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Placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment at 18 months: effect modification by maternal vitamin D status

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Abstract

Background Epidemiological studies that have simultaneously explored the effects of placental and cord blood inflammatory cytokine levels on neurodevelopment in offspring, as well as the role of maternal vitamin D in these associations, are lacking. To investigate the associations of placental and cord blood inflammatory cytokine levels with neurodevelopment in 18-month-old children, and the potential modification effect by maternal vitamin D.

Methods Based on the Ma'anshan birth cohort, the current study involved 1241 mother–child pairs. The placental inflammatory cytokine mRNA expression levels, cord serum inflammatory cytokine concentrations, and maternal serum vitamin D concentrations were determined. Children's neurodevelopmental outcomes were defined as the Chinese version of the Ages and Stages Questionnaire (Third Edition) subdomain scores below the established cutoff scores. Generalized linear models were utilized to assess the effects of placental and cord serum inflammatory cytokines on neurodevelopmental outcomes and to examine the modification effects of maternal vitamin D.

Results After adjusting for confounders, each one-unit increase in placental IL-6 (OR = 1.30, 95% CI: 1.09, 1.55, $P\text{-}_{FDR} = 0.024$), IL-8 (OR = 1.25, 95% CI: 1.05, 1.49, $P\text{-}_{FDR} = 0.036$), and IFN-γ level in the cord serum (OR = 1.74, 95% CI: 1.16, 2.61, $P\text{-}_{FDR} = 0.042$) was associated with an increased risk of fine motor delay. Elevated levels of placental TNF-α (OR = 1.38, 95% CI: 1.12, 1.69, $P\text{-}_{FDR} = 0.012$), IL-6 (OR = 1.29, 95% CI: 1.04, 1.61, $P\text{-}_{FDR} = 0.042$), and IL-8 (OR = 1.31, 95% CI: 1.06, 1.62, $P\text{-}_{FDR} = 0.036$) were associated with an increased risk of personal-social delay. Stratified analyses showed that lower maternal vitamin D levels (< 20 ng/mL) moderated the associations between inflammatory markers and delays in fine motor, gross motor, and personal-social subdomains.

Conclusions Elevated levels of specific inflammatory cytokines in the placenta and umbilical cord blood were associated with developmental delays on a parental-reported screening tool. Maternal vitamin D status can modify the adverse effects of the intrauterine pro-inflammatory milieu on the neurodevelopment of children.

Keywords Placenta, Umbilical cord blood, Cytokine, Neurodevelopment, Vitamin D, Birth cohort

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Background

The period from early pregnancy until childbirth is a critical window for fetal brain and neural development [1, 2]. During this delicate and complex stage, healthy neurodevelopmental processes can provide a solid foundation for the subsequent positive growth and development of individuals. Moreover, multiple prenatal factors can also lead to deviations from the typical trajectories of neurodevelopment [3], which may correspondingly result in a variety of adverse outcomes later in life, such as childhood neurodevelopmental delay [4], behavior and mental health outcomes [5], impaired academic performance [6], and low socioeconomic status [7].

The maternal immune activation (MIA)-induced inflammatory perturbations in utero are considered important risk factors for abnormalities in fetal neurodevelopment. Among the multiple inflammatory biomarkers, cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and interleukin-6 (IL-6) are the most frequently measured indicators of the inflammatory response [2, 8]. As key hubs for the exchange of nutrients and various metabolites at the mother-fetus interface, the placenta and umbilical cord play pivotal roles in the association between MIA and fetal neurodevelopment [9, 10]. MIA-induced inflammatory cytokines can either trigger a placental inflammatory response directly [11] or enter the fetus via the vertical transfer pathway through the umbilical cord [12], both of which can disrupt the precise balance between inflammatory cytokines in the maternal–fetal circulation and elicit a long-lasting effect on fetal neurodevelopmental processes via direct (e.g., inflammatory perturbations in the fetal brain) [2] or indirect pathways (e.g., altered placental secretion and metabolic function) [13].

Previous epidemiologic studies have reported the effects of inflammatory cytokine levels in the placenta or cord blood on multiple neurodevelopmental outcomes in offspring. Data from the Boston Birth Cohort revealed that placental histological chorioamnionitis (based on data from pathological reports) is a risk factor for offspring neurodevelopmental disorders (e.g., attention-deficit/hyperactivity disorder and autism spectrum disorder) [14]. In the Ma'anshan birth cohort (MABC), our team noted that placental inflammation (TNF-α, IFN-γ, C-reactive protein, IL-1β, IL-6, IL-8, IL-4, and IL-10) is associated with cognitive performance and behavioral problems in preschool children [15, 16]. Furthermore, a longitudinal study suggested that the levels of inflammatory cytokines (TNF-α, IFN-γ, and IL-12p70) in umbilical cord blood are associated with verbal and performance intelligence quotients in children (including preterm birth and small-for-gestational-age children) [17]. Wang et al. reported that higher high-sensitivity C-reactive protein levels in the cord blood of children increase the risk of neurodevelopmental delay [10]. However, previous studies have selected only a single biospecimen (either the placenta or umbilical cord blood) for the measurement of inflammatory cytokine levels, and the types of detected cytokines in different biospecimens have varied, thus underestimating the true impact of the intrauterine immune environment on offspring neurodevelopment. When considering that a consistent inflammatory cytokine profile in the placenta and cord blood can provide a complete picture of the fetal immune environment compared with a single biospecimen, there is an urgent need to simultaneously explore the effects of placental and cord blood inflammatory cytokine levels on neurodevelopment in offspring.

The development of safe, cost-effective, and highly feasible interventions for neurodevelopmental impairments in children has been an ongoing priority in public health. Recently, increasing evidence from prospective birth cohort studies has indicated that appropriate maternal vitamin D levels can attenuate the negative effects of prenatal immune function-related adverse environmental exposure on the neurodevelopmental process of the fetus [18–20]. As an essential nutrient for maintaining normal pregnancy, the level of vitamin D in pregnant women not only influences fetal neurodevelopment [21] but also affects the intensity of maternal and fetal inflammatory responses by regulating the differentiation, maturation, and function of immune cells (such as natural killer cells, macrophages, dendritic cells, B lymphocytes, and T lymphocytes) [22]. Therefore, it is important to elucidate whether maternal serum vitamin D status can modify the increased risk of neurodevelopmental delay in offspring due to exposure to an adverse intrauterine immune environment.

Based on data from the MABC, we aimed to evaluate the associations between placental and cord blood inflammatory cytokine levels and neurodevelopment in 18-month-old children, as well as the potential modification effect by maternal vitamin D.

Methods

Study population

In Ma'anshan city, China, 3474 pregnant women were recruited for the MABC (2013–2014). With informed consent obtained from the participants, the MABC collected demographic and medically relevant information (No. 20131195). Among the population, 3273 mothers with singleton live births were followed [23]. Placenta and cord blood samples were collected after delivery by obstetricians, and neurodevelopment assessments of the children were conducted at 18 months of age. After

excluding 1943 mother–child pairs without placenta and cord blood samples and 89 children without information on neurodevelopment assessments at 18 months, a total of 1241 mother–child pairs were included in our study (Additional file 1: Fig. S1).

Placental inflammatory cytokine mRNA expression assay

Placental tissues were collected within half an hour of delivery. After rinsing with normal saline, we removed an intact placental lobule (which was free of maternal decidua, calcification, and fascia) vertically from the full-thickness placenta at a periumbilical position of 5 cm. The extracted placental lobule was subsequently longitudinally sectioned into tissue pieces measuring less than or equal to 0.5 cm in size; these pieces were treated with RNAlater and stored at − 80 °C for measurement. The expression of placental tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), IL-6, IL-8, and IL-10 mRNA were determined by real-time quantitative polymerase chain reaction (RT-qPCR). The oligonucleotide sequences that were utilized in RT-qPCR are shown in Additional file 1: Table S1. To normalize all of the RT-qPCR data, 18S rRNA was selected as the endogenous reference RNA. The delta cycle threshold (ΔCt) was calculated to represent the difference between the target mRNA and the normalized RNA, and the ΔCt was calculated as the Ct mRNA minus Ct normalized mRNA. The detailed procedures have been previously described [15].

Cord serum inflammatory cytokine measurement

Umbilical cord blood samples were collected after delivery, and the serum samples were separated and stored at − 80 °C. The method that was used to measure inflammatory cytokines in cord serum has been reported elsewhere [24]. The detection rates of TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-10 were 99.99%, 96.13%, 94.76%, 100%, 100%, and 100%, respectively. The limits of detection (LODs) for TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-10 were 0.16, 0.48, 0.14, 0.11, 0.13, and 0.56 (pg/mL), respectively. The concentrations of inflammatory cytokines in cord serum below the LODs were replaced by the LODs divided by the square root of 2 for further analyses.

Maternal serum 25-hydroxyvitamin D (25(OH)D) measurement

Maternal blood samples from the three trimesters were collected and stored at − 80 °C until measurement. Maternal serum total 25(OH)D was determined via a Diasorin kit (DiaSorin Inc, Stillwater, MN, USA) by well-trained experimenters [25]. The intra- and inter-coefficients of variation were less than 10%. In our study, the maternal serum 25(OH)D concentrations were 18.34 ± 8.34 ng/mL, 21.38 ± 9.47 ng/mL, and 19.08 ± 9.63 ng/mL during the first, second, and third trimester, respectively. The average serum 25(OH)D concentrations of the three trimesters were calculated and divided into two groups ("deficiency, < 20 ng/mL" and "non-deficiency, ≥ 20 ng/mL") to reflect maternal vitamin D status during pregnancy [18, 26].

Assessment of child neurodevelopment

In MABC, neurodevelopment in 18-month-old children was assessed via the Chinese version of the Ages and Stages Questionnaire, Third Edition (ASQ-3). The ASQ-3 is an affordable, cost-effective, and validated instrument that effectively screens for potential early neurodevelopmental delays in Chinese children [27]. The ASQ-3 consists of the following five domains: communication, gross motor, fine motor, problem solving, and personal-social. Each dimension consists of six items with three options, including "yes," "sometimes," and "not yet," scoring 10, 5, and 0, respectively. The total score for each domain ranges from 0 to 60 points. In the current study, under the supervision and guidance of a professional pediatric psychologist, parents completed the ASQ-3 via face-to-face or phone interviews. A child's score below the cutoff scores (the mean score minus 2 standard deviations) in one of the domains was considered to indicate developmental delay in that domain [28].

Covariates

In the MABC, maternal age, pre-pregnancy body mass index (BMI), family monthly income, maternal smoking and drinking statuses, maternal fever, maternal infection or inflammation conditions, maternal folic acid supplementation during pregnancy, birth weight, the child's main caregiver, breastfeeding duration, and child age at neurodevelopmental testing were collected via structured questionnaires or medical records. The Pregnancy-Related Anxiety Questionnaire was employed to assess maternal pregnancy-related anxiety [29]. Placental efficiency was calculated as birth weight divided by placental weight [30]. Information on delivery mode, gestational age, and child sex was obtained from clinical medical records.

Statistical analysis

Student's *t*-test or the chi-square test was employed to compare characteristics between the included and source populations. The distributions of placental inflammatory cytokine mRNA expression levels, cord serum inflammatory cytokine concentrations, and ASQ domain-specific scores are presented as selected percentile values, and the neurodevelopmental delay of each domain is expressed as frequencies with percentages. The correlations

between different placental and cord serum inflammatory cytokines were assessed via Spearman's rank correlation coefficient. Due to the skewed distribution of the placental and cord serum inflammatory cytokine levels, natural logarithm-transformed (ln-transformed) values were calculated for further analyses.

Restricted cubic splines (RCS) were performed to explore the nonlinear associations between placental and cord serum inflammatory cytokines and children's developmental delay in each domain. In the RCS model, statistical significance was defined as a p value less than 0.05. Generalized linear models were utilized to estimate the associations between placental and cord serum inflammatory cytokines and suspected developmental delay in each domain, based on the ASQ-3 cutoff scores. The odds ratios (ORs) and their 95% confidence intervals (CIs) were used as indicators of the strength of these associations. In adjusted models, potential confounders were identified based on a directed acyclic graph (Additional file 1: Fig. S2), which included maternal age, pre-pregnancy BMI, delivery mode, family monthly income, smoking and drinking during pregnancy, maternal fever during pregnancy, maternal infection or inflammation conditions during pregnancy, maternal pregnancy-related anxiety, placental efficiency, gestational age, children sex, and children's age at neurodevelopmental testing. False discovery rate (FDR) corrected p values were calculated for multiple tests [31], and FDR corrected p values < 0.10 were considered to be statistically significant [32].

Stratified analyses were conducted to evaluate the influence of maternal vitamin D status on the associations between placental and cord serum inflammatory cytokines and developmental delay in each domain. We tested for maternal 25(OH)D status differences by adding a multiplicative interaction term (maternal 25(OH)D status × inflammatory cytokines) to the multivariable logistic regression models. Furthermore, these associations were also examined after stratification by trimester. In addition, analyses stratified by the sex of the children were conducted based on the sex-specific effects of inflammatory cytokines [16], and interaction terms (child sex × inflammatory cytokines) were added to the models. We also tested whether delivery mode affected the associations between placental and cord serum inflammatory cytokines and developmental delay in children. The multiplicative interaction term p values < 0.10 were considered to be statistically significant [33].

Three sensitivity analyses were conducted to test the robustness of the results. First, to investigate the effects of placental and cord serum inflammatory cytokines on neurodevelopment in full-term birth children, we excluded 39 preterm birth children. Second, we excluded 19 infants with low birth weights. Third, we further controlled for maternal folic acid supplementation during pregnancy, children main caregivers, and breastfeeding duration.

All of the analyses were performed via SPSS (version 23.0) and R (version 4.3.1). RCS was implemented in R via the "rcssci" package.

Results

Characteristics of participants

The characteristics of the participants are shown in Table 1 and Additional file 1: Table S2. The maternal age and pre-pregnancy BMI were 26.63 ± 3.55 years and 20.59 ± 2.88 kg/m^2, respectively. A total of 42.0% of the households had a per capita monthly income between 2500 and 4000 Chinese yuan (CNY). During pregnancy, the vast majority of mothers took folic acid supplements (91.2%), did not smoke or drink alcohol (91.0%), did not have a fever (87.7%), and were not in a state of infection or inflammation (91.9%). More than half of the pregnant women did not experience anxiety during pregnancy (52.6%), and the average serum 25(OH)D concentration was less than 20 ng/mL (58.7%). In addition, placental weight, placental efficiency, birth weight, gestational age, and children's age at neurodevelopmental testing were 571.96 ± 162.77 g, 6.39 ± 2.87, 3382.68 ± 429.32 g, 39.14 ± 1.27 weeks, and 18.16 ± 0.60 months, respectively. More than half of the children were boys (50.7%), were delivered by cesarean Sect. (55.1%), or were breastfed for more than 4 months (56.8%); additionally, their primary caregivers were parents and grandparents (73.2%).

Distribution of placental and cord serum inflammatory cytokines and children's neurodevelopment

With respect to placental inflammatory cytokines, the median values of the mRNA expression levels (ΔCt) for TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-10 were 6.09, 3.44, 2.77, 2.90, 2.05, and 2.79, respectively. In the umbilical cord serum, the median concentrations (pg/mL) of TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-10 were 12.81, 1.40, 0.46, 1.82, 6.91, and 7.25, respectively (Table 2). The correlations between placental and cord serum inflammatory cytokines are shown in Fig. 1. In addition, the prevalence of each domain-specific neurodevelopment delay in children is displayed in Table 3, including communication (4.8%), gross motor (3.6%), fine motor (5.9%), problem solving (4.3%), and personal-social (3.9%).

Table 1 Demographic characteristics of the participants [mean ± SD or *n* (%)]

Characteristics	Total (*n* = 1241)
Maternal and family characteristics	
Maternal age at enrollment (years)	26.63 ± 3.55
Pre-pregnancy BMI (kg/m^2)	20.59 ± 2.88
Delivery mode	
Vaginal delivery	557 (44.9)
Cesarean section	684 (55.1)
Family monthly income per capita (CNY)	
≤ 2500	342 (27.6)
2500–4000	522 (42.0)
> 4000	377 (30.4)
Smoking and drinking during pregnancy	
Yes	112 (9.0)
No	1129 (91.0)
Maternal fever during pregnancy	
Yes	153 (12.3)
No	1088 (87.7)
Maternal infection or inflammation conditions during pregnancy	
Yes	100 (8.1)
No	1141 (91.9)
Maternal pregnancy-related anxiety	
Yes	588 (47.4)
No	653 (52.6)
Maternal folic acid supplementation during pregnancy	
Yes	1132 (91.2)
No	109 (8.8)
Average concentrations of maternal serum 25(OH)D during pregnancy	19.60 ± 6.05
< 20 ng/mL	728 (58.7)
≥ 20 ng/mL	513 (41.3)
Placental characteristics	
Placental weight (g)	571.96 ± 162.77
Placental efficiency	6.39 ± 2.87
Children's characteristics	
Birth weight (g)	3382.68 ± 429.32
Gestational age (weeks)	39.14 ± 1.27
Children's age at neurodevelopmental testing (months)	18.16 ± 0.60
Sex	
Boys	629 (50.7)
Girls	612 (49.3)
Main caregivers	
Parents	246 (19.8)
Parents and grandparents	908 (73.2)
Others	87 (7.0)
Breastfeeding duration (months)	
< 1	363 (29.3)
1–4	173 (13.9)
> 4	705 (56.8)

SD Standard deviation, *BMI* Body mass index, *CNY* Chinese yuan

Table 2 Distribution of placental inflammatory cytokine mRNA expression and cord serum inflammatory cytokine concentrations (*n* = 1241)

Inflammatory cytokines	Percentile				
	10th	25th	50th	75th	90th
Placenta (ΔCt)					
TNF-α	0.64	1.86	6.09	14.90	30.53
IFN-γ	0.33	1.00	3.44	11.08	28.62
IL-1β	0.44	1.01	2.77	6.74	15.90
IL-6	0.56	1.12	2.90	7.27	16.25
IL-8	0.41	0.86	2.05	5.58	11.96
IL-10	0.50	1.12	2.79	8.48	23.02
Cord serum (pg/mL)					
TNF-α	5.05	8.63	12.81	17.64	22.70
IFN-γ	0.63	0.95	1.40	2.13	2.66
IL-1β	0.17	0.31	0.46	0.63	0.90
IL-6	0.62	1.08	1.82	2.86	5.792
IL-8	2.90	4.58	6.91	10.20	15.00
IL-10	3.37	5.44	7.25	9.30	14.55

CT Cycle threshold

Associations between placental and cord serum inflammatory cytokines and children's neurodevelopment

Figure 2 shows the associations between placental and cord serum inflammatory cytokine levels and the children's domain-specific neurodevelopment delay. Each one-unit increase in placental IL-6 (OR = 1.30, 95% CI: 1.09, 1.55, $P\text{-}_{FDR} = 0.024$) and IL-8 (OR = 1.25, 95% CI: 1.05, 1.49, $P\text{-}_{FDR} = 0.036$) was associated with an increased risk of fine motor delay. Furthermore, the IFN-γ level in the cord serum was positively associated with an increased risk of fine motor delay (OR = 1.74, 95% CI: 1.16, 2.61, $P\text{-}_{FDR} = 0.042$). Each one-unit increase in placental TNF-α (OR = 1.38, 95% CI: 1.12, 1.69, $P\text{-}_{FDR} = 0.012$), IL-6 (OR = 1.29, 95% CI: 1.04, 1.61, $P\text{-}_{FDR} = 0.042$), and IL-8 (OR = 1.31, 95% CI: 1.06, 1.62, $P\text{-}_{FDR} = 0.036$) was associated with an increased risk of personal-social delay. Additionally, the RCS results suggested that there were no nonlinear associations between placental (Additional file 1: Fig. S3) or cord serum (Additional file 1: Fig. S4) inflammatory cytokines and neurodevelopmental delay in children (all nonlinear *p* values > 0.05). Based on sex-stratified analyses (Additional file 1: Table S3), we observed a positive association between placental IFN-γ and gross motor delay in boys (OR = 1.35, 95% CI: 1.10, 1.66, $P\text{-}_{FDR} = 0.018$, $P\text{-}_{interaction} = 0.002$). Furthermore, we did not observe significant differences in the associations between placental and cord serum inflammatory cytokines and children's neurodevelopmental delay stratified by delivery mode (Additional file 1: Table S4).

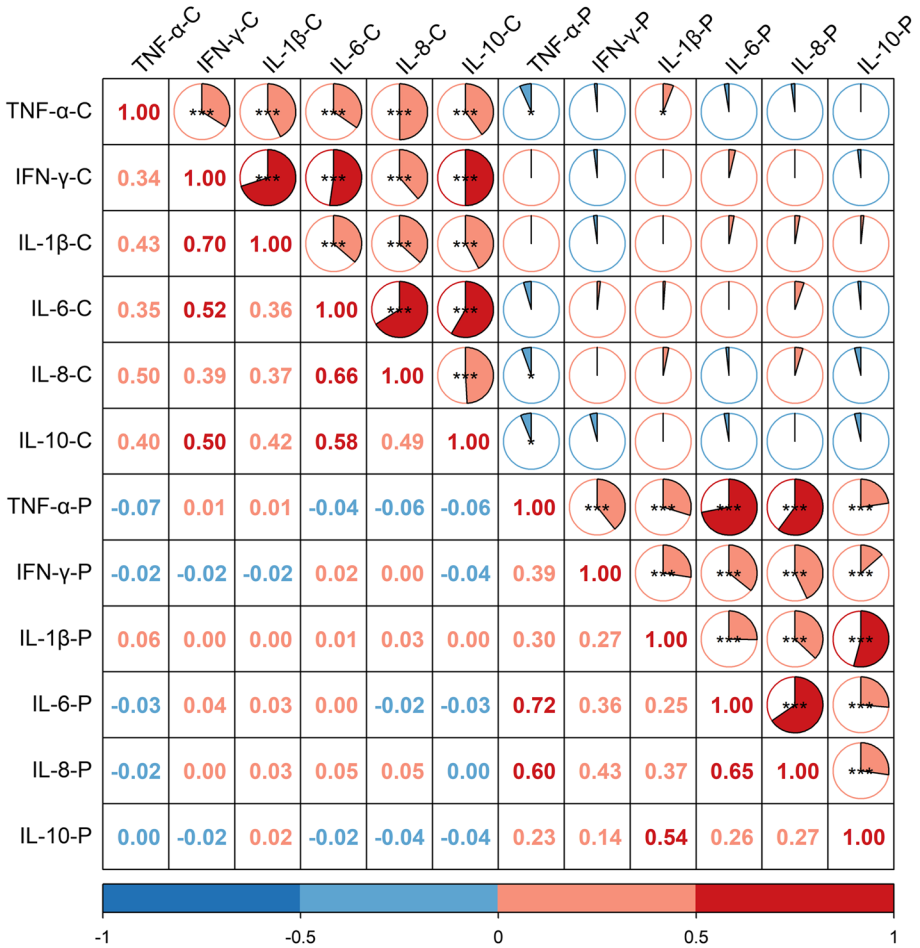

Fig. 1 Spearman correlation coefficients between placental and cord serum inflammatory cytokines. Abbreviations: C, cord serum; P, placenta. Note: **p* value < 0.05, ***p* value < 0.01, ****p* value < 0.001

Table 3 Distribution of children's neurodevelopmental assessments (*n* = 1241)

ASQ scores	Min	Percentile			Max	Developmental delay[a]
		25th	50th	75th		
Communication	10	40	50	60	60	59 (4.8)
Gross motor	10	55	60	60	60	45 (3.6)
Fine motor	15	50	55	60	60	73 (5.9)
Problem solving	10	45	50	55	60	53 (4.3)
Personal-social	20	45	50	55	60	49 (3.9)

ASQ Ages and Stages Questionnaire, Third Edition, *Min* minimum, *Max* maximum

[a] Number (percentage)

The modification effects of maternal vitamin D status on the associations between placental and cord serum inflammatory cytokines and children's neurodevelopment

The modification effects of maternal vitamin D status are shown in Fig. 3. Lower maternal serum vitamin D levels (< 20 ng/mL) aggravated cord serum IFN-γ-associated risks of gross motor delay (OR = 2.44, 95% CI: 1.23, 4.86, $P\text{-}_{FDR} = 0.066$, $P\text{-}_{interaction} = 0.071$). Placental TNF-α (OR = 1.30, 95% CI: 1.04, 1.63, $P\text{-}_{FDR} = 0.046$, $P\text{-}_{interaction} = 0.032$) and IL-6 (OR = 1.60, 95% CI: 1.24, 2.07,

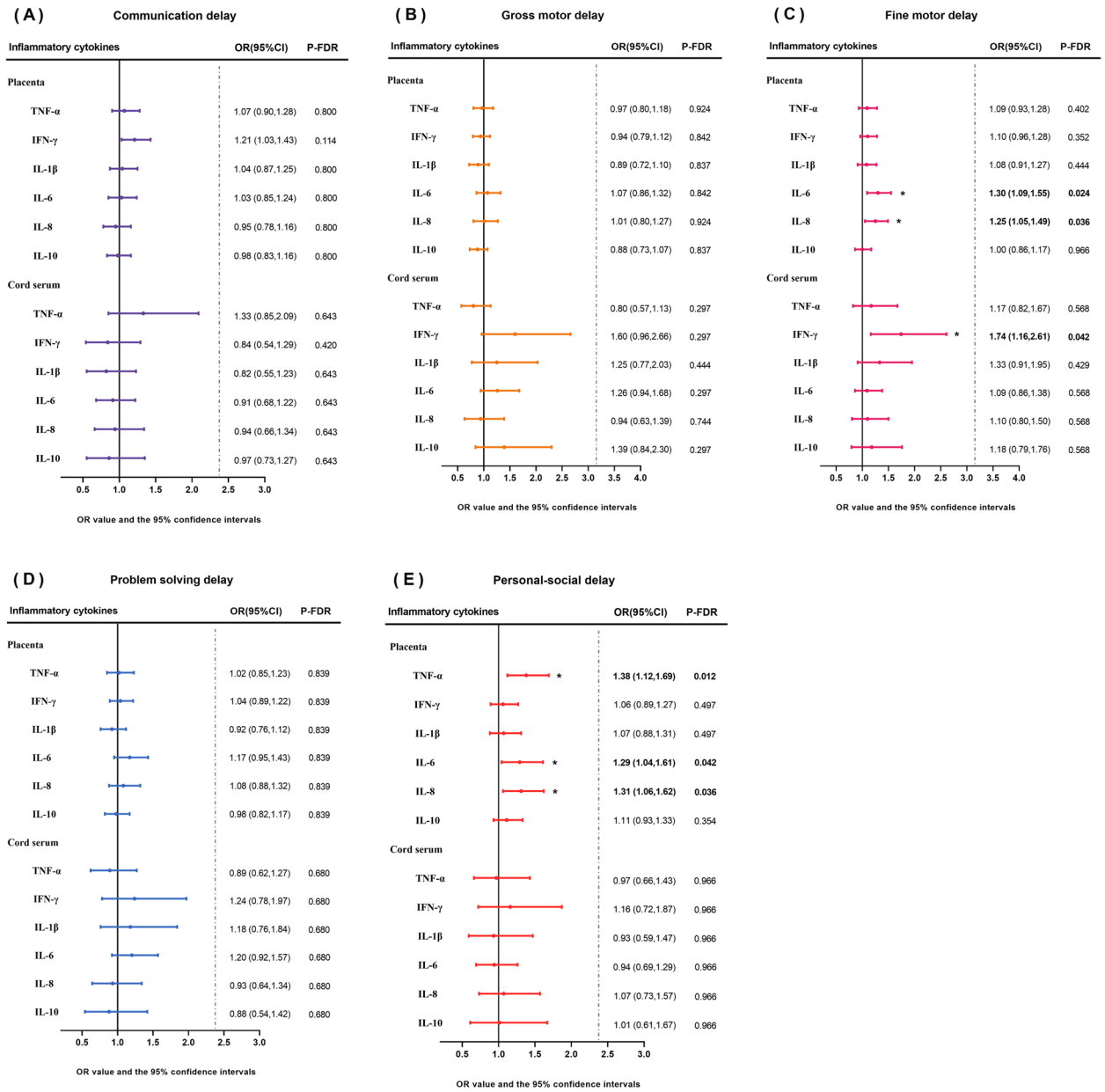

Fig. 2 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopmental delay. Models adjusted for maternal age, pre-pregnancy BMI, delivery mode, family monthly income per capita, smoking and drinking during pregnancy, maternal fever during pregnancy, maternal infection or inflammation conditions during pregnancy, maternal pregnancy-related anxiety, placental efficiency, gestational age, children sex, and children's age at neurodevelopmental testing

$P\text{-}_{FDR} \leq 0.001$, $P\text{-}_{interaction} = 0.040$), as well as cord serum TNF-α (OR = 1.94, 95% CI: 1.05, 3.60, $P\text{-}_{FDR} = 0.052$, $P\text{-}_{interaction} = 0.009$), IL-1β (OR = 1.71, 95% CI: 1.02, 2.88, $P\text{-}_{FDR} = 0.052$, $P\text{-}_{interaction} = 0.095$), IL-6 (OR = 1.41, 95% CI: 1.06, 1.86, $P\text{-}_{FDR} = 0.052$, $P\text{-}_{interaction} = 0.003$), IL-8 (OR = 1.56, 95% CI: 1.03, 2.39, $P\text{-}_{FDR} = 0.052$, $P\text{-}_{interaction} = 0.005$), and IL-10 (OR = 1.56, 95% CI: 0.95, 2.56, $P\text{-}_{FDR} = 0.079$, $P\text{-}_{interaction} = 0.042$), were all found to have stronger adverse associations with fine motor delay in the maternal vitamin D deficiency group. Moreover, higher levels of maternal serum vitamin D (≥ 20 ng/mL) attenuated the risk of fine motor delay induced by cord serum IL-6 (OR = 0.61, 95% CI: 0.38, 0.96, $P\text{-}_{FDR} = 0.093$, $P\text{-}_{interaction} = 0.003$) and IL-8 (OR = 0.57, 95% CI: 0.35, 0.91, $P\text{-}_{FDR} = 0.093$, $P\text{-}_{interaction} = 0.005$). Moreover, in the vitamin D deficiency group, each one-unit increase in

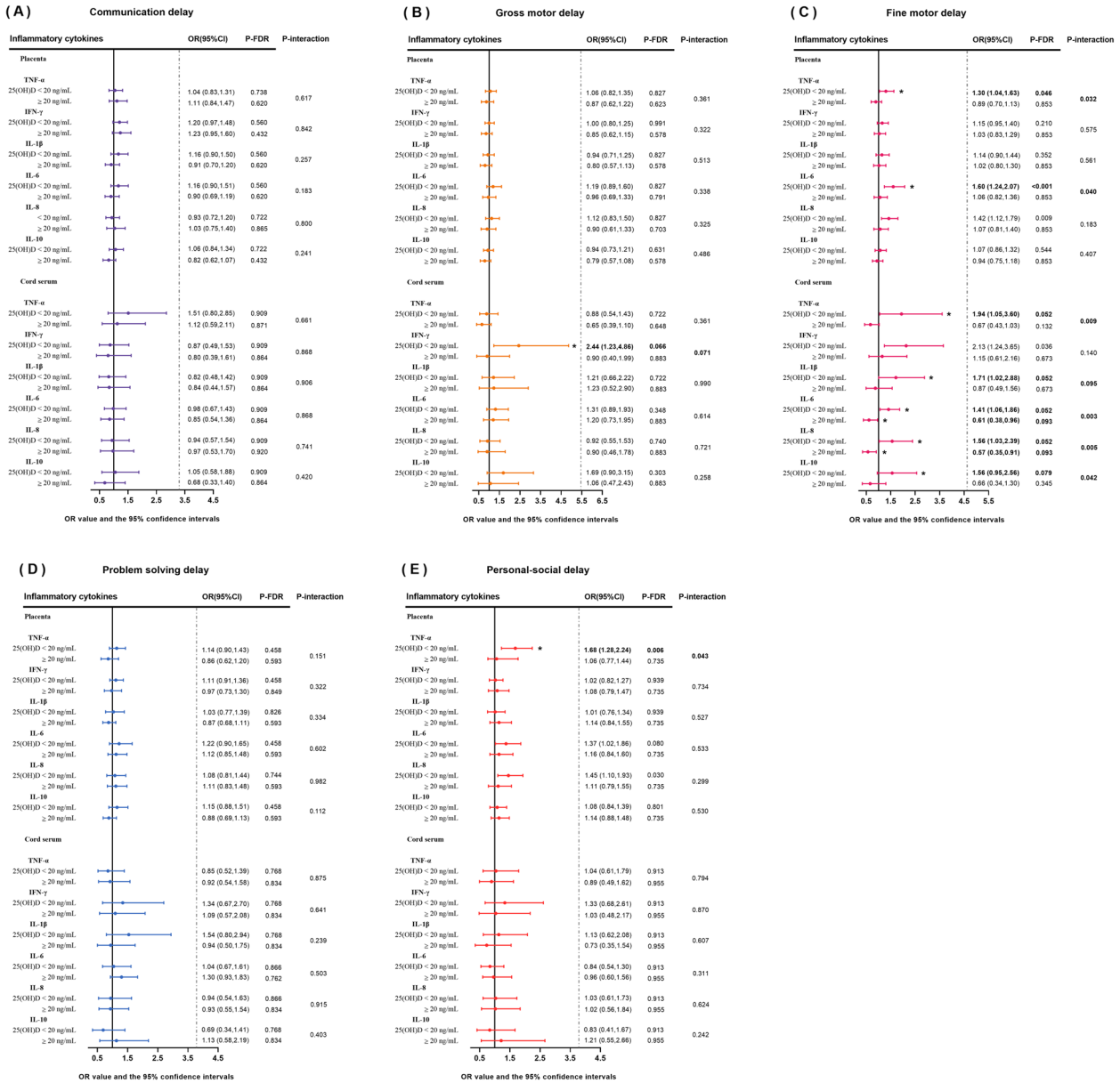

Fig. 3 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopmental delay stratified by maternal vitamin D status. Models adjusted for maternal age, pre-pregnancy BMI, delivery mode, family monthly income per capita, smoking and drinking during pregnancy, maternal fever during pregnancy, maternal infection or inflammation conditions during pregnancy, maternal pregnancy-related anxiety, placental efficiency, gestational age, children sex, and children's age at neurodevelopmental testing

placental TNF-α was positively associated with personal-social delay (OR = 1.68, 95% CI: 1.28, 2.24, $P\text{-}_{FDR} = 0.006$, $P\text{-}_{interaction} = 0.043$). Additionally, maternal serum vitamin D levels less than 20 ng/mL during the first trimester could aggravate the risk of fine motor delay induced by placental TNF-α (OR = 1.29, 95% CI: 1.05, 1.60, $P\text{-}_{FDR} = 0.032$, $P\text{-}_{interaction} = 0.011$) and IL-8 (OR = 1.42, 95% CI: 1.14, 1.76, $P\text{-}_{FDR} = 0.006$, $P\text{-}_{interaction} = 0.062$) (Additional file 1: Tables S5–S8).

Sensitivity analyses

In sensitivity analyses that excluded preterm birth children (Additional file 1: Table S9) and low birth weight children (Additional file 1: Table S10), the associations between placental and cord serum inflammatory cytokines and the children's domain-specific neurodevelopmental delay were similar to those in the main analyses. After additionally adjusting for maternal folic acid supplementation during pregnancy, children's main

caregivers, and breastfeeding duration, those associations did not substantially change (Additional file 1: Table S11).

Discussion

In this birth cohort study, we found that elevated levels of specific inflammatory cytokines in placental (TNF-α, IL-6, and IL-8) and cord blood (IFN-γ) samples were associated with an increased risk of domain-specific neurodevelopmental delay in 18-month-old children. Maternal serum vitamin D levels less than 20 ng/mL intensified the associations between placental and cord serum inflammatory markers and delays in fine motor, gross motor, and personal-social subdomains.

As an important component of the maternal–fetal interface, the placenta occupies a unique immunoecological niche and can maintain the immune homeostatic environment that is necessary for the normal course of pregnancy via complex immunoregulatory mechanisms [34]. The concept of the "placenta-brain axis" has been proposed to closely link the placenta and fetal central nervous system [35]. However, when immune homeostasis dominated by the placenta is dysregulated, it may adversely affect fetal neurodevelopment. A retrospective cohort study revealed that placental inflammatory villitis is a dominant risk factor for neonatal encephalopathy and subsequent adverse neurodevelopmental outcomes [36]. A case–control study revealed that placental inflammation increases the risk of neuropsychiatric disorders in children [37]. Our team previously reported the detrimental effects of elevated placental inflammatory cytokine levels on the preschoolers' behavioral and cognitive development [15, 16]. Similarly, the current study revealed that elevated placental TNF-a, IL-6, and IL-8 levels can lead to fine motor and personal-social development delays in toddlers. In summary, the pro-inflammatory milieu of the placenta may cause both short- and long-term adverse effects on offspring neurodevelopment. The potential mechanisms by which placental inflammation regulates fetal neurodevelopment are complex and diverse. For example, placental inflammation can cause insufficient placental development and impaired barrier function [38], induce placental endocrine changes [13, 39], affect placental metabolic function [40], and change the expression levels of genes related to fetal neurodevelopment in the placenta [13]. Furthermore, placental inflammation can influence the intensity of the fetal immune response [41], which can also activate inflammatory signaling pathways [42] and oxidative stress [43] in the fetal brain.

In the present study, we observed that elevated placental IFN-γ levels increased the risk of fine motor delay in boys. Consistent with our findings, previous studies have also suggested the sexually dimorphic effects of placental inflammation on offspring neurodevelopment. In a case–control study, Straughen et al. reported a stronger association between placental inflammation and autism spectrum disorder in boys [44]. The results from the MABC suggest that the adverse effects of placental inflammation on the attention-deficit/hyperactivity disorder symptoms and cognitive performance of boys are more pronounced [15, 29]. Sex-specific mechanisms of placental regulation of fetal neurodevelopment have been progressively identified and intensively explored. When additional immune challenges occur in the placenta, males are exposed to greater health risks because of their greater inflammatory tone [45]. In terms of endocrine action, substance transport, and other functions, the male placenta exhibits greater immune-related vulnerability [46]. Furthermore, placental inflammation increases Toll-like receptor 4 signaling in male fetal macrophages, which leads to excessive microglial phagocytosis of serotonin neurons in the dorsal septal nucleus of the developing septum and decreases serotonin bioavailability in the fetal brain [47].

The umbilical cord is the only conduit for substance exchange between the mother and the fetus. The cytokines in umbilical cord blood are able to enter the fetus through the fetal circulation pathway, which can reflect the level of fetal inflammation to a certain extent [48], and directly participate in the regulation of fetal neurological development [49]. A prospective cohort study indicated that high levels of various inflammatory cytokines in umbilical cord serum were associated with cerebral palsy in children at 5 years of age [50]. Based on non-invasive fetal magnetoencephalography, Mercado et al. reported that cord-blood inflammatory markers were strongly associated with fetal brain activity [49]. In addition, a study in Bangladesh noted that high levels of CRP and IL-6 in cord serum were associated with an elevated risk of fine motor delay in offspring [51]. Similarly, our findings revealed that elevated cord serum IFN-γ levels increased the risk of children's fine motor delay. The underlying mechanism linking cord serum IFN-γ levels and neurodevelopmental delay in children may involve microglial cell activation in the fetal brain. Microglia, which originate from the yolk sac, are macrophages that reside in the brain and exhibit remarkable functional diversity in regulating neurogenesis, synaptic development and refinement, myelination, and synaptic transmission during various stages of brain development [52]. As a fundamental mediator of microglial cell activation, IFN-γ is able to program microglia to an activated phenotype [53], thus leading to morphological and functional changes that impair normal brain developmental processes, thereby increasing susceptibility to neurodevelopmental delays in childhood [54].

Based on stratified analysis of maternal vitamin D levels, we found that maternal vitamin D deficiency may exacerbate the effects of an adverse intrauterine immune environment on the risk of childhood neurodevelopmental delays. Similarly, Wang et al. reported that adequate vitamin D in cord blood, which is strongly correlated with maternal vitamin D levels, attenuated the damaging effects of fetal immune activation on neurodevelopment in children [10]. In both regional birth cohorts, the modifying role of maternal vitamin D status in the associations of prenatal immune-related adverse environmental exposures with offspring neurodevelopment was identified [18, 19]. The immunomodulatory role of vitamin D at the maternal–fetal interface has gradually attracted increasing attention. Low levels of vitamin D during pregnancy may induce maternal and placental inflammation via multiple immunomodulatory pathways (e.g., innate immunity and adaptive immunity pathways) [55, 56], thus leading to fetal exposure to an imbalanced intrauterine immune environment. By interacting with the vitamin D receptor on immune cells, $1,25(OH)_2D_3$ (which is the main activated form of vitamin D) is able to inhibit the activation of the nuclear factor-kappa B signaling pathway, which correspondingly reduces the expression of inflammatory cytokines [57, 58]. Additionally, vitamin D status during pregnancy may modulate the maternal immune system by modifying the gut microbiota, which correspondingly affects the intrauterine inflammatory milieu and fetal neurodevelopment [59–61]. Furthermore, placental function, which is an important determinant of fetal neurodevelopment, is closely related to maternal vitamin D status [62]. Moreover, maternal serum 25(OH)D can enter the fetus through the placenta and influence the fetal neurodevelopmental process by participating in the differentiation of brain neuronal cells, neurotransmitter synthesis, antioxidant activity, and cytokine regulation [63, 64]. In summary, moderate vitamin D supplementation during pregnancy might be a potential mitigation strategy for impaired neurodevelopment in children associated with an adverse prenatal inflammatory environment. Future large-sample interventional studies in representative populations are needed to clarify the actual benefits of vitamin D supplementation during pregnancy on maternal and child health.

Using a prospective birth cohort, we measured inflammatory cytokine levels in both placenta and cord blood, which enabled a more comprehensive exploration of the actual effects of the prenatal intrauterine immune environment on the neural development of offspring. In addition, our findings suggest that maternal vitamin D supplementation during pregnancy attenuates the neurodevelopmental damage caused by the intrauterine pro-inflammatory milieu in offspring, which may facilitate subsequent interventional and translational studies related to vitamin D supplementation during pregnancy. However, several limitations must be noted. First, given the wide variety of inflammatory cytokines, our selection of only six biomarkers may have underestimated the impact of intrauterine immune activation on child neurodevelopment. Second, we did not assess the levels of inflammatory cytokines in the amniotic fluid or fetal brain tissue, nor did we measure the inflammatory state of the children after birth. Third, maternal serum inflammatory cytokine levels during pregnancy were not included in the current study. As a complement, we included factors associated with maternal immune activation, such as smoking and drinking during pregnancy, maternal fever, maternal infection or inflammation conditions, and maternal pregnancy-related anxiety, as covariates in the models. Fourth, we did not measure the vitamin D concentration in fetal cord blood. Fifth, neurodevelopmental assessments at a single age are not fully representative of neurological status throughout childhood. Subsequent studies are needed to further analyze the impacts of maternal–fetal immunity activities on neurodevelopmental outcomes at multiple time points and neurodevelopmental trajectories in offspring. Reporting bias may affect the accuracy of neurodevelopmental measurement in children. Furthermore, the ASQ is a screening measure and not a diagnostic assessment of development delays. Finally, the current study was conducted in Ma'anshan city, which is regionally representative. Future studies need to be conducted in different regions and ethnic groups to validate our findings.

Conclusions

Our findings suggest that a prenatal intrauterine pro-inflammatory milieu increases the risk of neurodevelopment delay in young children. The detrimental relationships between placental and cord serum inflammatory cytokine levels and domain-specific neurodevelopment delays in children were amplified with maternal vitamin D deficiency.

Abbreviations

MABC	The Ma'anshan birth cohort
RT-qPCR	Real-time quantitative polymerase chain reaction
MIA	Maternal immune activation
IL	Interleukin
TNF-α	Tumor necrosis factor-α
IFN-γ	Interferon-γ
LODs	Limits of detection
ASQ-3	The Ages and Stages Questionnaire, Third Edition
BMI	Body mass index
SD	Standard deviation
ORs	Odds ratios
CIs	Confidence intervals
RCS	Restricted cubic splines
FDR	False discovery rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04096-w.

Additional file 1. Fig. S1 Flow diagram of study participants. Fig. S2 Directed acyclic graph of the relationship between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment. Fig. S3 Restricted cubic spline for the relationships of placental inflammatory cytokines and children's domain-specific neurodevelopment. Fig. S4 Restricted cubic spline for the relationships of cord serum inflammatory cytokines and children's domain-specific neurodevelopment. Table S1 Sequences of the oligonucleotides utilized in RT-qPCR. Table S2 Demographic characteristics between the source population and the study population in Ma'anshan birth cohort [mean ± SD or *n* (%)]. Table S3 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay stratified by sex. Table S4 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay stratified by delivery mode. Table S5 Maternal serum vitamin D levels during the three trimesters [mean ± SD or *n* (%)]. Table S6 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay stratified by concentrations of maternal serum vitamin D during the first trimester. Table S7 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay stratified by concentrations of maternal serum vitamin D during the second trimester. Table S8 The associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay stratified by concentrations of maternal serum vitamin D during the third trimester. Table S9 Sensitivity analysis estimating associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay, excluded preterm birth children. Table S10 Sensitivity analysis estimating associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay, excluded low birth weight children. Table S11 Sensitivity analysis estimating associations between placental and cord serum inflammatory cytokines and children's domain-specific neurodevelopment delay, with additional adjusted for maternal folic acid supplementation during pregnancy, children main caregivers, and breastfeeding duration.

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Authors' contributions
FBT, SQY, KH, and XYW were responsible for the concept and design. MLG and FBT were responsible for drafting of the manuscript. MLG, ZY, YFW, and JT were responsible for the acquisition, analysis, or interpretation of data. MLG, JXZ, and HG were responsible for the statistical analysis. MLG and FBT were responsible for the obtained funding. SQY, HG, BLW, and PD were responsible for the administrative, technical, or material support. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Approval for the research procedures was obtained from Anhui Medical University's Ethics and Research Committee (No. 20131195). As children were too young to be able to make decisions, permissions for follow-ups and permissions for use of offspring's data were provided by women or other family members. Prior to enrollment, written informed consent was obtained from the participants on behalf of their families.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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