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Associations of inflammation related prenatal adversities with neurodevelopment of offspring in one year: a longitudinal prospective birth cohort study

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Abstract

Background The recent Maternal Immune Activation (MIA) theory suggests maternal systemic inflammation may serve as a mediator in associations between prenatal maternal adversities and neurodevelopmental diseases in offspring. Given the co-exposure to multiple adversities may be experienced by pregnant person, it is unclear whether a quantitative index can be developed to characterize the inflammation related exposure level, and whether this index is associated with neurodevelopmental delays in offspring.

Methods Based on Jiangsu Birth Cohort (JBC), a total of 3051 infants were included in the analysis. Inflammation related Prenatal Adversity Index (IPAI) was constructed using maternal data. Neurodevelopmental outcomes were assessed using the Bayley Scales of Infant and Toddler Development, third edition, screening test in one year. Multivariate linear regression and Poisson regression model were performed to analyze the associations between IPAI and neurodevelopment in offspring.

Results Compared with "low IPAI" group, offspring with "high IPAI" have lower scores of cognition, receptive communication, expressive communication, and fine motor. The adjusted β were − 0.23 (95%CI: -0.42, -0.04), -0.47 (95%CI: -0.66, -0.28), -0.30 (95%CI: -0.49, -0.11), and − 0.20 (95%CI: -0.33, -0.06). Additionally, the elevated risk for

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noncompetent development of cognition and receptive communication among "high IPAI" group was observed. The relative risk [RR] and 95% confidence interval [CI] were 1.35 (1.01, 1.69) and 1.37 (1.09, 1.72).

Conclusions Our results revealed a significant association between higher IPAI and lower scores across cognition, receptive communication, expressive communication, and fine motor domains, and an increased risk of noncompetent development in the cognition and receptive communication domains.

Keywords Pregnancy, Adversities, Inflammation, Index, Offspring, Neurodevelopment

Introduction

Neurodevelopmental delays, typically observed in early childhood and encompassing delays in language development, cognitive function, and motor skills [1], affect a significant proportion of children, ranging from 6.4 to 11.5% [2]. These delays are associated with an increased risk of conditions such as autism spectrum disorder and attention-deficit/hyperactivity disorder, which in turn adversely affect their academic performance and future economic status prospects [3]. Evidence is accumulating to suggest that prenatal adversities, encompassing factors such as maternal obesity [4–6], diabetes, hypertensive disorders [7, 8], psychosocial factors [9], socioeconomic status [10], physical activity [11], and diet [12, 13], play a significant role in the development of neurodevelopmental delays in children [14]. Notably, an increasing number of studies have proposed that maternal systemic inflammation may mediate the connection between prenatal exposures and neurodevelopmental delays in offspring [15]. Consequently, the Maternal Immune Activation (MIA) hypothesis has emerged, positing that exposure to an adversity induced dysregulated maternal immune environment during pregnancy can impact fetal neurodevelopment [16]. Thus, various prenatal adversities may affect fetal neurodevelopment through a shared MIA pathway, and the cumulative effect of single adverse exposure on fetal neurodevelopment remains uncertain. However, the integration of co-exposure factors related to the MIA hypothesis into a unified exposure index and their overall impact on fetal neurodevelopment still require further clarification.

During pregnancy, the second trimester emerges as a critical period for fetal brain development because cortical lamination during this phase represents the brain's largest and most vital information processing network, and is actively progressing [17–19]. Therefore, any adverse exposures experienced in utero during this delicate and sensitive period may lead to neurodevelopmental abnormalities. We hypothesized that co-exposure to multiple maternal adversities during the second trimester of pregnancy could lead to a cumulated negative effect on noncompetent development in offspring.

In this longitudinal cohort study, we aimed to construct an Inflammation related Prenatal Adversity Index (IPAI), and then to examine the associations between IPAI and neurodevelopment of offspring at one year of age using data of the Jiangsu Birth Cohort (JBC).

Methods and materials

Study design and participants

This population-based cohort study was conducted within the JBC, a prospective and longitudinal cohort study in Eastern China [20]. In short, couples were recruited during early pregnancy (≤14 weeks) or when they were planning to become pregnant and were followed up in their regularly scheduled prenatal and postnatal visits. Participants were asked to complete the questionnaires including lifestyle, behavioral traits, health and diseases, and medication with face-to-face help from professionally trained staff in the first (10–14 weeks), second (22–26 weeks), and third (30–34 weeks) trimester of gestation. After birth, children were followed up by telephone after 42 days and 6 months. When they reached one year old, they were invited back to the hospital where they were born to undergo systematic physical examination and neurodevelopment assessment by a professional doctor. Every participant provided written informed consent before inclusion.

From April 2014 to June 2020, among 17,854 couples recruited of JBC, a total of 15,670 pregnancies resulted in 16,480 live-born infants. The present study included mother-infant pairs fulfilling the following criteria: (1) live birth; (2) the complete variables in IPAI; (3) infants with complete data of intelligence test result follow-up in the first year (11-12.5 months). Since the Bayley Scales of Infant and Toddler Development, Version-III (Bayley-III) Screening Test has been implemented since November 2018 to assess the neurodevelopment of infants, we included 6,328 pregnancies to reach one year of age in November 2018. Among them, 3,489 pregnancies were excluded for the following reasons: missing values for variables related to inflammation (n=1,712), failure to follow-up (n=848), secondary enrollment (n=1), completion of the Bayley-III screening test beyond 12.5 months of age (n=928). Finally, 2,839 pregnancies with 3,051 infants were included (Supplementary Fig. 1). Based on this sample size, power is 85.41% and 80.73%, respectively.

Exposure assessment

Based on factors affecting offspring neurodevelopment reported in previous literature [8, 11, 21–25] and data from this cohort, we finally selected 6 variables to use to calculate the IPAI, including socioeconomic status [26], complication of pregnancy [27], psychological state [28, 29], maternal pre-pregnancy body mass index (BMI) [30], physical activity [31] and diet [32, 33] (**appendix 1 pp 2–8**). The specific scoring rules are shown in Table 1.

Socioeconomic status, including household income and maternal education at children birth, was assigned based on the data distribution of the population and previous literature [34]. Psychological state was jointly assessed by three self-filled scales: Center for Epidemiological Survey, Depression Scale (CES-D) [35], Self-Rating Anxiety Scale (SAS) [36] and Perceived Stress Scale (PSS-10) [37], and then assigned points according to the cut-off value. Physical activity was assigned points based on a combination of metabolic equivalent (MET) and weekly exercise time. Diet was assigned based on the inflammatory properties of food and the median intake of the population. Complication of pregnancy included hypertensive disorders in pregnancy (HDP) and hyperglycemia in pregnancy (HIP). Socioeconomic status, psychological state, physical activity and diet were collected by trained staff using a tablet-based questionnaire. Complication of pregnancy was abstracted from medical records. Pre-pregnancy height and weight were each measured twice by trained study personnel using calibrated instruments.

Each inflammation-related adversity was dichotomized or mapped into the 0.00–2.00 interval, with 0.00 indicating the least severe state of inflammation and 2.00 indicating the most severe state of inflammation. The IPAI was calculated for each participant as the 6 inflammation-related adversity are added together.

The IPAI is a continuous variable that ranged from 0.00 to 12.00, with a higher value indicating a worse status of inflammation related exposure. Based on the distribution

Table 1 List of 8 variables of mothers included in the IPAI

Variables	Details of variables	Coding of variables
Household income, CNY	A. < 50,000 B. 50,000-100,000 C. 100,000-200,000 D. 200,000-300,000 E. ≥ 300,000	Options C, D, and E: 0; Options A and B: 1.
Maternal education at children birth, years	A. 0 ~ 6 B. 7 ~ 9 C. 10 ~ 12 D. 13 ~ 16 E. ≥ 17	Options C, D, and E: 0; Options A and B: 1.
Hypertensive disorders in pregnancy	Information on maternal hypertensive disorder was retrieved from electronic medical records and questionnaire during the 2nd trimester of pregnancy.	Without maternal hypertensive disorder: 0; With maternal hypertensive disorder: 1.
Hyperglycemia in pregnancy	Information on maternal diabetes was retrieved from electronic medical records and questionnaire during the 2nd trimester of pregnancy.	Without maternal diabetes: 0; With maternal diabetes: 1.
Psychological state	The psychological state of pregnant women is assessed by three self-filled scales: SAS, CES-D and PSS-10.	A normal score on three scales: 0; An abnormal score on one or two scales: 1; An abnormal score on three scales: 2.
Maternal pre-pregnancy BMI	Data for height and weight was obtained from a baseline questionnaire, then BMI was calculated by weight (kg) / height $(m)^2$.	BMI less than 24: 0; BMI between 24-27.9: 1; BMI greater than or equal to 28: 2.
Physical activity	The intensity of exercise was evaluated according to the MET value, and then the score is assigned according to the weekly exercise time.	Moderate-intensity exercise greater than or equal to 150 min/week or high-intensity exercise greater than or equal to 75 min/week: 0; Moderate-intensity exercise less than 150 min/week or high-intensity exercise less than 75 min/week: 1; Never exercise: 2.
Diet	We calculated a dietary inflammation score based on the intake of 16 types of food. First, all food types were divided into inflammatory foods and anti-inflammatory foods, and then assigned 0 or 1 points according to the median amount of people consumed. The total score is sixteen points, and the higher the score, the more inflammatory foods are consumed.	The dietary inflammation score < 7: 0; The dietary inflammation score ≥ 7 and < 9: 1; The dietary inflammation score ≥ 9: 2.

Abbreviation: IPAI, inflammation related prenatal adversity index; SAS, self-rating anxiety scale; CES-D, center for epidemiological survey, depression scale; PSS-10, perceived stress scale; BMI, body mass index; MET, metabolic equivalent

of score, we further categorized the IPAI into three levels: low IPAI group (IPAI≤2.00), moderate IPAI group (2.00<IPAI<5.00), and high IPAI group (IPAI≥5.00).

Neurodevelopment

The Bayley Scales of Infant and Toddler Development, third edition, screening test (Bayley-III Screening Test) was used to evaluate the neurodevelopment of children aged 11–12.5 months in this study. It consists of five domains: cognition, receptive communication, expressive communication, fine motor, and gross motor. The JBC Study have taken a series of measures in order to ensure the validity and reliability of the neurodevelopment evaluation. All the psychologists have been strictly trained and evaluated before taking up their posts, and after parental consent, the whole process was filmed and randomly checked monthly by an appointed developmental neuropsychologist. Corrected for prematurity, each domain could be divided into at risk, emerging, and competent (Table S1). In this study, participants in the category of at-risk and emerging were classified as noncompetent for analysis. The reliability and validity of Bayley-III Screening Test have been shown to be good to excellent.

Covariates

Information on covariates was primarily extracted from the questionnaires and medical records, including maternal age at delivery, parity (nulliparous/multiparous), child sex (male/female), child age at examination (days), and duration of breast feeding (<6/≥6 months).

Statistical analysis

Baseline characteristics were presented by three categories of inflammation status (i.e., IPAI≤2.00, IPAI>2.00 to <5.00, and IPAI≥5.00) as means (SD) for continuous variables or percentages for categorical variables, with adjustment for maternal age at delivery, parity, child sex, child age at examination, and duration of breast feeding.

The association between IPAI and scores in neurodevelopment was estimated by using a linear regression model, and the association between IPAI and noncompetence in neurodevelopment was estimated by using a Poisson regression model. Regression models were fitted with the use of a generalized linear mixed model given the nonindependence of observations from twin pairs.

In addition, several sensitivity analyses were performed to assess whether the potential associations could be attributed to the confounding by the risk of twins and preterm birth or structural birth defects.

We did all statistical analyses using of R software (Version 4.1.3, R Foundation for Statistical Computing, http://www.cran.r-project. org/). All *p* values were two-sided and the level of statistical significance was defined as *p* less than 0.05.

Results

In this study, a total of 3,051 infants at one year of age from 2,839 families were included. Among them, 1,096 mothers with 1,139 infants were categorized into the "low IPAI" group, 1,094 mothers with 1,176 infants into the "moderate IPAI" group, and 649 mothers with 736 infants into the "high IPAI" group. Compared to mothers in "low IPAI" group, mothers in "moderate and high IPAI" groups were more likely to be older, to be multiparous, to be treated with ART. Compared to infants born to mothers in "low IPAI" group, infants born to mothers with "moderate and high IPAI" were more likely to be caesarean, to be twins, to be male, to be low birth weight and preterm birth (Table 2). Table S2 presented participants' characteristics of sample excluded and included in the analysis. For all variables, the missing rate were below 5% (Table S3).

Associations between IPAI and scores of infant neurodevelopment in five domains were presented in Table 3. In the adjusted model, compared with the "low IPAI" group, the scores of the "moderate IPAI" group decreased by 0.30 (95%CI: -0.46, -0.13) points in the receptive communication domain, and 0.20 (95%CI: -0.37, -0.04) points in the expressive communication domain, respectively. The scores of the "high IPAI" group decreased by 0.23 (95%CI: -0.42, -0.04) points in the cognition domain, 0.47 (95%CI: -0.66, -0.28) points in the receptive communication domain, 0.30 (95%CI: -0.49, -0.11) points in the expressive communication domain, and 0.20 (95%CI: -0.33, -0.06) points in the fine motor domain, respectively. There was a dose-response relationship in these four domains.

Associations between IPAI and noncompetent development of infant's neurodevelopment in five domains were presented in Table 4. In addition to the expressive communication domain, the proportion of noncompetent development in four domains (cognition, receptive communication, fine motor and gross motor) increased with increasing IPAI. In particular, the prevalence of noncompetent development in receptive communication was higher, ranging from 14.2 to 20.1%. The elevated risk was observed for noncompetent development of cognition, receptive communication and expressive communication among "moderate IPAI" group. The RR and 95%CI were 1.30 (1.01, 1.69), 1.26 (1.02, 1.55) and 1.43 (1.02, 2.01), respectively. The elevated risk was observed for noncompetent development of cognition and receptive communication among "high IPAI" group. The RR and 95%CI were 1.35 (1.01, 1.80) and 1.37(1.09, 1.72), respectively.

Associations were robust to all sensitivity analyses, including [1] exclusion of preterm birth and twins [2],

Table 2 Baseline characteristics of offspring exposed in inflammation related prenatal adversity index (IPAI) groups

Variable	Low IPAI (*n* = 1139)	Moderate IPAI (*n* = 1176)	High IPAI (*n* = 736)	*p*
Maternal age at delivery, years[a]	29.90 (3.61)	30.14 (3.91)	30.34 (4.03)	0.056
Parity[b]				0.218
Nulliparous	860 (80.8)	825 (77.8)	482 (79.3)	
Multiparous	204 (19.2)	236 (22.2)	126 (20.7)	
Mode of conception[b]				< 0.001
Spontaneous	775 (70.7)	667 (61.0)	288 (44.4)	
ART	321 (29.3)	427 (39.0)	361 (55.6)	
Center[b]				0.001
Changzhou	241 (22.0)	254 (23.2)	158 (24.3)	
Nanjing	620 (56.6)	563 (51.5)	304 (46.8)	
Suzhou	235 (21.4)	277 (25.3)	187 (28.8)	
Mode of delivery[b]				< 0.001
Caesarean	497 (45.6)	556 (51.0)	403 (62.3)	
Vaginal	593 (54.4)	534 (49.0)	244 (37.7)	
Smoking during pregnancy[b]				0.026
Yes	2 (0.2)	1 (0.1)	5 (0.8)	
No	1094 (99.8)	1093 (99.9)	644 (99.2)	
Plurality[b]				< 0.001
Singleton	1050 (92.2)	1010 (85.9)	555 (75.4)	
Twins	89 (7.8)	166 (14.1)	181 (24.6)	
Infant sex[b]				0.186
Boy	587 (51.5)	622 (52.9)	411 (55.8)	
Girl	552 (48.5)	554 (47.1)	325 (44.2)	
Gestational age, weeks[a]	39.26 (1.56)	38.96 (1.64)	38.38 (2.18)	< 0.001
Preterm birth, < 37 weeks[b]				< 0.001
Yes	78 (6.8)	136 (11.6)	139 (18.9)	
No	1061 (93.2)	1040 (88.4)	597 (81.1)	
Birth weight, gram[a]	3306.79 (483.86)	3256.38 (529.57)	3173.10 (623.02)	< 0.001
Low birth weight, < 2500g[b]				< 0.001
Yes	54 (4.8)	102 (8.7)	89 (12.1)	
No	1079 (95.2)	1069 (91.3)	644 (87.9)	0.982
Breastfeeding duration, months[b]				< 0.001
< 6	168 (14.8)	241 (20.5)	189 (25.8)	
≥ 6	970 (85.2)	932 (79.5)	544 (74.2)	
Age at assessment, years[a]	1.00 (0.02)	1.00 (0.02)	1.00 (0.02)	

Abbreviation: SD: standard deviation; IPAI: inflammation related prenatal adversity index; ART: assisted reproductive technology

[a] Expressed as mean (SD)

[b] Expressed as frequency (percentage)

[c] Infants include twins

exclusion of offspring with structural birth defects. See **Table S4-S7** for details.

Discussion

In this prospective cohort, we constructed the IPAI based on six maternal adversities factors to analyze the associations between prenatal inflammation related adversities and neurodevelopment of infants at one year of age. We found that higher IPAI was associated with lower scores across cognition, receptive communication, expressive communication, and fine motor domains. In particularly, increased IPAI was also associated with an increased risk of noncompetent development in cognition and receptive communication domains.

Our findings gain some support from several previous studies which focused on neurodevelopmental disorders. A birth cohort in Japan analyzed maternal dietary inflammatory index (DII) scores one year before pregnancy, and evaluated effects on the neurodevelopment of offspring aged three years. They found that delayed development in communication, fine motor, problem-solving, and social skills at age three years increased along with the DII category [38]. A population-based study in Sweden reported that offspring of parents with lower socioeconomic status

Table 3 Associations of prenatal inflammation related adversity index with infant's neurodevelopmental scores

Outcome	No.[a]	Crude Model		Adjusted Model[b]	
		β (95%CI)	*P*	β (95%CI)	*P*
Cognition					
Low IPAI	16.00 (1.87)	Ref.		Ref.	
Moderate IPAI	15.85 (2.03)	-0.14 (-0.30, 0.02)	0.089	-0.15 (-0.31, 0.02)	0.078
High IPAI	15.71 (1.91)	-0.28 (-0.46, -0.09)	0.003	-0.23 (-0.42, -0.04)	0.018
P-trend		0.004		0.020	
Receptive communication					
Low IPAI	11.47 (1.97)	Ref.		Ref.	
Moderate IPAI	11.13 (1.98)	-0.33 (-0.49, -0.17)	< 0.001	-0.30 (-0.46, -0.13)	< 0.001
High IPAI	10.93 (1.94)	-0.52 (-0.71, -0.34)	< 0.001	-0.47 (-0.66, -0.28)	< 0.001
P-trend		< 0.001		< 0.001	
Expressive communication					
Low IPAI	11.98 (1.93)	Ref.		Ref.	
Moderate IPAI	11.74 (1.99)	-0.23 (-0.39, -0.06)	0.006	-0.20 (-0.37, -0.04)	0.017
High IPAI	11.68 (1.94)	-0.30 (-0.48, -0.11)	0.002	-0.30 (-0.49, -0.11)	0.002
P-trend		0.002		0.003	
Fine motor					
Low IPAI	13.09 (1.42)	Ref.		Ref.	
Moderate IPAI	12.96 (1.44)	-0.12 (-0.24, -0.01)	0.040	-0.11 (-0.23, 0.01)	0.065
High IPAI	12.83 (1.38)	-0.25 (-0.38, -0.12)	< 0.001	-0.20 (-0.33, -0.06)	0.005
P-trend		< 0.001		0.006	
Gross motor					
Low IPAI	14.64 (1.59)	Ref.		Ref.	
Moderate IPAI	14.55 (1.59)	-0.07 (-0.20, 0.06)	0.298	-0.04 (-0.18, 0.09)	0.530
High IPAI	14.46 (1.65)	-0.17 (-0.32, -0.01)	0.033	-0.10 (-0.26, 0.05)	0.191
P-trend		0.034		0.192	

[a] Expressed as mean (SD)

[b] Adjusted for parity, breast-feeding duration, maternal age at delivery, child sex and child age at examination

had a 40% elevated risk of autism spectrum disorder [39]. A meta-analysis indicated that compared with children of mothers with normal weight, those mothers were overweight or obese prior to pregnancy were at an 17–51% increased risk for compromised neurodevelopmental outcomes [24]. In a cohort study in Denmark, prenatal exposure to maternal type 2 diabetes during pregnancy was associated with an 33% increased risks of overall and type-specific mental disorders in offspring [40]. A South African study found that maternal symptoms of prenatal depression were associated with lower language development scores in their offspring at age 2 years [41]. A randomized controlled trial nested into the 2015 Pelotas (Brazil) Birth Cohort found that compared with the control group, children from women in the exercise group had higher language score at age 2 years [42]. However, these studies only evaluated associations between single exposure and neurodevelopmental outcomes. Although each study reported an effect size, the total effect of multiple factors is still unclear. In our prospective cohort study, we observed an 30% increased risk of adverse receptive communication outcome in moderate IPAI group and an 40% increased risk in high IPAI group, compared with low IPAI group. It's important to note that the effect size of the increased IPAI score is not much higher than the effect size of a single exposure, though the high IPAI means a co-exposure of multiple adversities factors. It may be suggested that the assessment of a single exposure may have limitations in controlling for confounding bias. The IPAI may reflect an overall comprehensive effect of combined exposure.

The biological mechanisms underlying prenatal inflammation related adversities and neurodevelopment in offspring are not completely understood. MIA has been a hot hypothesis in recent years [16]. Evidence from human and animal studies indicates that maternal immune activation programmes the fetal brain and immune system through inflammatory and epigenetic mechanisms during key periods of central nervous system (CNS), microglial and immune system development [43]. Maternal inflammatory factors induce the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which activate Toll-like receptors on maternal peripheral innate immune cells and placental cells, leading to cytokine production [44, 45]. It is worth noting that elevated levels of cytokine IL-1β may play a mechanistic role in the cross-generational effects of children's language development

Table 4 Associations of prenatal inflammation related adversity index with the risk of non-competent in five domains of neurodevelopment in infants

Outcome	No.[a]	Crude Model		Adjusted Model[b]	
		RR (95%CI)	*P*	RR (95%CI)	*P*
Cognition					
Low IPAI	108 (9.5)	Ref.		Ref.	
Moderate IPAI	140 (11.9)	1.26 (0.98, 1.61)	0.076	1.30 (1.01, 1.69)	0.042
High IPAI	97 (13.2)	1.39 (1.06, 1.83)	0.019	1.35 (1.01, 1.80)	0.039
P-trend		0.024		0.056	
Receptive communication					
Low IPAI	162 (14.2)	Ref.		Ref.	
Moderate IPAI	216 (18.4)	1.29 (1.05, 1.58)	0.014	1.26 (1.02, 1.55)	0.032
High IPAI	148 (20.1)	1.41 (1.13, 1.77)	0.002	1.37 (1.09, 1.72)	0.007
P-trend		0.004		0.011	
Expressive communication					
Low IPAI	57 (5.0)	Ref.		Ref.	
Moderate IPAI	87 (7.4)	1.48 (1.06, 2.06)	0.022	1.43 (1.02, 2.01)	0.036
High IPAI	44 (6.0)	1.19 (0.81, 1.77)	0.376	1.20 (0.81, 1.79)	0.363
P-trend		0.506		0.472	
Fine motor					
Low IPAI	28 (2.5)	Ref.		Ref.	
Moderate IPAI	41 (3.5)	1.42 (0.88, 2.29)	0.154	1.41 (0.87, 2.30)	0.163
High IPAI	28 (3.8)	1.55 (0.92, 2.61)	0.102	1.37 (0.79, 2.37)	0.261
P-trend		0.126		0.326	
Gross motor					
Low IPAI	99 (8.7)	Ref.		Ref.	
Moderate IPAI	109 (9.3)	1.07 (0.81, 1.40)	0.643	1.06 (0.80, 1.40)	0.682
High IPAI	80 (10.9)	1.25 (0.93, 1.68)	0.137	1.20 (0.89, 1.63)	0.231
P-trend		0.131		0.226	

[a] Expressed as frequency (percentage)

[b] Adjusted for parity, breast-feeding duration, maternal age at delivery and child sex

[23]. Temporal cortex and inferior frontal cortex play an important role in language function [46]. A study in a mouse model of maternal immune activation demonstrated that Il-1 receptor (Il1r) and Interleukin 1 Receptor Accessory Protein Like 1 (Il1rapl1) mRNA levels in the offspring's frontal cortex initially rose during early synaptogenesis but decreased during its peak [47]. Microglia play an important role in synaptic transmission, information processing and the homeostatic landscape of the CNS [48]. Defects in microglial synaptic pruning, result in pathological malformation of neuronal circuits and contribute to the pathophysiology of several cognitive impairments including autistic spectrum and psychiatric disorders [49].

The rate of poor receptive communication development was significantly higher than in the other four domains. A view, strongly favored by evidence accumulating over several decades, is that poor receptive communication results from damage to a cortical region separate from both sensory speech perception and speech articulation systems. The function of this region, which includes the posterior Superior Temporal Gyrus (pSTG) and adjacent cortex in the superior temporal sulcus and supramarginal gyrus, is to store and mentally activate phonological (speech sound) forms [50]. A rat study revealed that MIA induces presynaptic protein deficits and down-regulation of postsynaptic scaffolding proteins in the pSTG region in the adolescent rat offspring, in addition to elevated blood cytokine levels, microglial activation, increased pro-inflammatory cytokines expression and increased oxidative stress in the cerebral cortex. Thus, this may affect receptive communication development [51].

Our study has strength in two aspects. Firstly, this is the first study to establish an IPAI and to report a significant association between this index and neurodevelopmental outcomes at one year of age. In addition, we used data of well-designed large-scale birth cohort with long-term follow-up, which provided comprehensive variable acquisition and high data quality. Two limitations also should be noted. First, we lacked biological indicators that reflected maternal inflammatory states, such as cytokines and c-reaction protein (CRP), and could not be analyzed further. Second, despite the good design and strict quality control measures of our study, we were unable to fully consider all confounding factors.

In this prospective birth cohort study, we, for the first time, formulated the IPAI based on six maternal adversities factors. Our results revealed a significant association between higher IPAI and lower scores across cognition, receptive communication, expressive communication, and fine motor domains, and an increased risk of non-competent development in the cognition and receptive communication domains. These findings not only contribute substantial population evidence supporting the Maternal Immune Activation (MIA) hypothesis but, more significantly, highlighted the crucial role of avoiding maternal inflammation-related adversities in preventing infant neurodevelopmental delays.

Abbreviations

MIA	Maternal Immune Activation
IPAI	Inflammation related Prenatal Adversity Index
JBC	Jiangsu Birth Cohort
Bayley-III	Bayley Scales of Infant and Toddler Development, Version-III
BMI	Body mass index
CES-D	Center for Epidemiological Survey, Depression Scale
SAS	Self-Rating Anxiety Scale
PSS-10	Perceived Stress Scale
MET	Metabolic equivalent
HDP	Hypertensive disorders in pregnancy
HIP	Hyperglycemia in pregnancy
DII	Dietary inflammatory index
CNS	Central nervous system
PAMPs	Pathogen-associated molecular patterns
DAMPs	Damage-associated molecular patterns
Il1rapl1	Interleukin 1 Receptor Accessory Protein Like 1
pSTG	posterior Superior Temporal Gyrus
CRP	C-reaction protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-024-06839-8.

Additional file 1: Supplementary methods. Questionnaire used in the Jiangsu Birth Cohort (JBC). **Supplementary Table 1.** Bayley grading table. **Supplementary Table 2.** Participant characteristics of sample excluded and included in the analysis. **Supplementary Table 3.** The characteristics of missing data. **Supplementary Table 4.** Associations of IPAI with infant's neurodevelopmental scores excluding infant with preterm birth and twins. **Supplementary Table 5.** Associations of IPAI with the risk of non-competent in five domains of neurodevelopment in infants excluding infant with preterm birth and twins. **Supplementary Table 6.** Associations of IPAI with infant's neurodevelopmental scores excluding infant with structural birth defects. **Supplementary Table 7.** Associations of IPAI with the risk of non-competent in five domains of neurodevelopment in infants excluding infant with structural birth defects.**Supplementary Fig. 1.** Flowchart of included and excluded pregnancies.

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Author contributions

MG, X-XZ and W-TW contributed to conceptualization, investigation, formal analysis, data curation and writing - original draft. KY, Y-QJ, TJ, HL, QL and RQ contributed to investigation and data curation. S-YT, LH, XX, CL, Y-YD, KK, T-YS, Y-XL contributed to investigation. YJ and X-MH contributed to validation and funding acquisition. G-FJ, H-XM, H-BS and B-ZH contributed to conceptualization, project administration and supervision. Y-CG, YL and J-BD contributed to conceptualization, writing - review & editing and supervision. All authors approved the final version.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to our containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations under Ethics approval and consent to participate. All procedures were approved by the institutional review board of Nanjing Medical University, China NJMUIRB (2017) 002. All participants gave their written informed consent at the time of recruitment. Additionally, prior to administering the Bayley-III Screening Test, we secured an additional informed consent specifically for this assessment from each child's guardian.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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