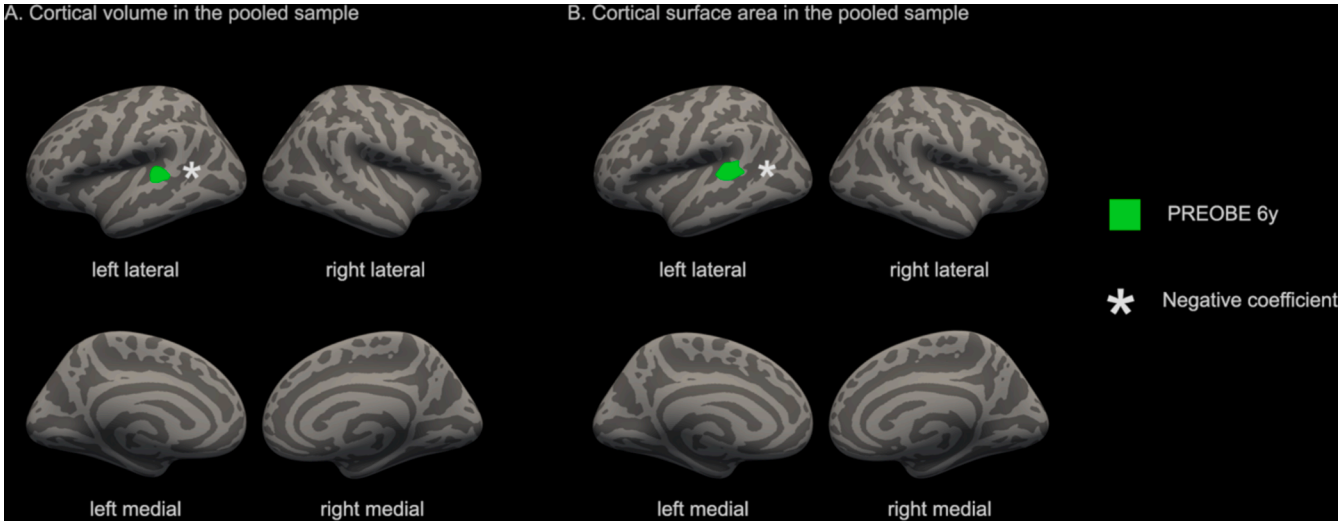

Fig.3. Cortical clusters associated with elevated prenatal maternal CRP (>10 mg/L) in the clinical cohort. Associations between offspring cortical morphology and categorical prenatal maternal CRP (>10 mg/L compared to <3 mg/L) in the clinical cohort PREOBE. Maternal CRP was collected during the second trimester (24 weeks) of pregnancy. The model was adjusted for participant age at MR imaging, gestational week of CRP measurement, maternal smoking, alcohol use, pre-pregnancy BMI, age, and education. Panel A represents cortical volume and panel B represents surface area, the shown clusters are from pooled analysis of both sexes.

There were no linear, and three quadratic associations between maternal CRP and offspring cortical morphology. In females, maternal CRP (0–10 mg/L) exhibited a U-shaped association with cortical thickness of the right paracentral and superior frontal gyrus (b = 0.259, SE = 0.067) in Generation R (10 y). In males, maternal CRP displayed an inverted U-shaped association with surface area in the left superior frontal gyrus (b = −0.130, SE = 0.036) in Generation R (10 y), and cortical volume in the right medial occipitotemporal gyrus (b = −3.045, SE = 0.843) in FinnBrain (5 y), Table 2 and Fig. 1. No significant clusters were detected when female and male participants were pooled, or in meta-analyses of all three population-based cohorts.

3. Associations between acute maternal inflammation and offspring cortical measures

In males, no associations were detected between high CRP (>10 mg/L) and cortical measures. In females, high compared to low maternal CRP (<3 mg/L) was associated with greater cortical surface area in the right frontal lobe (b = 0.154, SE = 0.041) in FinnBrain (5 y) and lower cortical surface area in the left superior parietal cortex (b = −0.137, SE = 0.035) in NFBC1986 (26 y), Table 3 and Fig. 2.

High maternal CRP was associated with greater cortical volume in the left (b = 0.941, SE = 0.214) and right frontal lobe (b = 0.391, SE = 0.100) in the FinnBrain sample (5 y); the former survived, but diminished, when adding males to the sample (b = 0.696, SE = 0.182). Finally, in females, high maternal CRP was associated with lower cortical volume of the left occipital lobe (b = −0.385, SE = 0.094) in the 26-year-old sample (NFBC1986). No associations were observed in *meta*-analysis of categorical findings across cohorts.

4. Replication in a clinical sample

Replication of all analyses was performed in a clinical sample, PREOBE, enriched for the presence of inflammation markers. In males, quadratic maternal CRP (0–10 mg/L) was associated with cortical thickness in three clusters, cortical volume in four clusters, and surface area in three clusters but no associations survived post-hoc sensitivity analysis, Table S3 and Figure S2. In the categorical analysis of the pooled sample of males and females, high maternal CRP (>10 mg/L) was associated with lower cortical volume (b = −0.473, SE = 0.114) and lower surface area in the left superior temporal cortex (b = −0.110, SE = 0.028), Table 3 and Fig. 3.

8. Discussion

The current study performed vertex-wise statistics to evaluate the relationship between MIA and cortical morphology in 2635 typically developing offspring ranging from five to twenty-eight years old in four European birth cohorts. Maternal prenatal CRP (<10 mg/L), after adjustment for numerous covariates, was observed to follow a quadratic relationship with cortical morphology in three distinct clusters of the cortex of male and female children, whereas high (>10 mg/L) vs. low (<3 mg/L) CRP predicted morphology predominantly in females.

Our study observed no linear associations between maternal CRP and offspring cortical morphology in the population-based cohorts. Maternal prenatal CRP (<10 mg/L) followed a quadratic association with cortical morphology in two distinct clusters in males and one in females. The clusters in males were localised in occipital and frontal regions, with the rest of the brain unaffected, and comprise inverted U-shaped associations with cortical volume in the right lingual gyrus (FinnBrain) and with surface area in the left superior frontal gyrus (Generation R). The one cluster in females was in the right paracentral lobule, with a U-shaped association for cortical thickness (Generation R). These findings are highly regional and may not have been detected if studying global mean cortical morphology. Meta-analysis across population-based cohorts aimed to accumulate possible common sub-threshold effects but showed no associations, indicating that all clusters are specific to that cohort/age.

Extending our analyses to a clinical context enriched for inflammation in PREOBE revealed no linear or quadratic association. (Although there were 10 clusters in males with quadratic associations, these were found to be driven by individual outliers and were therefore removed, see Supplementary material). Given that the distribution of CRP in PREOBE was not limited those below 10 mg/L, the lack of associations between maternal CRP and offspring cortical morphology in this sample provides further evidence for a quadratic relationship only within a normal physiological range of 0–10 mg/L.

The choice of CRP as the immune biomarker in this study is likely to capture multiple sources of MIA which converge on CRP regardless of the initial stimulus, including low-level infection, autoimmune sequelae, high adiposity, and other environmental factors linked to inflammation. While we did not explore cellular and molecular mechanisms, the

association between maternal CRP and cortical morphology may suggest an immune influence on the key processes governing cortical development, namely neural progenitor cell (NPC) proliferation, migration, differentiation, and survival (Budday et al., 2015). Given that CRP binds primarily to antigens expressed on pathogens and dying cells (Ansar and Ghosh, 2013), it is unlikely to exert a direct effect in this manner. Rather, it is more likely that, as a marker for overall immune activity, serum CRP represents other elements of the inflammatory milieu which do act directly. Serum CRP is highly correlated with, and chiefly regulated by, IL-6 and IL-17, which are both known to directly and potently influence neuronal development and are responsible for the brain and behavioural deficits in animal models of MIA (Choi et al., 2016; Kummer et al., 2021; März et al., 1997; Patel et al., 2007; Wu et al., 2017). IL-17 stimulates CRP production from hepatocytes, both directly by signal transduction and activation of the transcription factors NF-κB and CEBP-β (Patel et al., 2007), and indirectly through its interaction with IL-6. CRP may therefore act as a proxy for IL-6 and IL-17 levels, which act directly on neurons, although there may also be other immune molecules involved which are less well described than IL-6 or 17. CRP may even be acting directly – while this seems less likely, it cannot be ruled out, as non-canonical roles have been described for CRP in binding Fcγ receptors which are expressed in neurons and known to activate various signalling pathways including MAPK (Marnell et al., 2005; van der Kleij et al., 2010).

It is important in the current context to consider the possible mechanisms of the quadratic, but not linear, associations of MIA with cortical morphology, suggesting an "optimal" level of immune activity. Two of the primary processes which drive cortical development – NPC proliferation and differentiation into neurons – exhibit a biphasic, ∩-shaped response to various endogenous and exogenous ligands, such as in the context of lymphocyte activation, via activation of the neurogenic P13K/Akt, ERK/p38, and Wnt/β-catenin signalling pathways (Calabrese, 2005; Calabrese et al., 2022). This implies a degree of hormesis, whereby the inflammatory cytokines represented by circulating CRP could elicit a dose-dependent, bi-phasic response in NPCs. If the ∩-shaped effects of cytokines are conserved for NPC proliferation, differentiation, or migration, this would proposedly manifest as nonlinear associations between MIA and cortical thickness, volume, and surface area, such as are reported herein.

An important point of caution is that positive coefficients for a quadratic variable which is right-skewed are less robust against modest outlier or chance effects, as these can be exaggerated by squaring the data, and false positives become more likely – this is especially pertinent to smaller samples, such as FinnBrain and PREOBE, which are more sensitive to outliers. To minimise the impact of these statistical limitations, the data were centred by $\log_{10}$ transformation, α was adjusted to $p = 0.025$ to account for testing each hemisphere separately, and all significant clusters which emerged from the quadratic models were subjected to post-hoc sensitivity analysis where data was plotted and visually inspected for highly influential data points, and any findings which did not remain statistically significant after exclusion of these data points were considered spurious and removed (three in FinnBrain and ten in PREOBE). Nonetheless, these limitations cannot be disregarded when interpreting the data.

To test the distinct hypothesis that the cortex is affected by exposure to maternal CRP above 10 mg/L (which is thought to reflect an acute infection, injury, or other disease state (Ansar and Ghosh, 2013)), we performed a secondary analysis comparing subjects exposed to low (0–3 mg/L) or high (>10 mg/L) maternal CRP. High maternal CRP predicted cortical morphology in five clusters in females. The clusters were generally larger than those in quadratic models and widespread throughout the brain. These comprise two clusters for surface area (one in FinnBrain and one in NFBC1986) and three for cortical volume (two in FinnBrain and one in NFBC1986), including one cluster in the left medial orbitofrontal gyrus in FinnBrain which remained, albeit diminished, when males were pooled into the analysis. These findings may share common mechanisms with the effects of maternal viral infection during pregnancy on neuropsychiatric disorder risk in humans (Jiang et al., 2016; Kendell and Kemp, 1989; Khandaker et al., 2013), and MIA-induced brain and behavioural deficits in animal studies, which generally recapitulate a quite severe immune activation (Kreitz et al., 2020; Wu et al., 2017; Xu et al., 2021).

Perhaps the most striking aspect of our findings is their near-ubiquitous sex-specificity. When males and females are pooled, there is no association of maternal CRP (<10 mg/L) with any outcome of offspring cortical morphology in the three non-clinical cohorts. In contrast, when stratified by sex, three sex-specific clusters are observed (one in 5-year-olds, and two in 10-year-olds). High maternal CRP (>10 mg/L) is associated with morphology predominantly in females, although in this case there are also some associations within the pooled samples. Notably, while no previous study has examined the cerebral cortex in association with maternal inflammation, there is abundant evidence that MIA exerts sex-divergent effects on other aspects of brain development (Gilman et al., 2016; Goldstein et al., 2014, 2021) and our findings may provide a neuroanatomical correlate for this. At a functional level, males appear to be more sensitive to MIA, but our findings show an association with cortical morphology predominantly in females. This may represent a loss of a non-pathological association between maternal immune physiology and brain development in males, or be explained by currently unknown effects in other brain regions or tissues. Sex-divergent effects of MIA are mechanistically plausible, given substantial sex differences in placental immune physiology, with particularly strong differences in chemokine expression which could mediate sex-dependent placental responses to MIA (Braun et al., 2022). There are also considerable sex differences in steroid hormones in utero, with higher levels of circulating androgens in both male fetuses and mothers pregnant with males fetuses (Meakin et al., 2021), which is likely to attenuate or at least modulate the effects of MIA in males due the strong anti-inflammatory role of androgens (Traish et al., 2018). Some earlier studies have also reported an association of MIA with brain structure regardless of sex (Graham et al., 2018; Rasmussen et al., 2019; Suleri et al., 2022), although these studies were conducted mostly in infants and limited by small sample size, and none examined the cerebral cortex. Collectively, these data demonstrate the importance of performing sex- and gender-based analyses.

It is difficult to disentangle the contributions of subject age, sample size, and intrinsic differences between the cohorts, to the heterogeneity of the findings. All clusters from the quadratic (CRP < 10 mg/L) models are from the younger cohorts, FinnBrain and Generation R, with the implication that the brain may recover from the effects of low-level MIA by early adulthood. This is compatible with the normal developmental trajectory of human grey matter, as the rate of change in cortical morphology is more dynamic in early childhood, and decreases with age (Bethlehem et al., 2022; Gilmore et al., 2018). This is likely to be potentiated by puberty-related cortical reprogramming (Vijayakumar et al., 2021). Unlike the quadratic findings, the associations with pathologically high CRP in females are still present at 26 years old, suggesting the effects of MIA of this nature may persist into adulthood. While there are substantial differences across cohorts, it should be kept in mind that all reported findings were adjusted for important covariates including maternal pre-pregnancy BMI, age, socioeconomic status and cigarette smoking during pregnancy, which are all known to elicit strong effects in offspring development but can be managed statistically due to the cohort setting. However, given the current multicentre cross-sectional study design, it cannot be stated unequivocally that the differences between the cohorts are due strictly to age, which would require repeated measures on the same subjects.

The present study has some important strengths, namely the prospective collection of maternal blood samples to study antecedence of exposure; the use of high-resolution structural MR imaging for studying *in vivo* cerebrocortical anatomy and surface-based statistics which examine the entire cortex without relying on artificially segmented

regions of interest. This is the largest reported sample to date, from multiple prospective birth cohorts with subject ages spanning 20 years of youth, analysed using a harmonised protocol; we were also able to use a sample enriched for inflammation markers to determine whether these associations are replicated in a more clinical setting, and a *meta*-analysis corrected for false discovery rate, a method that has been used in other settings to detect cross-cohort effects (Dall'Aglio et al., 2023; Estévez-López et al., 2023), although ours is the first study to do so in the context of MIA.

Nevertheless, there are limitations to this work, particularly the statistical limitations concerning the quadratic models and lack of repeated measurements. There are differences in the gestational age at which maternal CRP is measured between some cohorts, and although age is accounted for as a confounder within each cohort, it cannot be fully controlled for in the meta-analysis which uses the vertex-wise results from each individual cohort as its basis, due to the non-overlapping ages in the study design. While all clusters reported in this study are from fully-adjusted models which have been controlled for confounding by maternal age, BMI, education, smoking, and alcohol consumption, they do not account for the potential role of maternal mental health or substance abuse, as the heterogeneity of these data between cohorts made it difficult to harmonise their use. Additionally, there are differences between the assay used to measure CRP at each site, and while data from different sites were not pooled, this adds to the heterogeneity of the cohorts and may influence whether particular samples are slightly above or below the 10 mg/L threshold, and unfortunately the current study design does not allow us to control for this. The non-specificity of CRP is both a strength and a limitation of its use in the current context. The broadness is beneficial in that it is more likely to capture different causes of immune activation which converge on CRP, and it is routinely measured in clinical practice for its relevance to infectious and inflammatory diseases (Ansar and Ghosh, 2013), offering increased feasibility of expanding or replicating the current findings in other cohorts than would be possible with a more specific immune mediator; conversely, its lack of specificity offers no insight into the biological pathways involved in these associations, which can only be speculated based on its relationship with other inflammatory cytokines, such as IL-6 (Ansar and Ghosh, 2013; Kalabalikis et al., 1999).

9. Conclusions

In the current study, we found nonlinear sex-specific associations between MIA and regional cortical morphology in developmental birth cohorts of different ages. Our findings from three non-clinical birth cohorts and one enriched for inflammation demonstrate that maternal CRP within a normal physiological range has sex-specific quadratic associations with cortical morphology, whereas exposure to high maternal CRP (>10 mg/L) is associated with cortical morphology predominantly in females, thus illustrating the sex specificity of immune-brain associations during development. Overall, these data provide a much more detailed view of the association between MIA and brain development than has previously been reported. Our findings are in line with the increased risk of neurodevelopmental and psychiatric disorders in offspring following exposure to MIA. Most of these conclusions would not be possible without the involvement of multiple cohorts, illustrating the importance of multicentre collaborations in developmental neuroscience.

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Anni Niskanen: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Aaron Barron:** Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Hatim Azaryah:** Software, Formal analysis. **Martta Kerkelä:** Writing – review & editing, Data curation. **Elmo Pulli:** Writing – review & editing, Investigation, Data curation. **Jetro J. Tuulari:** Writing – review & editing, Software, Methodology, Conceptualization. **Minna Lukkarinen:** Writing – review & editing, Investigation. **Linnea Karlsson:** Writing – review & editing, Investigation. **Ryan L. Muetzel:** Writing – review & editing, Software, Methodology, Data curation, Conceptualization. **Cristina Campoy:** Writing – review & editing, Methodology, Conceptualization. **Andrés Catena:** Writing – review & editing, Formal analysis. **Henning Tiemeier:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Golam M. Khandaker:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Hasse Karlsson:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Juha Veijola:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Lassi Björnholm:** Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.11.010.

Data availability

The data used in this study may be made available to external researchers interested in collaboration upon request on the cohort sites (FinnBrain https://sites.utu.fi/finnbrain/en/; Generation R https://generationr.nl/; NFBC1986 https://www.oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank/northern-finland-birth-cohorts). National or international data-sharing legislation may require a material transfer agreement for predefined data use. Open data sharing has been limited due to legal and ethical regulations. Requests or questions regarding data availability should be sent to the corresponding author or contacts listed on the cohort websites.

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