Association between Placental Inflammatory Pathology and Offspring Neurodevelopment at 8 Months and 4 and 7 Years of Age

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Objective To examine whether placental inflammatory pathology is associated with subsequent child neurodevelopment.

Study design We used the data of US Collaborative Perinatal Project cohort study. Placentas were examined by pathologists and child neurodevelopment was evaluated at 8 months and 4 and 7 years of age. Multivariable logistic regression modelling was used to assess the association. A mediation analysis was used to evaluate whether the association was mediated through shorter gestational age.

Results Multivariable analysis after adjusting for confounders showed that placental inflammatory pathology was significantly associated with low Bayley motor (adjusted OR (aOR), 2.15; 95% CI, 1.50-3.06) and mental scales (aOR, 1.51; 95% CI, 1.05-2.17) at 8 months and an IQ of 70-84 (aOR, 1.13; 95% CI, 1.01-1.26) at 4 years of age. The association diminished at 7 years of age (IQ of <70, aOR 1.20 [95% CI, 0.97-1.48]; IQ of 70-79, aOR 1.03 [95% CI, 0.89-1.18]). The mediation analysis demonstrated that associations between placental inflammatory pathology and development were primarily due to direct effects of placental inflammatory pathology rather than indirect effects of shorter gestational age.

Conclusions Placental inflammation was associated with adverse offspring neurodevelopment up to 4 years of age. *(J Pediatr 2020;225:132-7)*.

The developmental origins of health and disease hypothesis posited that in utero environment could shape the health trajectory of the offspring throughout life.[1] During this process, the placenta, which supplies oxygen and nutrients and acts as a neuroendocrine organ, plays a key role in early life programming.[2] It also mediates a series of complex maternal-fetal interactions, such as integrating nutrients and prenatal stress signals into chromatin changes. Insults to the placental microenvironment can impair these processes and disrupt fetal brain development.[3]

A number of studies have linked abnormal placental gross morphologic and histopathologic features with a wide range of adverse neurodevelopmental outcomes. For example, chorioamnionitis, one of the intrauterine infection indicators, has been associated with childhood speech delay and hearing loss at 18 months of age, moderate to severe psychomotor disability at 2 years of age, poorer cognitive outcome, and weaker memory and learning functions at 5 years of age.[4-6] In a meta-analysis including 17 studies with 125 256 patients with chorioamnionitis and 5 994 722 controls, the investigators found a significant association between preterm histologic chorioamnionitis and cerebral palsy.[7]

As a key organ regulating the fetal environment, the placenta is critical to fetal health. Its pathology may adversely affect placental transport and endocrine functions and lead to reprogramming of fetal organ development via epigenetic modifications and, consequently, impact both short- and long-term neurobehavioral development in offspring.[8,9] Therefore, further understanding of placental pathologic features might help us to predict future infant cognitive neurobehavioral outcomes.[8]

We have previously demonstrated that the placental inflammatory measures had a high prognostic relevance to child morbidity.[10] The purpose of this study was to determine the association between placental inflammatory pathology and subsequent neurodevelopmental outcomes at 8 months and 4 and 7 years of age.

Methods

We used data from the Collaborative Perinatal Project (CPP), a prospective cohort study of pregnancy and child health conducted at 12 hospitals in the United States from 1959 to 1976 (www.Archives.gov). A detailed description of the CPP is provided elsewhere.[11] Pregnant women were enrolled at their first prenatal visit, with an average gestational age of 21.3 ± 8.4 weeks. During the

CPP	Collaborative Perinatal Project
SES	Socioeconomic status

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pregnancy, detailed information was collected on demographic factors, socioeconomic status (SES), behavior, and disease. The recruitment rate was greater than 95% and the follow-up rate was up to 96% during pregnancy.[12] After delivery, placentas were sent for pathologic examination and infants were assessed and followed to 7 years of age. In our study, we included only singleton liveborn mother-child pairs. Women with multiple births, missing maternal age or sex of infants, extreme values for gestational age (<28 or >45 weeks), and children without neurodevelopment assessment or placental examination were excluded, leaving 32 326 for the final analysis.

Placental Pathologic Evaluation

The CPP placental pathologic measurements were performed by trained pathologists, including 103 gross and microscopic histologic assessments on the cord, membranes, fetal surface, maternal surface, cut surface, decidua, terminal villi, and intervillous space according to Dr Benirschke's protocol.[13] Gross morphology assessments were carried out immediately after birth. Placental samples were taken from the umbilical cord, fetal membrane roll, a full layer of the placental tissue with about 3 cm from the attachment of the umbilical cord, and any suspicious abnormalities in the gross morphology assessments for microscopic histologic assessments.[13] Pathologists were blinded to clinical conditions when making the pathologic diagnosis in 98% of the gross morphology assessments and 97% of the microscopic histologic assessments.[13]

In our previous study, 5 experienced placental pathologists worked in tertiary hospitals for more than 15 years selected 26 placental morphologic and histopathologic measures relevant to inflammation by consensus.[10,12] Measures were recoded into categorical variables. The detailed description of the placenta pathologic measurement, selection and classification were described previously and presented in **Table I**.[10,12] In our analysis, we focused on 10 measures specific to histologic chorioamnionitis (UMBIVEIN, UMBIARTY, CORDSUBS, NECRAMNI, BACTCOLY, AMNIMEM, CHORMEM, AMNIPLAC, CHORPLAC, FETLVESS). If any one of these pathologic findings was positive, the composite inflammatory index was coded as 1; otherwise, it was 0.

Neurodevelopmental Outcomes

The CPP conducted neurologic and psychological examinations with standardized instruments and procedures, and psychologists verified the extreme scores to ensure the reliability.[14] At 8 months of age, the infants were assessed using the Bayley Scales of Infant Development. The motor score, ranging from 0 to 43, was categorized as low (0-19), suspect (20-26), or normal (27-43). The mental score, ranging from 0 to 103, was categorized as low (0-55), suspect (56-74), or normal (75-103).[14,15] The Stanford-Binet IQ scale was used to assess child IQ at 4 years of age and the score was

Table I. Definition of placental measures in the CPP database, 1959-1976

Variable	Clinical meaning	Coding
Gross examination		
COLRCORD	Color of cord	0: Others; 1: Yellow
MEM_F	Membranes and fetal surface: description of membranes	0: Others; 1: Velamentous vessels
DECI_NEC	Membranes and fetal surface: Decidual necrosis	0: Not seen grossly or not massive; 1: Massive
MEM_EDEM	Membranes and fetal surface: Membranes edematous	0: Not seen grossly or not massive; 1: Massive
COLOSURF	Membranes and fetal surface: Color	0: Others; 1: Brownish-yellow
OPACMEM	Membranes and fetal surface: Opacity of membranes	0: Not opaque; 1: Opaque
pbw_ratio	Placental weight–birthweight ratio	0: Placental weight–birthweight ratio ≤90th percentile for a given gestational week; 1: Placental weight–birthweight ratio >90th percentile for a given gestational week
Microscopic examination		
UMBIVEIN	Cord: neutrophilic infiltration in umbilical vein	0: Not seen or slight; 1: Marked
UMBIARTY	Cord: neutrophilic infiltration in umbilical artery	0: Not seen or slight; 1: Marked
CORDSUBS	Cord: neutrophilic infiltration in cord substance	0: Not seen or slight; 1: Marked
NECRAMNI	Membranes: epithelium of amnion- necrosis	0: Not seen or slight; 1: Marked
BACTCOLY	Membranes: epithelium of amnion- bacterial colonies	0: Not seen; 1: Present
AMNIMEM	Membranes: neutrophilic infiltration in amnion of membrane roll	0: Not seen or slight; 1: Marked
CHORMEM	Membranes: neutrophilic infiltration in chorion of membrane roll	0: Not seen or slight; 1: Marked
AMNIPLAC	Membranes: neutrophilic infiltration at amnion of placental surface	0: Not seen or slight; 1: Marked
CHORPLAC	Membranes: neutrophilic infiltration at chorion of placental surface	0: Not seen or slight; 1: Marked
FETLVESS	Membranes: neutrophilic infiltration in fetal surface vessels	0: Not seen or slight; 1: Marked
NECRMARG	Decidua: necrosis at margin	0: Not marked; 1: Marked
NECRCAPS	Decidua: necrosis in capsularis	0: Not marked; 1: Marked
NECRBASA	Decidua: necrosis in basalis	0: Not marked; 1: Marked
NEUTMARG	Decidua: neutrophilic infiltration at margin	0: Not seen or slight; 1: Marked
NEUTCAPS	Decidua: neutrophilic infiltration in capsularis	0: Not seen or slight; 1: Marked
NEUTBASA	Decidua: neutrophilic infiltration in basalis	0: Not seen or slight; 1: Marked
LYMPMARG	Decidua: lymphocytic infiltration at margin	0: Not seen or slight; 1: Marked
LYMPCAPS	Decidua: lymphocytic infiltration in capsularis	0: Not seen or slight; 1: Marked
LYMPBASA	Decidua: lymphocytic infiltration in basalis	0: Not seen or slight; 1: Marked

categorized into 5 groups: less than 70, 70-84, 85-114, 115-129, and 130-181, corresponding with 1 and 2 SDs of the mean.[14,15] The assessment at 7 years of age used the Wechsler Intelligence Scale for Children and the scores were classified into four groups: less than 70, 70-79, 80-119, and 120 or higher.[14,15]

Factors that might affect the relationship between placental pathology and neurodevelopment were chosen as potential confounders according to the previous literature.[14] They were adjusted in the analysis, including: maternal age (grouped as <20, 20-34, and ≥35 years old), maternal race (white, black, and other races), SES index (devised by the Bureau of the Census based on family income as well as household head's education and occupation, and categorized into 5 categories, with 1 and 5 being the lowest and highest, respectively), education levels (less than high school, high school, and college and above), body mass index before pregnancy (defined as weight in kg divided by squared height in meters, and grouped as <25.0, 25.0-29.9, and ≥ 30.0 kg/m^2), smoking (no/yes), parity (0, 1, and >1) and infant sex (male/female).[16]

Statistical Analyses

We first described the maternal and perinatal characteristics and compared the rate between those with and without placental inflammatory pathology using standard χ^2 tests. Then, a multivariable logistic regression model was used to explore the relationship between the placental inflammatory pathology and Bayley scale at 8 months and child IQ at 4 and 7 years of age. Model 1 included the following potential confounders: maternal age, race, SES, education levels, body mass index before pregnancy, smoking status, parity, and infant sex.[14] Model 2 further adjusted for gestational age in addition to all the variables included in model 1.

To determine whether the association between placental inflammatory pathology and neurodevelopmental outcomes was mediated through shorter gestational age, a mediation analysis was conducted by fitting generalized linear model for the mediator (gestational age) and logistic regression for the neurodevelopmental outcomes via R software version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) medflex package neModel function.[17] We calculated the natural direct effect and natural indirect effect. The natural direct effect was interpreted as the effect of placental inflammatory pathology on abnormal IQs if the mediator (gestational age) were set to what it would have been with the normal placental pathology. The natural indirect effect referred to the effect of placental pathology on abnormal IQs when inflammation was present after setting the mediator value to what it would have been with vs without placental pathology.[18]

All the analyses were carried out in R software. Complete case approach was used to deal with missing value. CPP database was publicly available data with de-identified information (www.Archives.gov) and was exempt from the Ethics Committee review by the Xinhua Hospital, Shanghai Jiao Tong University School of Medicine.[11]

Table II. Characteristics of included and excluded subjects (n = 54 371)

Characteristics	Proportion of the included subjects, % (n = 32 326)	Proportion of the excluded subjects, % (n = 22 045)	*P* value
Maternal age (years)			.01
<20	23.1	24.3	
20-34	69.5	68.3	
≥35	7.3	7.4	
Race			<.01
Non-Hispanic white	47.7	44.6	
Non-Hispanic black	45.2	48.8	
Others	7.1	6.7	
Maternal educational levels			<.01
Less than high school	28.4	30.3	
High school	59.2	57.9	
College and above	12.5	11.8	
SES			<.01
1	7.2	8.9	
2	30.7	32.5	
3	31.0	31.3	
4	20.3	18.7	
5	10.8	8.7	
Prepregnancy body mass index (kg/m^2)			.51
<25	79.5	79.8	
25-29.9	15.6	15.2	
≥30	4.9	5.0	
Smoking during pregnancy			<.01
No	52.4	54.6	
Yes	47.6	45.4	
Parity			.94
0	37.4	37.2	
1	24.1	24.2	
>1	38.5	38.6	
Preterm birth			<.01
No	85.2	81.8	
Yes	14.8	18.2	
Infant sex			.96
Male	50.8	50.8	
Female	49.2	49.2	

P values are χ^2 test between included and excluded subjects.

Results

A total of 32 326 eligible infants with detailed information and assessment of placental pathology and neurodevelopment were included in the analysis. The subject selection process is illustrated in the **Figure** (available at www.jpeds.com). **Table II** compares the maternal and infant characteristics between included and excluded subjects. In our study, 7782 women (24.1%) had positive placental inflammatory pathology. Placental inflammatory pathology was associated with sociodemographic factors of older age, other race, overweight/obesity before pregnancy, smoking, multiparity, lower education and SES, preterm birth, and a male fetus (**Table III**; available at www.jpeds.com; all $P < .05$).

Table IV. Multivariable analysis of neurodevelopmental outcomes in relation to placental inflammatory pathology

Neurodevelopmental outcomes	Model 1, aOR_1 (95% CI)	Model 2, aOR_2 (95% CI)
Bayley motor scale assessments at 8 months		
Abnormal low (0-19)	2.21 (1.55-3.14)	2.15 (1.50-3.06)
Suspect (20-26)	0.93 (0.80-1.08)	0.92 (0.79-1.07)
Normal (27-43)	–	–
Bayley mental scale assessments at 8 months		
Abnormal low (0-55)	1.56 (1.09-2.24)	1.51 (1.05-2.17)
Suspect (56-74)	0.98 (0.85-1.14)	0.98 (0.84-1.13)
Normal (75-103)	–	–
Stanford-Binet IQ scale at 4 years		
<70	1.19 (0.97-1.47)	1.19 (0.96-1.46)
70-84	1.13 (1.01-1.26)	1.13 (1.01-1.26)
85-114	–	–
115-129	0.99 (0.85-1.15)	0.99 (0.85-1.15)
≥130	0.72 (0.51-1.01)	0.71 (0.51-1.00)
Wechsler 7-year Intelligence Full-scale IQ		
<70	1.20 (0.97-1.49)	1.20 (0.97-1.48)
70-79	1.03 (0.89-1.19)	1.03 (0.89-1.18)
80-119	–	–
≥120	0.96 (0.76-1.20)	0.96 (0.76-1.20)

Model 1 is a logistic model adjusted for maternal age, race, education levels, SES, pre-pregnancy body mass index, smoking, parity, and infant sex.
Model 2 is a logistic model adjusted for maternal age, race, education levels, SES, prepregnancy body mass index, smoking, parity, infant sex, and gestational age.

Table V. Mediation analysis of the association between placental inflammatory pathology and neurodevelopment through gestational age

Neurodevelopmental outcomes	Natural direct effect aOR_{NDE} (95%CI)	Natural indirect effect aOR_{NIE} (95%CI)
Bayley motor scale assessments at 8 months		
Abnormal low (0-19)	2.25 (1.60-3.17)	0.97 (0.92-1.03)
Suspect (20-26)	0.94 (0.80-1.09)	0.99 (0.96-1.01)
Normal (27-43)	–	–
Bayley mental scale assessments at 8 months		
Abnormal low (0-55)	1.57 (1.11-2.23)	1.01 (0.97-1.06)
Suspect (56-74)	0.99 (0.86-1.14)	0.99 (0.97-1.01)
Normal (75-103)	–	–
Stanford-Binet IQ scale at 4 years		
<70	1.18 (0.96-1.47)	1.01 (0.99-1.03)
70-84	1.13 (1.01-1.27)	1.00 (0.99-1.01)
85-114	–	–
115-129	0.99 (0.85-1.16)	0.99 (0.98-1.01)
≥130	0.71 (0.51-1.03)	0.99 (0.97-1.02)
Wechsler 7-year Intelligence Full-scale IQ		
<70	1.21 (0.98-1.50)	1.00 (0.99-1.02)
70-79	1.03 (0.89-1.19)	1.00 (0.99-1.02)
80-119	–	–
≥120	0.96 (0.76-1.21)	1.00 (0.99-1.02)

aOR_{NDE}, aOR for natural direct effect in mediation analysis; aOR_{NIE}, aOR for natural indirect effect in mediation analysis.
Adjusted for maternal age, race, educations, SES, pre-pregnancy body mass index, smoking, parity, and infant sex.

The associations between placental inflammatory pathology and child neurodevelopmental outcomes at 8 months, 4 and 7 years of age are presented in Table IV. The multivariable analysis after adjusting for confounders (excluding gestational age) shows that the placental inflammatory pathology was significantly associated with low Bayley motor (aOR, 2.21; 95% CI, 1.55-3.14) and mental scales (aOR, 1.56; 95% CI, 1.09-2.24) at 8 months and IQ 70-84 (aOR, 1.13; 95% CI, 1.01-1.26) at 4 years of age. However, the association diminished at 7 years of age (IQ of <70, aOR 1.20 [95% CI, 0.97-1.49]; IQ of 70-79, aOR 1.03 [95% CI, 0.89-1.19]). Further adjustment for gestational age at birth did not substantially change the results.

Finally, we tested whether the association between placental inflammatory pathology and abnormal child neurodevelopment was mediated by shorter gestational age after controlling for potential confounders. Table V indicates that the low Bayley and IQ scores were largely due to direct rather than indirect effects.

Discussion

Our study indicated that placental inflammatory pathology increased the offspring's risk of delayed neurodevelopment up to 4 years of age. The association was not mediated through shorter gestational age in pregnancies with placental inflammatory pathology.

Accumulating evidence demonstrates that an unfavorable fetal intrauterine environment can alter brain development and behavioral phenotype and exert a profound impact on child long-term health.[8,19] The placenta plays a critical role in transferring inflammatory signals from mother to fetus.[20] In a review by Wang et al, antenatal inflammation was found to be the strongest predictor of brain lesions: fetal exposure to the bacterial mimetics, such as lipopolysaccharide, increased the sensitivity of the brain to subsequent hypoxic or ischemic outcomes, even persisting into adulthood.[21] After lipopolysaccharide administration to pregnant mice, the placenta exhibited inflammatory cell infiltration and altered gene expression related to neurogenesis and neurite outgrowth.[22] Offspring manifested impaired social preferences and reduced motivational behaviors in adulthood.[23] Furthermore, placental inflammation has been shown to activate the signal cascade and release cytokines and chemokines passing across post-capillary venules into the Virchow-Robin space, and transmitting inflammatory signals to other cells in the central nervous system, resulting in prolonged neuroinflammation.[24]

The Extremely Low Gestational Age Newborn study collected blood on postnatal days 1, 7, and 14 from 939 extremely premature infants and measured 25 inflammation-related protein concentrations.[25] Elevated levels of inflammation-related proteins such as IL-6, IL-8, myeloperoxidase, and tumor necrosis factor-α were associated with increased risk of early cognitive impairment, microcephaly, and attention problems assessed using the Bayley Scales of Infant and Toddler Development II and the Child Behavior Check List at 2 years of age.[25] In the first 2 weeks after birth, elevated levels of C-reactive protein, tumor necrosis factor-α, IL-8, intercellular adhesion

molecule-1, and erythropoietin were related to cognitive impairment assessed by the Differential Ability Scales-II at 10 years of age.[26] In the Philadelphia cohort of the CPP, individuals exposed to elevated maternal levels of IL-4, IL-5, and IL-13, anti-inflammatory Th2 cytokines were significantly less likely to develop psychosis in adulthood, whereas an elevated level of tumor necrosis factor-α was associated with increased odds of schizophrenia and other psychoses in the offspring.[27,28]

Our results were consistent with the previous studies in that placental inflammatory pathology demonstrated a long-lasting impact on neurodevelopment, with a 2.15-fold increased risk of low motor scores and 1.51-fold risk of low mental scores at 8 months, and a 1.13-fold increased risk of an IQ of 70-84 at 4 years. This increased risk occurred during early childhood but was mitigated at 7 years of age. This catch-up may be due to compensatory parental care or physiologic recovery of the brain injury. Unfortunately, CPP did not collect information to allow us to further explore the recovery process and mechanisms.[29] Moreover, IQ only reflects 1 aspect of neurodevelopment, and other unmeasured outcomes, such as executive function, social abilities, and learning and attentional limitations may also be affected. Their degrees of recovery remain uncertain.

In addition to a direct effect of the inflammatory response on the fetal brain, placental inflammation may also lead to premature birth and, in turn, affect infant brain development.[19] These 2 effects intertwine with each other and have not been disentangled in previous studies.[29] Our study demonstrated that, although gestational age partially accounted for the total effect on neurodevelopment delays, the direct effect of the inflammatory response on fetal brain remained dominant. This new finding underscores the significance of placental inflammation on fetal brain development and its long-term impact.

The CPP cohort is notable for detailed placental pathology and a very large prospective placental database, including long-term follow-up of child development. Placental gross morphology and histopathology were carefully examined with a standard protocol, and the neurodevelopment evaluations were well-documented. In this study, we used a composite measure of inflammation because the combination of sensitive and specific measures was more predictive than a single measure to evaluate the placenta owing to its large reserve capacity.[10] The prospective nature of this study was a strength because recall bias was avoided. However, the cohort was relatively old, and the distribution of maternal characteristics might have changed during the past 50 years. A potential limitation is the exclusion of more than one-third of the cohort because of missing data for key variables. Although the large sample size led to statistical differences in some of the maternal characteristics between included and excluded mother-child pairs, they were numerically very similar. Thus, the exclusion was unlikely to introduce substantial bias into the analysis. Finally, although we have adjusted for a variety of confounders, unmeasured confounding factors such as family environment as well as nutritional factors might have also altered the associations to an unknown degree.

In this study, placental inflammation was associated with adverse offspring neurodevelopment up to 4 years of age. Overall, the study provides evidence that placental inflammatory pathology is associated with fetal neurodevelopment. These findings lend further support to the importance of healthy in utero environment on child long-term development. ■

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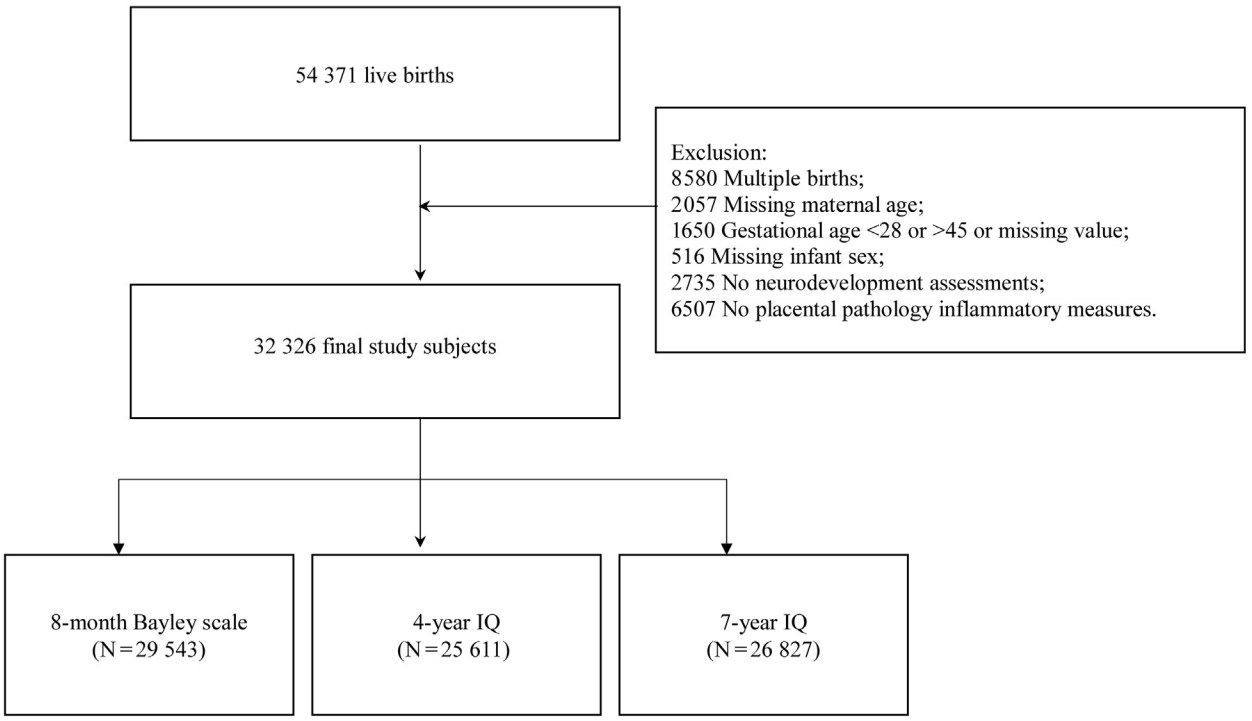

Figure. Flowchart.

Table III. Characteristics of women with and without placental inflammatory pathology (n = 32 326)

Characteristics	Proportion of the women with inflammatory pathology (%)	Rate of the inflammatory pathology (%)	*P* value
Maternal age (years)			.03
<20	23.5	24.5	
20-34	68.5	23.7	
≥35	7.9	26.0	
Race			<.01
Non-Hispanic white	44.0	22.3	
Non-Hispanic black	47.9	25.6	
Others	8.0	27.2	
Maternal educational levels			<.01
Less than high school	32.2	27.3	
High school	57.4	23.4	
College and above	10.3	19.9	
SES			<.01
1	8.2	27.3	
2	34.4	26.8	
3	31.7	24.6	
4	17.7	20.8	
5	8.1	18.0	
Prepregnancy body mass index (kg/m^2)			<.01
<25	77.9	23.9	
25-29.9	16.6	25.9	
≥30	5.6	27.9	
Smoking			.01
No	51.0	23.4	
Yes	49.0	24.7	
Parity			<.01
0	34.2	20.9	
1	24.1	22.8	
>1	41.6	24.7	
Preterm birth			<.01
No	83.6	23.6	
Yes	16.4	26.7	
Infant sex			<.01
Male	53.5	25.4	
Female	46.5	22.7	

P value is χ^2 test for women with and without placental inflammatory pathology.