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Associations of early pregnancy air pollution with adverse birth outcomes and infant neurocognitive development in the Complex Lipids in Mothers and Babies (CLIMB) cohort

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Associations of early pregnancy air pollution with adverse birth outcomes
 and infant neurocognitive development in the Complex Lipids in Mothers
 and Babies (CLIMB) cohort
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1		
2 3 4	25	Abstract
5 6	26	Objectives: to investigate the associations of traffic-related air pollution exposures in early
7 8	27	pregnancy with birth outcomes and infant neurocognitive development
9 10 11	28	Design: cohort study
12	29	Setting: in the maternity clinics of two centres (the First Affiliated Hospital of Chongqing
13 14	30	Medical University (FCQMU) and Chongqing Health Centre for Women and Children
15 16	31	(CHC)).
17	22	D estining a transmission between 20 and 40 second strands and second states at 11, 14 seconds
18 19	32	Participants: women who were between 20 and 40 years of age and were at 11–14 weeks
20 21	33	gestation with a singleton pregnancy were eligible for participation. Women were excluded if
22 23	34	they had a history of premature delivery before 32 weeks of gestation, maternal milk allergy
24	35	or aversion, or severe lactose intolerance. 1,273 pregnant women enrolled in 2015-2016 and
25 26	36	1,174 live births were included in this analysis.
27 28	37	Interventions: Air pollution concentrations at their home addresses, including particulate
29	38	matter (PM) with diameter $\leq 2.5 \mu m$ (PM _{2.5}) and nitrogen dioxide (NO ₂), during pre-
30 31	39	conception and each trimester period (TI, T2, T3) were estimated using land-use regression
32 33	40	(LUR) models.
34 35	41	Primary and secondary outcome measures: birth outcomes (i.e., birthweight, birth length,
36 37	42	preterm birth (PTB), low birth weight (LBW), large for gestational age (LGA) and small for
38 39	43	gestational age (SGA) status) and neurodevelopment outcomes measured by the Chinese
40 41	44	version of Bayley Scales of Infant Development (CBSID)).
42 43	45	Results: An association between SGA and per Interquartile range (IQR) increases in NO ₂ was
44	46	found during the whole pregnancy (Odd ratio (OR): 1.60, 99% confidence interval (CI): 1.03,
45 46	47	2.48) after co-adjusted for $PM_{2.5}$. Both $PM_{2.5}$ and NO_2 exposure in the 90 days prior to
47 48	48	conception (but not during) were associated with lower PDI score (β : -6.15, 99% CI: -9.69, -
49 50	49	2.61; β: -2.83, 99% CI: -4.27, -0.93, respectively).
51 52	50	Conclusions: NO ₂ levels during pregnancy were associated with increased risk of SGA, while
53 54	51	both $PM_{2.5}$ and NO_2 pre-conception were associated with adverse neurodevelopment outcomes
55 56	52	at 12 months of age.
57 58 59 60	53	Keywords: Air pollution; birth outcomes; child cognition
1		

We developed an LUR model to capture spatial and temporal variations of air pollution

This is one of the few studies to investigate both pre-conception and prenatal PM_{2.5} and

NO₂ exposure with neurodevelopment outcomes among young infants, in the context

Our sample size was relatively small, limiting the statistical power to assess several

The performance of the NO_2 spatiotemporal model was moderate (COR-R²: 0.39),

which may introduce exposure misclassification and therefore bias in the coefficients.

atic misclassi.

of a relatively high air pollution urban environment.

We defined exposure windows for clinically-defined trimesters.

at individual level to reduce exposure misclassification if using monitoring stations.

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2 3 4	54	Article summary
5 6 7	55	Strength and limitation
$\begin{array}{c} 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 56\\ 57\\ 58\\ 56\\ 57\\ 58\end{array}$	55 56 57 58 59 60 61 62 63 64 65	 We developed an at individual level This is one of the NO₂ exposure with of a relatively hig Our sample size outcomes. We defined expose The performance which may introd
57		

66 Introduction

Air pollution is a major environmental factor that has been linked to a range of adverse health outcomes in children. Maternal exposure to air pollutants during pregnancy, especially PM_{25} and NO₂, has been found to be associated with adverse birth outcomes, including PTB(1), term low birth weight (TLBW)(2), and small for gestational age (SGA) status (3). According to the developmental origins of health and disease (DOHaD) hypothesis, prenatal environmental exposures to air pollution may lead to adverse birth outcomes and subsequently increase the susceptibility to the development of certain diseases later in life (4). A number of epidemiological studies have linked prenatal air pollutant exposure to neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and cognitive impairment (5). Although the underlying biological mechanisms are still unclear, some studies indicated that prenatal air pollution exposure may induce systemic oxidative stress that triggers intrauterine inflammation, leading to damage to several fetal organs, including the brain (6, 7).

It is also unclear that whether the adverse effects of air pollution start earlier before conception. Three months before conception was considered as a critical developmental window for gametogenesis. Air pollution exposure during three months preconception or early stages of pregnancy may have adverse effects on gametogenesis of sperm (8, 9) and ova cells (10). Exposures to $PM_{2.5}$ in preconception period have been associated with various neurodevelopmental outcomes, such as neural tube defects (11), lower psychomotor development scores (12), higher risk of ASD (13, 14), and higher risk of intellectual disability (15). While there is growing evidence for the effects of preconception $PM_{2.5}$ exposure on the risk of adverse neurodevelopmental outcomes, no study examined the effects of preconception NO₂ exposure. There are also inconsistencies across studies and heterogeneities in health outcomes and air pollutant levels (12).

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91 Many studies have reported the effects of prenatal exposure to air pollution on 92 neurodevelopmental function in children. However, the reported associations vary, due to the 93 heterogeneous assessments of air pollutants exposure and neurodevelopmental outcomes (5, 94 16). Moreover, most of these studies were conducted in relatively developed countries where 95 pollution is lower; little evidence has come from populations in developing countries such as 96 China (17-20), that are more likely to experience more severe air pollution exposure.

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97 The current study leveraged the Complex Lipids in Mothers and Babies (CLIMB) cohort, a 98 prospective birth cohort recruited in Chongqing, China(21), with trimester-specific maternal 99 $PM_{2.5}$ and NO₂ air pollution exposure derived from a spatio-temporal LUR model (22). The 100 aim of this analysis was to examine the association between $PM_{2.5}$ and NO₂ air pollution pre-101 and during pregnancy, with birth and infant neurocognitive development outcomes at 12 102 months of age.

A key aspect in all studies like this one is the accuracy of documenting exposure; a recent Chinese study determined air pollution exposure based on the nearest monitoring station data (18) may not reflect the temporal and spatial variability of pollutant exposures among participants. The current study employed common air pollutant exposure models based on advanced geographic information systems (GIS), to address some of the limitations of previous studies (23).

In addition, the timing of in exposure is also critical in determining the effects of exposure on developmental outcomes. Indeed, the evidence from previous studies on the sensitive time window for exposure pre- and during pregnancy remains inconclusive. Some studies have indicated that the early-to-mid pregnancy phase may be a critical period in terms of the impact of air pollution on neurodevelopment(17, 24). Early pregnancy is particularly important for neurogenesis and neuromigration, making it a susceptible period (25). However, actual findings have been varied, with some studies showing stronger associations for middle or late pregnancy (18, 19, 26). More studies identifying critical periods are needed to enhance our understanding of how pre-conception and prenatal air pollution exposure affect neurodevelopment. With this cohort, we are able to examine the effects of exposure pre-conception, at each trimester, as well as across the entire pregnancy.

45 120

47 121 Methods

4950 122 Study population

A description of participant recruitment in the CLIMB cohort has been described previously (27). In brief, women who were between 20 and 40 years of age and were at 11-14 weeks gestation with a singleton pregnancy were eligible for participation. Women were excluded if they had a history of premature delivery before 32 weeks of gestation, maternal milk allergy or aversion, or severe lactose intolerance.

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From September 2015 to November 2016, a total of 1,500 women were recruited into the cohort. Participants attended six visits at the First Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for Women and Children: 11-14 weeks' gestation (visit 1), 22-28 week's gestation (visit 2), 32-34 week's gestation (visit 3), at birth (visit 4), 6 weeks postnatal (visit 5), and 12 months postnatal (visit 6).

Women who withdrew from the study (n = 146), terminated their pregnancy (n = 29), miscarried (n = 12) or were lost to follow-up (n = 40) were excluded from the analysis, leaving a sample size of 1,273 women. Analyses were restricted to mothers whose detailed residential addresses during pregnancy were known (Figure 1). A total of 1,174 live births were thus included in the pregnancy and neonatal outcomes analysis. Subsequently, at 1 year follow-up, 946 children were included in the analysis of neurodevelopment outcomes.

Exposure assessment

The address of participants was collected at the first visit. Exposure assessment based on spatiotemporal land use regression (LUR) models for PM_{2.5} and NO₂ were developed for the study region. The study area focused on the urban center of the Chinese municipality of Chongqing (Figure 2). A description of the methodology of exposure modelling has been reported previously (22). Briefly, the models included both spatial and temporal components of exposure. PM_{2.5} and NO₂ concentration data were collected from 17 routine monitoring sites operated by the Chongqing Environmental Monitoring Center in 2015-2016. For the spatial component of models, we calculated annual average concentrations of each pollutant in 2015, and fit linear regression models using five groups of geographic data (road network, land use, topography, vegetation, and population density) as spatial predictor variables. For the temporal component of models, we calculated the residuals from the spatial component at each monitoring site on a daily basis by subtracting the predicted annual average concentration from the observed daily average concentrations measured in 2015 and 2016, and then fitted generalised additive models (GAM) using seven groups of meteorological data (temperature, amount of rainfall, rainfall events, relative humidity, horizontal visibility, wind direction and wind speed) as temporal predictor variables. The meteorological variables were used to account for the influence of weather on the change in air pollution concentration over time. To account for the remaining spatial autocorrelation, the smoothed terms of longitude and latitude were fit to spatiotemporal residuals which were calculated by subtracting the sum of the spatial

160 temporal predictions from the measured daily average concentrations in 2015 and 2016. The 161 performance of the $PM_{2.5}$ spatiotemporal models was good (COR-R²: 0.72) and the NO₂ 162 spatiotemporal model was moderate (COR-R²: 0.39) when providing concentration estimates 163 in absolute terms.

164 Combining the family address coordinates of each pregnant woman and the gestation period of 165 the pregnancy (calculated from the date of last menstrual period to the date of delivery), we 166 used this spatiotemporal model to estimate the average exposure of each pregnant woman in 167 90 days prior to pregnancy (90D), first trimester (T1), second trimester (T2), third trimester 168 (T3) and whole pregnancy period (WP), respectively.

Outcomes

171 Birth Outcomes

Birth outcomes were determined by experienced obstetricians and abstracted from the medical records. Birth outcomes included: birthweight (in grams), birth length (in centimetres), PTB, low birth weight (LBW), large for gestational age (LGA) and SGA status (28). PTB was defined as delivery before 37 weeks. LBW was defined as weighing less than 2500 g at birth. LGA and SGA were indicated by birth weight greater than and less than the 90th and 10th percentile within this study for the gestational age by sex respectively (29). Term low birth weight was not considered due to a small sample size of only 8 cases.

180 Neurodevelopment outcomes

The Chinese version of Bayley Scales of Infant Development (CBSID) was used to assess mental and psychomotor development for infants in this study. The CBSID is appropriate for evaluation of infants from 2–30 months old (30) and takes into consideration each infant's age in days. Infants were assessed at around 12 months (range from 11 months and 15 days to 12 months and 15 days) by a trained examiner, with ages corrected for preterm birth. These scales have been formally adapted to the Chinese language and locally standardized to become culturally appropriate, with two main indexes: the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The MDI component comprised 163 items and assessed age-appropriate items related to cognitive functioning, personal and social

development, and language development (see eTable 1 in the Supplement). The PDI component comprised 81 items and assessed age-appropriate fine and gross motor skills (see eTable 2 in the Supplement). The test provided raw scores for mental and psychomotor development that were converted to standardized (in terms of age in days) MDI and PDI scores, based on norms for the Chinese population. As with other forms of the Bayley test these index scores have a mean of 100, and a standard deviation of 15, with a lower score reflecting poorer performance (31). If an infant refused to cooperate with the examiners to finish the task, a second assessment was arranged within two weeks. If the infant could not cooperate at the second BSID assessment, their data were classified as missing.

200 Covariates

Socio-demographic data were collected through interviews by trained nurses. The following potential confounders were identified: maternal age at enrolment (in years), infant sex (male/female), maternal BMI at 11–14 weeks' gestation (kg/m²), parity (Yes/No), monthly household income level (categorized as: <2,000 yuan, 2,000–7,000 yuan, 7,000–10,000 yuan, or >10,000 yuan), season of birth (categorized as: Spring (Mar-May), Summer (Jun-Aug), Autumn (Sep-Nov) or Winter (Dec-Feb)). Marital status (single/married) and smoking or drinking during pregnancy (Yes/no) were not taken into account in this analysis because of the homogeneity of the study population (i.e., 98.6% women were married and 99.6% women reported not smoking or drinking alcohol during pregnancy).

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211 Statistical analyses

Data were described in terms of mean \pm SD or median (IQR) for continuous variables, or as percentages for categorical variables. Modelled PM_{2.5} and NO₂ exposure levels in 90D, T1, T2, T3 and WP were considered separately. We examined the correlation between each of the exposures in the different pregnancy periods. For birth outcomes, multivariable linear regression was used for continuous outcomes (e.g., birth weight and birth length) to estimate β coefficient and their 95% confidence intervals (CIs) and multivariable logistic regression for binary outcomes (e.g., PTB, LBW, LGA and SGA status) to estimate odds ratio (OR) and 99% CIs. For mental and psychomotor development (e.g., MDI and PDI scores), multivariate linear), multivariable linear regression models were fit to estimate β coefficient and their 99%CIs.

 Models were adjusted for maternal age at enrolment, infant sex, maternal BMI at 11-14 weeks gestation, primiparity, monthly household income level, and season of birth. We also ran co-exposure models to estimate associations of one air pollutant with outcomes adjusted for the other air pollutant (i.e., PM_{2.5} in T1 adjusted for NO₂ in T1). Effect estimates are reported for each IQR increase of PM2.5 and NO2. We also tested for indirect effects of NO2 on PDI mediated by SGA with "medsem" commands. All analyses were performed using STATA version 17. A p-value of <0.01 was considered statistically significant to address multiple comparisons in the analyses.

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1							
2 3 4	229	Results					
5 6 7	230	Study Participants					
8 9 10	231	Participant characteristics are presented in Table 1. Of those participating women, the mean					
	232	age was 28 years and mean BMI was 21.5 kg/m ² . 98.0% of women were of Han ethnicity, 77.9%					
11 12	233	were primiparous, and 67.6% had completed tertiary education. 33 (2.8%), 30 (2.6%), 108					
13 14	234	(9.2%), 84 (7.2%) of the 1,174 births considered in this analysis were classified as PTB, LBW,					
15	235	LGA and SGA, respectively. For those 946 children who completed the BSID test, the mean					
16 17	236	MDI score was 94.7 (SD: 17.7) and the mean MDI score was 87.4 (SD: 14.9).					
18 19	237						
20 21							
22	238	Exposure assessment					
23 24	239	Median PM _{2.5} exposure levels were 57.31 μ g/m3 (IQR: 5.76) and median NO ² exposure					
25 26	240	levels were 50.46 µg/m3 (IQR: 5.51) during the whole pregnancy period (eTable 3 in the					
27 28	241	Supplement). For PM _{2.5} , the concentration in the pre-conception and T1 were considerably					
29	242	lower than other periods, close to 10 μ g/m3. The between-trimester and 90D values for NO ₂					
30 31	243	were generally moderately correlated (Pearson's $r > 0.5$). The correlation coefficients of					
32 33	244	$PM_{2.5}$ were more variable between time periods reflecting the high variability of $PM_{2.5}$					
34 35	245	concentrations, with values ranging from -0.78 to +0.68. Correlations between $PM_{2.5}$ and					
36	246	NO_2 in the same pregnancy period were moderately correlated (Pearson's r ~0.6, eTable 4 in					
37 38	247	the Supplement).					
39 40 41	248						
42 43	249	Association with birth outcomes					
44 45	250	In the unadjusted models (eTable 5 in the Supplement), higher exposure concentrations of					
46 47	251	$PM_{2.5}$ in T3 were significantly associated with lower birth length (β : -0.32, 99% CI: -0.57, -					
48 49	252	0.07; per IQR increase). A risk between SGA and increases in NO ₂ (per IQR) was found in T2					
50	253	(OR: 1.46, 99% CI: 1.01, 2.11), T3 (OR: 1.58, 99% CI: 1.03, 2.42) and in the whole pregnancy					
51 52	254	period (OR: 1.44, 99% CI: 1.04, 2.00). We observed no evidence of associations of NO ₂ with					
53 54	255	overall birth weight, birth length and other adverse birth outcomes (e.g., PTB, LBW, and LGA).					
55 56	256	In the adjusted models (Table 2), we found slightly reduced effect size for NO_2 and SGA in					
57 58	257	the whole pregnancy period (OR: 1.33, 99% CI:0.92, 1.75) compared with the unadjusted					
59 60	258	model. We observed no evidence of associations with birth length in the adjusted models. After					

co-adjustment for PM_{2.5} (see eTable 6 in the Supplement), the association of NO₂ with SGA became significant in the whole pregnancy period (OR: 1.60, 99% CI: 1.03, 2.48)

Association with infant neurodevelopment outcomes

In unadjusted models, PM_{2.5} exposure in the 90 days prior to conception was associated with lower MDI and PDI scores in offspring (β: -3.54, 99% CI: -5.94, -1.13; β: -3.42, 95% CI: -5.44, -1.40) (eTable 7 in the Supplement). We also observed an unexpected positive association between $PM_{2.5}$ exposures in second trimester with MDI (β : 4.21, 99% CI: 1.87, 6.56) and PDI (β:2.63, 99%CI: 0.65, 4.61). Exposure to NO₂ was associated with lower PDIs in the 90 days prior to conception (-2.86, 99% CI: -4.46, -1.26), and T3 (-1.97, 99% CI: -3.70, -0.23). We did not observe any association between NO₂ and MDI in any pregnancy periods.

In the adjusted models (Table 5), we found $PM_{2.5}$ exposure in the 90 days prior to conception was associated with lower PDI scores (β : -6.15, 99% CI: -9.69, -2.61). Similarly, there was also a significant association of increased NO₂ exposure and lower PDI score (β : -2.83, 99% CI: -4.27, -0.93). However, the positive association between PM_{2.5} exposures in second trimester with PDI (β: 3.76, 99% CI: 0.49, 7.02) remained. We did not observe any association with MDI in any pregnancy periods.

In the co-exposure models (see eTable 8 in the Supplement), PM_{2.5} exposure in the 90 days prior to conception was associated with lower PDI scores (β : -4.74, 99% CI: -8.67, -0.81). We also observed a positive association between $PM_{2.5}$ exposures in second trimester with PDI (β : 5.51, 99% CI: 1.86, 9.16). Exposure to NO₂ was significantly associated with lower PDI in the second trimester (β : -2.11, 99% CI: -4.11, -0.12) and whole pregnancy period (β : -1.68, 99% CI: -3.28, -0.08). In the mediation analyses, we did not observe any indirect effect for $PM_{2.5}$ and NO₂ on BSID scores mediated by SGA in all pregnancy periods (see eTable 9 and 10 in the Supplement).

Discussion

We analyzed associations between modelled PM_{2.5} and NO₂ pre- and during pregnancy with birth and neurodevelopment outcomes in singleton children born in a south-western metropolis of China in 2015-16. We found the likelihood of SGA increased by 60% per IQR higher

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exposure to NO₂ in the whole pregnancy periods after adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11-14 weeks' gestation, primiparity, monthly household income level, and season of births and PM_{2.5}. For childhood cognitive development, increased exposure to PM_{2.5} and NO₂ in the 90 days prior to conception were both associated with lower PDI scores, with the effect size per IQR being higher for PM_{2.5} than for NO₂. We also found a positive association between PM2.5 exposures in second trimester with PDI. While SGA was associated with NO₂ exposures, SGA was not found to mediate the effects of PM_{2.5} and NO₂ on BSID scores in this study.

Many studies from other geographic areas, including Europe (32-34), the United States (24, 26), and Asia (17, 35-37) have found that prenatal air pollution exposure has a negative impact on a variety of neurodevelopmental outcomes. Our finding of a negative association between prenatal NO₂ air pollution exposure and infant neurocognitive development is consistent with these reports. A recent Chinese birth cohort study of 15,778 child-mother pairs in Foshan reported that maternal NO₂ exposure during pregnancy was associated with increased risk of suspected developmental delay (OR: 1.06, 95% CI: 0.94, 1.19) measured by a five-domain scale and developmental quotient (DQ) (17). A birth cohort study of 520 mother-child pairs in South Korea reported that maternal NO₂ exposure during pregnancy was associated with impairment of psychomotor development ($\beta = -1.30$, p = 0.05) but – as in the present study -not with cognitive function ($\beta = -0.84$, p = 0.20) (35). However, results from previous research varied by air pollutants. For example, a Chinese study of 1193 mother-newborn pairs in Changsha found significant associations between PM_{2.5} exposure in trimester 2 and lower neurobehavioral developmental scores, while other air pollutants such as PM_{10} , carbon monoxide (CO), and Sulfur dioxide (SO₂) had null or even reverse associations. In this study, we observed that the negative effect of NO₂ exposure during pregnancy on PDI is significant at 5% level, whereas no such effect was found for PM_{2.5}; in the co-exposure model, this negative effect of NO₂ was stronger and became significant at 1% level after adjustment for $PM_{2.5}$. This heterogeneity may relate to the time of exposure assessment, the type of instruments or evaluators, and the levels of air pollution. In addition, air pollution mixtures may have differed among the study regions, thus there are several potential explanations for the heterogeneity of the findings.

To date, most studies on prenatal air pollution exposure and child neurodevelopment have been conducted in developed countries with relatively low levels of air pollution. In this study, the level of air pollution was higher (median PM_{2.5}: 57.31 µg/m³, IQR: 5.76; median NO₂:

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 $50.46 \,\mu\text{g/m}^3$, IQR: 5.51) compared to studies in developed countries such as Europe and the United States. In a multi-centre European cohort, the mean PM_{2.5} and NO₂ exposure levels during pregnancy were 13.4 μ g/m³ and 11.5 μ g/m³ (32). Researchers found that the psychomotor development score significantly decreased by 0.68 points (95% CI: -1.25, -0.11) for every 10 μ g/m³ increase in NO₂, and there was also a non-significant decrease of 1.64 points (95% CI: -3.47, 0.18) for every 5 µg/m³ increase in PM_{2.5} during pregnancy (32). Noticeably, we did not find associations of either NO₂ or PM_{2.5} during pregnancy with neurodevelopmental delay. Factors such as the types of pollutants and concentrations may differ between China and other regions with a lower air pollution level, leading to variations in the observed effects.

Contrary to expectations, we found significant positive associations between prenatal exposure to PM_{2.5} air pollution in the second trimester and PDI. Given the prior literature and the high variability observed here, we believe that this is likely spurious/sample specific. Several epidemiological studies have reported associations between prenatal exposure to high levels of PM_{25} and lower neurodevelopment in children ranging in age from 6 months to 6 years (12, 33, 38-40). In agreement with our findings, a multi-centre cohort study from six European countries investigated the effects of prenatal exposure to multiple air pollutants including PM_{2.5}, PM₁₀, coarse particles, NO₂ and nitrogen oxides (NOx) among 9482 children between 1 and 6 years; the authors found nonsignificant positive associations between prenatal PM_{2.5} exposure and normal neurodevelopment (β : 1.64, 95% CI: -3.47, 0.18; per 5 µg/m³ increase in PM_{2.5}) (32). Similarly, another study examining the effects of multiple pollutant exposures on early childhood cognition at 40 days of age in a highly exposed area of Spain also found PM₁₀, PM_{coarse}, PM_{2.5absorbance}, NO₂, NO_x, and Ozone (O₃) were linked to lower motor function in children, except for $PM_{2.5}$ (41). The inconsistent findings could be because of heterogeneity between studies in terms of exposure (e.g., exposure assessment methods used, PM2.5 exposure levels, or composition of $PM_{2.5}$).

Aside from the conflicting findings regarding prenatal PM_{2.5} exposure and neurodevelopmental outcomes, results regarding the most potential sensitive time windows before and during pregnancy are also inconclusive. Some studies suggested that early-to-mid pregnancy might be a potential sensitive period (17, 24), while other studies found stronger associations for mid-ate pregnancy, thus results are equivocal (18, 19, 26). The potential biological mechanisms by which air pollution could affect neurodevelopment are not yet clearly understood. There is evidence suggesting that exposure to prenatal PM_{2.5} could potentially induce maternal immune activation during pregnancy (42). Higher levels of cytokines or reactive oxygen species may

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potentially interfere fetal neurodevelopment through three mechanisms: crossing the placental barrier into the fetal body, inducing fetal immune dysregulation, and contributing to inadequate placental perfusion that affects nutritional processes and oxygenation of maternal blood(43). More research is needed to investigate trimester effects of air pollution on neurodevelopment and provide better understanding on the underlying biological mechanisms. Our study is the first to consider an exposure window 90 days prior to conception for NO₂. A novel observation is that effects of NO₂ or PM_{2.5} air pollution on child cognition can be seen at least 90 days prior to conception, representing a potentially vulnerable periods in relation to air pollution on neurodevelopment. Similar results were found in previous study recruited 1329 mother-child pairs in Wuhan, China (12). This study reported a higher level of PM_{2.5} during preconception (Median: 76.1 μ g/m³) and in the first trimester (Median: 82.3 μ g/m³). This study found for each doubling of PM_{2.5} exposure during preconception, children's PDI scores was reduced by 8.23 (95% CI: -10.01, -6.44) points. A potential explanation is that preconception air pollution exposures induce genetic and epigenetic alterations in sperm, that increase the risk of adverse health outcomes in offspring(44, 45). To date, all studies examined the effect of maternal preconception exposure while omitting paternal exposures (16). Future studies should consider the effect of preconception paternal exposure in relation to childhood health outcomes.

This study has several strengths. We developed an LUR model to capture spatial and temporal variations of air pollution at individual level to reduce exposure misclassification if using monitoring stations. This is one of the few studies to investigate both pre-conception and prenatal PM_{2.5} and NO₂ exposure with neurodevelopment outcomes among young infants, in the context of a relatively high air pollution urban environment.

A major limitation of this study was that our sample size was relatively small, limiting the statistical power to assess several outcomes, although the higher exposures in Chongqing than in some other studies may increase probability of detecting effects. In terms of limitations, due to a lack of information on participant time-activity patterns, exposure estimates in this study refer only to ambient concentrations at home addresses, and no other activity spaces (e.g., indoor, workplace, commuting) were considered. We may have thus underestimated total air pollution exposure. Second, we defined exposure windows for clinically-defined trimesters; sensitive periods may be shorter or longer than 3 months, or they may exist in the overlap of multiple trimesters. However, we were unable to investigate the sensitive time windows using established methods such as distributed lag non-linear models due to the lack of highly time-resolved air pollution estimates. Third, the performance of the NO₂ spatiotemporal model was

moderate (COR-R²: 0.39), which may introduce exposure misclassification and therefore bias
in the coefficients. Finally, we were unable to include some other air pollutants such as
polycyclic aromatic hydrocarbons (PAH), black carbon (BC) and Ozone, which have bene
found particular harmful to neurodevelopment in children (46).

11 392

393 Conclusion

This study provides evidence for an association between NO_2 exposure pre- and during pregnancy with birth and neurodevelopmental outcomes in a birth cohort in Chongqing, China. Exposure to NO_2 and $PM_{2.5}$ exposure before pregnancy was associated with a lower psychomotor development score and further studies are warranted.

2			
3 4	399	List of abbreviations	
5 6 7		ADHD	Attention deficit hyperactivity disorder
7 8 9		ASD	Autism spectrum disorder
10 11		BMI	Body mass index
12 13 14		BSID	Bayley Scales of Infant Development
14 15 16		CBSID	Chinese version of Bayley Scales of Infant Development
17 18		CI	Confidence interval
19 20 21		CLIMB	Complex Lipids in Mothers and Babies
22 23		CO	Carbon monoxide
24 25 26		DOHaD	Developmental origins of health and disease
28 27 28		DQ	Developmental quotient
29 30		GIS	Geographic information systems
31 32 33		IQR	Interquartile range
34 35		LBW	Low birth weight
36 37		LGA	Large for gestational age
38 39 40		LUR	Land-use Regression
41 42		MDI	Mental Development Index
43 44 45		NO _x	Nitrogen oxides
46 47		NO ₂	Nitrogen dioxide
48 49		OR	Odd ratio
50 51 52		O ₃	Ozone
53 54		PDI	Psychomotor Development Index
55 56 57		PM	Particulate matter
57 58 59 60		PM _{2.5}	Particulate matter with diameter $\leq 2.5 \mu m$

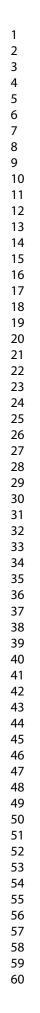
	РТВ	Preterm birth
	SGA	Small for gestational age
	SO_2	Sulfur dioxide
	TLBW	Term low birth weight
	T1	First trimester
	T2	Second trimester
	Т3	Third trimester
	WP	Whole pregnancy period
	90D	90 days prior to pregnancy
400		
	400	SGA SO ₂ TLBW T1 T2 T3 WP 90D

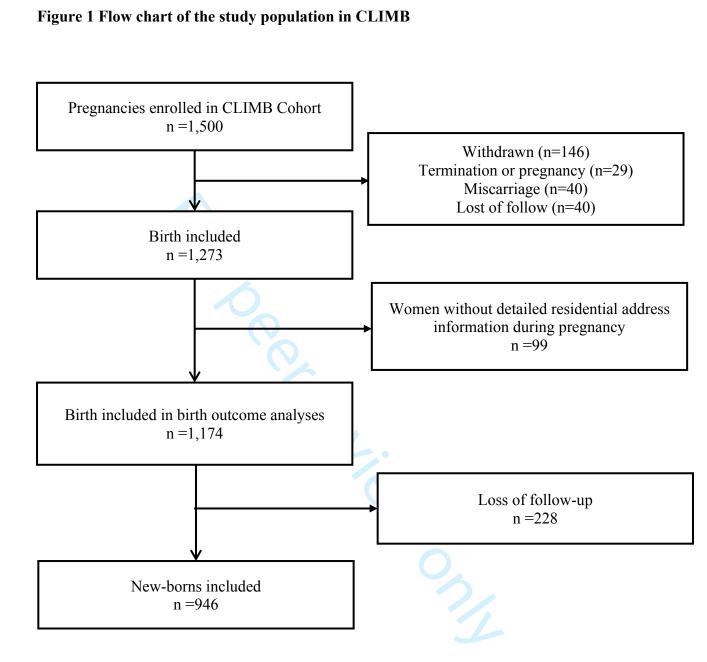
1 2		
3 4	401	Declarations
5 6 7	402	Ethics approval and consent to participate
7 8	403	Ethical approval for this study was granted by the Ethics Committee of Chongqing Medical
9 10	404	University (#2014034). The participants provided their written informed consent to
11 12	405	participate in this study. Written informed consent was obtained from the individual(s) for the
13 14	406	publication of any potentially identifiable images or data included in this article.
15 16	407	Availability of data and materials
17 18	408	The data that support the findings of this study are available from Chongqing Medical
19 20	409	University but restrictions apply to the availability of these data, which were used under
21 22	410	license for the current study, and so are not publicly available. Data are however available
23 24	411	from the authors upon reasonable request and with permission of Chongqing Medical
25	412	University.
26 27 28	413	Conflicts of interests
29 30 31	414	The authors declare that they have no conflicts of interests.
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34 35	416	This work was supported by the National Natural Science Foundation of China (No. 81971406,
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39 40	419	Program of Chongqing Medical University (W0083), and Smart Medicine Research Project of
41 42	420	Chongqing Medical University (No. ZHYX202103), Zunyi science and technology plan
43 44	421	project (Zunshikehe HZ (2022)153).
45 46	422	Author statement
47 48	423	Y. X., T.L.H., H.Z. and P.B. conceived and designed research; T.Z., Y.X. and H.Z. recruited
49 50	424	the patients and collected the samples; T.K., A.H., and J.G. constructed the air pollution
51 52	425	model; Y.C. analyzed, interpreted the data and prepared the figures; Y.C and T.K were major
53	426	contributors in writing the manuscript text; YSC, JC, TLH, YX, ALH, and PNB substantively
54 55	427	revised the manuscript; All authors read and approved the final manuscript.
56 57 58 59 60	428	Acknowledgement

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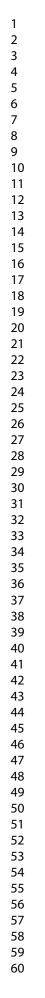
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Tables and figures





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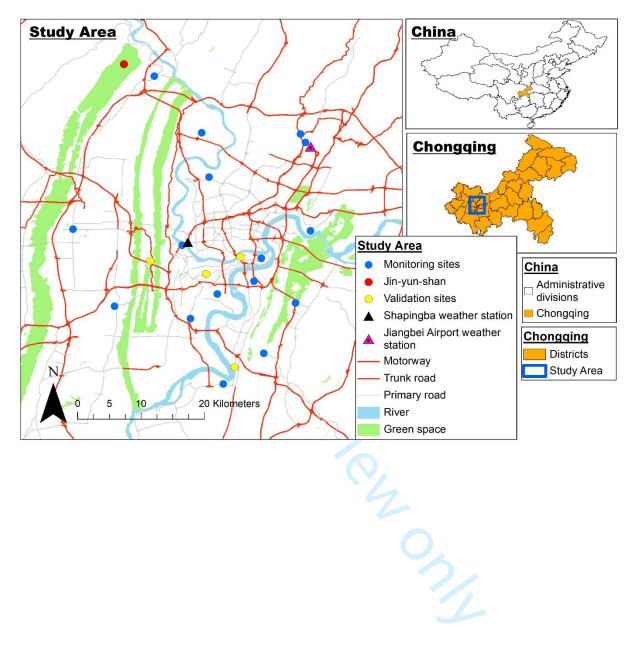


Table 1 Characteristics of study sample in the CLIMB cohort (N = 1,174)

Characteristic of mothers	N	n (%) or mean ± SD	Characteristic of child	Ν	n (%) or mean ± SD
Maternal age (Years)	1,174	28.7 ± 3.5	(week)	1,174	39.4 ± 1.5
BMI (kg/m ²)	1,174	21.5 ± 2.9	Birth weight (g)	1,165	3314.4 ± 428
Han ethnicity (%)	1,174		Birth length (cm)	1,149	49.7 ± 1.9
Yes		1,151 (98.0%)	Apgar score at 1 min	1,035	9.4 ± 1.3
No		23 (2.0%)	Apgar score at 5 min	1,035	9.9 ± 3.0
Marital status (%)	1,174		New born sex	1,172	
Single		16 (1.4%)	Female		9.9 ± 3.0 561 (47.9%) 611 (52.1%) 33 (2.8%) 1,141 (97.2%)
Married		1,158 (98.6%)	Male		611 (52.1%)
Primiparity (%)	1,174		Birth outcomes		
Yes		914 (77.9%)	Preterm birth (PTB)	1,174	
No		260 (22.1%)	Yes		33 (2.8%)
History of miscarriage or abortion (%)	1,174		No		1,141 (97.2%
Yes		553 (47.1%)	Low birth weight (LBW)	1,174	
No		621 (52.9%)	Yes		30 (2.6%)
Smoking/drinking during pregnancy (%)	1,174	\sim	No		1,141 (97.2%
Yes		5 (0.4%)	Large for gestational age (LGA)	1,174	
No		1,169 (99.6%)	Yes		108 (9.2%)
Education level	946		No		1,066 (90.8%
Low: High school or below		306 (32.3%)	Small for gestational age (SGA)	1,174	
High: College/uni or above		640 (67.6%)	Yes		84 (7.2%)
lob	946		No		1,090 (92.8%
Full-time		762 (80.5%)	BSID test	946	
Housewife		82 (8.7%)	MDI (mean ± SD)		94.7 ± 17.7
Others		102 (10.8%)	PDI (mean ± SD)		87.4 ± 14.9
Household income (Monthly)	946		Birth season	1,174	
<2000 RMB		186 (19.7%)	Spring (Mar-May)		411 (35.01%)
2000-4000 RMB		329 (34.8%)	Summer (Jun-Aug)		263 (22.40%)
1000-7000 RMB		292 (30.9%)	Autumn (Sep-Nov)		$84 (7.2\%)$ $1,090 (92.8\%)$ 94.7 ± 17.7 87.4 ± 14.9 $411 (35.01\%)$ $263 (22.40\%)$ $198 (16.87\%)$
7000-10000 RMB		139 (14.7%)	Winter (Dec-Feb)		302 (25.72%)

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3 4	435 T	Cable 2 Associations between	en PM _{2.5} and NO ₂ expos	ure in different pre	gnancy periods and	= ,3	comes (adjusted m	10dels)
5 6			Mean diffe	erence		ng for 2 Odd	d ratios	
7 8			Birth weight, grams	Birth length, cm	PTB (case: 33)		LGA (case: 108)	SGA (case: 84)
9 10 11			99% CI	99% CI	99% CI	s relatec 99% CI	99% CI	99% CI
11 12 13	P	Per IQR increase in	(N=941)	(N=927)	(N=945)	ed to text (N=945) to text	(N=945)	(N=945)
13 14 15	Estimated	90 days prior to conception	59.73 (-40.56, 160.01)	0.15 (-0.28, 0.58)	0.24 (0.06, 1.01)	0.49 (0.19 de 6)	1.4 (0.59, 3.33)	1.66 (0.58, 4.73)
16 17	exposure	First trimester	6.21 (-99.01, 111.42)	0.04 (-0.42, 0.50)	0.88 (0.19, 4.02)	0.76 (0.1 a m 194)	0.86 (0.36, 2.05)	1.33 (0.45, 3.95)
18 19	to PM _{2.5}	Second trimester	-37.64 (-129.82, 54.54)	0.02 (-0.38, 0.42)	1.62 (0.37, 7.05)		1 (0.46, 2.20)	0.94 (0.41, 2.15)
20 21		Third trimester	4.2 (-97.55, 105.95)	-0.17 (-0.62, 0.27)	0.92 (0.20, 4.17)	0.92 (0.2≱, 4 3 6)	1.29 (0.53, 3.13)	0.83 (0.33, 2.06)
22 23		Total pregnancy	8.01 (-56.57, 72.59)	0.02 (-0.27, 0.30)	0.77 (0.31, 1.91)	0.62 (0.2 mg, 156)	1.15 (0.65, 2.02)	0.84 (0.45, 1.57)
24 25	Estimated	90 days prior to conception	-1.03 (-54.75, 52.68)	-0.04 (-0.27, 0.20)	0.84 (0.37, 1.91)		1.31 (0.82, 2.10)	1.45 (0.88, 2.38)
26 27	exposure	First trimester	-9.78 (-63.78, 44.22)	0.04 (-0.19, 0.28)	0.9 (0.41, 2.00)		1.21 (0.76, 1.92)	1.57 (0.94, 2.62)
28 29 20	to NO ₂	Second trimester	-20.82 (-71.18, 29.54)	-0.06 (-0.28, 0.16)	1.31 (0.61, 2.81)	1.34 (0.6 ⁶ , 2 ⁸ , 2 ⁸ , 8)	1.21 (0.78, 1.89)	1.36 (0.85, 2.19)
30 31 32		Third trimester	-9.5 (-70.66, 51.65)	-0.01 (-0.28, 0.26)	0.79 (0.32, 1.97)	0.95 (0.3gg, 2gg3)	1.42 (0.83, 2.42)	1.51 (0.84, 2.71)
32 33 34		Total pregnancy	-8.45 (-46.96, 30.06)	0 (-0.17, 0.17)	0.97 (0.54, 1.74)	1.04 (0.57, 139)	1.2 (0.86, 1.69)	1.33 (0.92, 1.91)
34 35 36	Models adju	usted for maternal age at enrol	ment, infant's sex, maternal	BMI at 11–14 weeks'	gestation, primiparity	y, monthly hous	income level, and sea	ison of births.
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41 42				23		que de		
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Table 3 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and BSID scores (adjusted models)

		Mean di	fference
		MDI 99% CI	PDI 99% CI
F	Per IQR increase in	(N=946)	(N=946)
Estimated	90 days prior to conception	-1.98 (-6.21, 2.25)	-6.15 (-9.69, -2.61)
exposure	First trimester	-1.66 (-6.08, 2.76)	-2.11 (-5.84, 1.62)
to PM _{2.5}	Second trimester	3.79 (-0.08, 7.66)	3.76 (0.49, 7.02)
	Third trimester	-2.73 (-7.01, 1.55)	-1.37 (-4.99, 2.26)
	Total pregnancy	-0.27 (-2.99, 2.45)	0.23 (-2.07, 2.53)
Estimated	90 days prior to conception	-0.72 (-2.98, 1.55)	-2.83 (-4.72, -0.93)
exposure	First trimester	0.59 (-1.68, 2.86)	-1.91 (-3.83, 0.00)
to NO ₂	Second trimester	0.56 (-1.56, 2.68)	-0.75 (-2.54, 1.04)
	Third trimester	0.51 (-2.06, 3.09)	-1.92 (-4.09, 0.26)
	Total pregnancy	0.41 (-1.22, 2.03)	-1.15 (-2.52, 0.21)

Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income level, and season of births.

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440 Reference

2		
3	440	Reference
4		
5 6	441	1. Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iniguez C. Preterm birth and
0 7	442	exposure to air pollutants during pregnancy. Environmental Research. 2010;110(8):778-85.
8	443	2. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). The Lancet
9	444	Respiratory Medicine. 2013;1(9):695-704.
10	445	
11	445	
12		the association between traffic-related air pollution and adverse pregnancy outcomes in Canada,
13	447	1999–2008. Environmental Research. 2016.
14	448	4. Barker DJ. The origins of the developmental origins theory. Journal of internal medicine.
15	449	2007;261(5):412-7.
16	450	5. Volk HE, Perera F, Braun JM, Kingsley SL, Gray K, Buckley J, et al. Prenatal air pollution
17	451	exposure and neurodevelopment: A review and blueprint for a harmonized approach within ECHO.
18	452	Environmental research. 2021;196:110320.
19	453	6. Feng S, Dan G, Liao F, Zhou F, Wang X. The health effects of ambient PM2.5 and potential
20	454	mechanisms. Ecotoxicology and Environmental Safety. 2016;128:67-74.
21	455	7. Massa NR, Guangyun M, Xingyou Z, Xiumei H, Zhu C, Sampankanpanich SC, et al. Intrauterine
22	456	Inflammation and Maternal Exposure to Ambient PM2.5 during Preconception and Specific Periods
23	457	of Pregnancy: The Boston Birth Cohort. Environ Health Perspect. 2016;124(10):1608-15.
24 25	458	8. Vecoli C, Montano L, Andreassi MG. Environmental pollutants: genetic damage and
25 26	459	epigenetic changes in male germ cells. Environmental Science and Pollution Research.
20	460	2016;23:23339-48.
28	461	9. Marcho C, Oluwayiose OA, Pilsner JR. The preconception environment and sperm
29	462	epigenetics. Andrology. 2020;8(4):924-42.
30	462	
31		10. Udagawa O, Furuyama A, Imai K, Fujitani Y, Hirano S. Effects of diesel exhaust-derived
32	464	secondary organic aerosol (SOA) on oocytes: Potential risks to meiotic maturation. Reproductive
33	465	Toxicology. 2018;75:56-64.
34	466	11. Zhang J-Y, Wu Q-J, Huang Y-H, Li J, Liu S, Chen Y-L, et al. Association between maternal
35	467	exposure to ambient PM10 and neural tube defects: a case-control study in Liaoning Province, China.
36	468	International Journal of Hygiene and Environmental Health. 2020;225:113453.
37	469	12. Li J, Liao J, Hu C, Bao S, Mahai G, Cao Z, et al. Preconceptional and the first trimester
38	470	exposure to PM2. 5 and offspring neurodevelopment at 24 months of age: Examining mediation by
39	471	maternal thyroid hormones in a birth cohort study. Environmental Pollution. 2021;284:117133.
40 41	472	13. Jo H, Eckel SP, Chen J-C, Cockburn M, Martinez MP, Chow T, et al. Gestational diabetes
41	473	mellitus, prenatal air pollution exposure, and autism spectrum disorder. Environment international.
43	474	2019;133:105110.
44	475	14. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism spectrum disorder and
45	476	particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis
46	477	within the Nurses' Health Study II cohort. Environmental health perspectives. 2015;123(3):264-70.
47	478	15. Grineski S, Alexander C, Renteria R, Collins TW, Bilder D, VanDerslice J, et al. Trimester-
48	479	specific ambient PM2.5 exposures and risk of intellectual disability in Utah. Environmental Research.
49	480	2023;218:115009.
50	481	16. Blanc N, Liao J, Gilliland F, Zhang JJ, Berhane K, Huang G, et al. A systematic review of
51	482	evidence for maternal preconception exposure to outdoor air pollution on Children's health.
52	483	Environmental Pollution. 2022:120850.
53	484	17. Su X, Zhang S, Lin Q, Wu Y, Yang Y, Yu H, et al. Prenatal exposure to air pollution and
54 57	485	
55 56		neurodevelopmental delay in children: A birth cohort study in Foshan, China. Science of The Total
56 57	486	Environment. 2022;816:151658.
57 58	487	18. Chen B, Huang S, He J, He Q, Chen S, Liu X, et al. Sex-specific influence of prenatal air
58 59	488	pollutant exposure on neonatal neurobehavioral development and the sensitive window.
60	489	Chemosphere. 2020;254:126824.

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19. Wang P, Zhao Y, Li J, Zhou Y, Luo R, Meng X, et al. Prenatal exposure to ambient fine particulate matter and early childhood neurodevelopment: A population-based birth cohort study. Science of The Total Environment. 2021;785:147334. 20. Lei X, Zhang Y, Wang Z, Lu Z, Pan C, Zhang S, et al. Effects of prenatal exposure to PM2.5 and its composition on cognitive and motor functions in children at 12 months of age: The Shanghai Birth Cohort Study. Environment International. 2022;170:107597. 21. Huang S, Mo T-T, Norris T, Sun S, Zhang T, Han T-L, et al. The CLIMB (Complex Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel randomised controlled trial to investigate the effect of supplementation of complex lipids in pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring. BMJ open. 2017;7(10):e016637. Harper A, Baker PN, Xia Y, Kuang T, Zhang H, Chen Y, et al. Development of spatiotemporal 22. land use regression models for PM2. 5 and NO2 in Chongqing, China, and exposure assessment for the CLIMB study. Atmospheric Pollution Research. 2021;12(7):101096. 23. Volk HE, Perera F, Braun JM, Kingsley SL, Gray K, Buckley J, et al. Prenatal air pollution exposure and neurodevelopment: A review and blueprint for a harmonized approach within ECHO. Environ Res. 2021;196:110320. 24. Ha S, Yeung E, Bell E, Insaf T, Ghassabian A, Bell G, et al. Prenatal and early life exposures to ambient air pollution and development. Environmental research. 2019;174:170-5. Bennet L, Walker DW, Horne RS. Waking up too early-the consequences of preterm birth on 25. sleep development. The Journal of physiology. 2018;596(23):5687-708. 26. Chiu Y-HM, Hsu H-HL, Coull BA, Bellinger DC, Kloog I, Schwartz J, et al. Prenatal particulate air pollution and neurodevelopment in urban children: examining sensitive windows and sex-specific associations. Environment international. 2016;87:56-65. Huang S, Mo T-T, Norris T, Sun S, Zhang T, Han T-L, et al. The CLIMB (Complex Lipids In 27. Mothers and Babies) study: protocol for a multicentre, three-group, parallel randomised controlled trial to investigate the effect of supplementation of complex lipids in pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring. BMJ Open. 2017;7(10):e016637. 28. Albert BB, Derraik JG, Xia Y-Y, Norris T, Zhang T, Han T-L, et al. Supplementation with milk enriched with complex lipids during pregnancy: a double-blind randomized controlled trial. Plos one. 2021;16(2):e0244916. 29. Zhao X, Xia Y, Zhang H, Baker PN, Norris T. Birth weight charts for a Chinese population: an observational study of routine newborn weight data from Chongging. BMC Pediatr. 2019;19(1):426. 30. Shourong Y, Xuerong L, Zhiwei Y. The revising of the bayley scales of infant development (BSID) in China. Chin J Clin Psychol. 1993;2:71-5. 31. Chen Y-T, Zhang T, Chen C, Xia Y-Y, Han T-L, Chen X-Y, et al. Associations of early pregnancy BMI with adverse pregnancy outcomes and infant neurocognitive development. Scientific Reports. 2021;11(1):1-8. 32. Guxens M, Garcia-Esteban R, Giorgis-Allemand L, Forns J, Badaloni C, Ballester F, et al. Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts. Epidemiology. 2014:636-47. Lertxundi A, Baccini M, Lertxundi N, Fano E, Aranbarri A, Martínez MD, et al. Exposure to fine 33. particle matter, nitrogen dioxide and benzene during pregnancy and cognitive and psychomotor developments in children at 15 months of age. Environment international. 2015;80:33-40. 34. Porta D, Narduzzi S, Badaloni C, Bucci S, Cesaroni G, Colelli V, et al. Air pollution and cognitive development at age 7 in a prospective Italian birth cohort. Epidemiology. 2016;27(2):228-36. 35. Kim E, Park H, Hong Y-C, Ha M, Kim Y, Kim B-N, et al. Prenatal exposure to PM10 and NO2 and children's neurodevelopment from birth to 24 months of age: Mothers and Children's Environmental Health (MOCEH) study. Science of the Total Environment. 2014;481:439-45.

Lin C-C, Yang S-K, Lin K-C, Ho W-C, Hsieh W-S, Shu B-C, et al. Multilevel analysis of air 36. pollution and early childhood neurobehavioral development. International journal of environmental research and public health. 2014;11(7):6827-41. Yorifuji T, Kashima S, Diez MH, Kado Y, Sanada S, Doi H. Prenatal exposure to traffic-related 37. air pollution and child behavioral development milestone delays in Japan. Epidemiology. 2016;27(1):57-65. 38. Tozzi V, Lertxundi A, Ibarluzea JM, Baccini M. Causal effects of prenatal exposure to PM2. 5 on child development and the role of unobserved confounding. International Journal of Environmental Research and Public Health. 2019;16(22):4381. 39. Hurtado-Díaz M, Riojas-Rodríguez H, Rothenberg SJ, Schnaas-Arrieta L, Kloog I, Just A, et al. Prenatal PM2. 5 exposure and neurodevelopment at 2 years of age in a birth cohort from Mexico city. International journal of hygiene and environmental health. 2021;233:113695. Lertxundi A, Andiarena A, Martínez MD, Ayerdi M, Murcia M, Estarlich M, et al. Prenatal 40. exposure to PM2.5 and NO2 and sex-dependent infant cognitive and motor development. Environmental Research. 2019;174:114-21. Iglesias-Vázquez L, Binter A-C, Canals J, Hernández-Martínez C, Voltas N, Ambros A, et al. 41. Maternal exposure to air pollution during pregnancy and child's cognitive, language, and motor function: ECLIPSES study. Environmental Research. 2022;212:113501. 42. Umezawa M, Onoda A, Korshunova I, Jensen AC, Koponen IK, Jensen KA, et al. Maternal inhalation of carbon black nanoparticles induces neurodevelopmental changes in mouse offspring. Particle and Fibre Toxicology. 2018;15:1-18. 43. Monk C, Lugo-Candelas C, Trumpff C. Prenatal developmental origins of future psychopathology: mechanisms and pathways. Annual review of clinical psychology. 2019;15:317-44. 44. Xu R, Zhong Y, Li R, Li Y, Zhong Z, Liu T, et al. Association between exposure to ambient air pollution and semen quality: A systematic review and meta-analysis. Science of The Total Environment. 2023;870:161892. Braun JM, Messerlian C, Hauser R. Fathers matter: why it's time to consider the impact of 45. paternal environmental exposures on children's health. Current epidemiology reports. 2017;4:46-55. Lopuszanska U, Samardakiewicz M. The relationship between air pollution and cognitive 46. functions in children and adolescents: a systematic review. Cognitive and Behavioral Neurology. 2020;33(3):157-78.

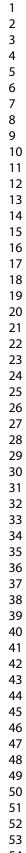
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Pregnancies enrolled in CLIMB Cohort	
	Withdrawn (n=146)
	Termination or pregnancy (n=29)
Birth included	
	Women without detailed residential address
	information during pregnancy
Birth included in birth outcome analyses	
n=1,174	
	Loss of follow-up
New-borns included	

Figure 1 Flow chart of the study population in CLIMB

441x367mm (130 x 130 DPI)

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58 59 60

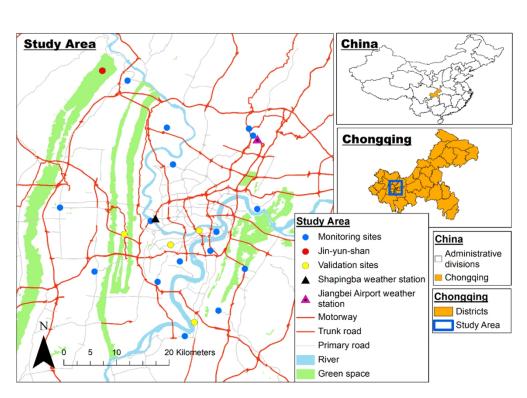


Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors, 2015; https://data.nextgis.com/en/region/CN-50/).

402x284mm (87 x 87 DPI)

BMJ Open

Associations of early pregnancy air pollution with adverse birth outcomes and infant neurocognitive development in the Complex Lipids in Mothers and Babies (CLIMB) cohort

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*: Contributed equally

Supplement

eTable 1 Mental Development Index (Chinese version)

智力量表

(※可偶尔观察到)

	I			I
序号	月龄	条目	计分	
1	0.1	对铃声反应		
2	0.1	抱起时安静		
3	0.1	对摇鼓声反应		
4	0.1	对尖声反应:(电灯开关)		
5	0.1	短暂地注视红环		
6	0.2	短暂地注视人	10	
7	0.4	稍长时间地注视红环		
8	0.5	眼的水平协调活动(红环)		-
9	0.7	眼的水平向天活动(光)		
10	0.7	眼睛追随移动的人		
11	0.7	对说话声反应		
12	0.8	眼的垂直协调活动(光)		
13	0.9	发声一至两次		
14	1	眼的垂直协调活动(红环)		
15	1.2	眼的旋转协调活动(光)		
16	1.2	眼的旋转细条活动(光环)		



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1	7	1.3	※自由环视周围	
18	8	1.5	社交笑:测试者谈话与微笑时	
19	9	1.6	眼转向红环	
20	0	1.6	眼转向光	
2	1	1.6	※发声至少四次	
22	2	1.7	期待性兴奋	
23	3	1.7	对面部的纸有反应	
24	4	1.9	能用视觉辨认母亲	
2	5	1.9	社交笑:测试者微笑与安静时	
20	6	2	※对测试者的微笑和说话有发声反应	
2	7	2.1	※用眼睛寻找声源(详细说明)	
28	8	2.2	※发出两种不同的声音	
29	9	2.2	对手的遮蔽眨眼	10
30	0	2.2	对面孔的消失有反应	
3:	1	2.4	注视方木	
32	2	2.6	从一物转看另一物	
33	3	2.6	眼睛追随铅笔	
34	4	2.7	对抱起有预感性的调节反应	
3	5	2.9	目光追随横过桌面的球	
3	6	2.9	头追随悬摆的环	
3	7	3.1	头追随逐渐消失的勺子	
3	8	3.2	操作红环	
39	9	3.3	简单地玩摇鼓	

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40	3.4	※轻轻地抚摸桌沿	
41	3.4	※意识到陌生环境	
42	3.5	头转向铃声	
43	3.6	头转向摇鼓声	
44	3.6	※手碰手的玩耍	
45	3.6	将红环送入口中	
46	3.7	伸手够悬环	
47	3.8	看自己的手	
48	4.2	接近悬环(优势手)	
49	4.4	※发声时的姿态(描述)	
50	4.4	※主动抚摸桌沿	vonj
51	4.4	接近镜像	
52	4.4	注意小糖丸	
53	4.6	伸手取方木	
54	4.7	喜欢嬉戏	
55	4.9	伸手时眼手协调	
56	4.9	拾起方木(优势手)	
57	5	保持两块方木	
58	5	持久地看红环	
59	5	头部跟着掉下的勺转动	
60	5	探索性地玩纸	
61	5	对镜像微笑	
62	5	坚持够东西	

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辦别生人 起倒扣的茶杯 敲打玩耍 索性地玩细绳 素性地玩细绳 手取第二块方木 由一手向另一手传递物体 对产生响声感兴趣 巧而直接地拾起方木 对镜像开玩笑 把柄举起茶杯 找掉落的勺子 拉细绳获取红环 留三块方木中的两块		
 敲打玩耍 索性地玩细绳 手取第二块方木 由一手向另一手传递物体 对产生响声感兴趣 巧而直接地拾起方木 对镜像开玩笑 把柄举起茶杯 找掉落的勺子 拉细绳获取红环 		
索性地玩细绳 手取第二块方木 由一手向另一手传递物体 对产生响声感兴趣 巧而直接地拾起方木 对镜像开玩笑 把柄举起茶杯 找掉落的勺子		
手取第二块方木 由一手向另一手传递物体 对产生响声感兴趣 巧而直接地拾起方木 对镜像开玩笑 把柄举起茶杯 找掉落的勺子 拉细绳获取红环		
由一手向另一手传递物体 对产生响声感兴趣 巧而直接地拾起方木 对镜像开玩笑 把柄举起茶杯 找掉落的勺子 拉细绳获取红环		
对产生响声感兴趣 巧而直接地拾起方木 对镜像开玩笑 把柄举起茶杯 找掉落的勺子 拉细绳获取红环		
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留三块方木中的两块		
		h .
发出四个不同的音节		
配合玩游戏		
当地牵拉细绳获取红环		
摇铃,对细节感兴趣		
图获得三块方木		
目的地摇铃		
选择性地倾听熟悉的词语		
对 da-da 或类同词		
	图获得三块方木 目的地摇铃	图获得三块方木



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86	8.2	注意测试者的乱写	
87	8.3	将手指插入桩板洞中	c.
88	8.6	观看书中图画	
89	8.9	对他人的言语要求有反应	
90	9.1	拿起茶杯获得方木	
91	9.8	寻找盒子里面的东西	
92	10.3	遵照命令将方木放入茶杯(放入数)	
93	10.7	企图模仿乱写	
94	10.8	模仿用勺子搅拌	
95	10.9	遵照命令停止	
96	10.9	推动小汽车	ġ
97	11	模仿地拍打哨娃	
98	11.1	※重复引入发笑的把戏	
99	11.2	解开裹着的方木	h .
100	11.2	将三块方木放入杯中	
101	11.4	※快速而不清的表达	5
102	11.4	揭开兰盒子的盖	
103	11.5	翻开书页	
104	11.5	摇晃悬环的	
105	11.8	将骰子放入盒中(6个)	
106	12	恰当地握持画笔	
107	12.2	模仿说单词(记录用过的词)	
108	12.4	重复地插一根桩钉	

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109	12.5	用手势表达想要的东西	
110	12.9	自动乱写	ÿ
111	12.9	能说两个词	
112	13	搭两层塔	
113	13.1	出示鞋子或其他衣服或自己的玩具	
114	13.2	从瓶中移出小糖丸	
115	13.3	掺九块方木放入杯中	
116	14.3	※盖上圆盒	
117	14.4	兰色模板:放置一个圆形模块	
118	14.8	用棍子够取玩具	
119	15.4	搭三层塔	ې د
120	15.7	在 70 秒钟内插完桩钉	
121	16.1	指出娃娃身体的各部分:三个部位以上	
122	16.3	粉红模板:放置圆形模块	
123	16.6	兰色模板:放置两个圆形模块	
124	17.2	用笔模仿画一划	
125	17.5	在 42 秒钟内插完桩钉	
126	17.6	说出一物名	
127	17.7	对娃娃执行指令(在通过部位打钩:椅、杯、鼻)	e v
128	18.1	用语言表达要求	
129	18.6	不用于一划的乱写?	
130	18.8	兰色模板:放置两个圆快和方块	
131	18.8	指出三幅画	

132	19.1	能说两个单词的句子	
133	19.2	说出一副画名	
134	19.2	说出两幅画名	
135	19.3	找出两物	
136	19.8	在 30 秒钟内插完桩钉	
137	20.4	粉红模板:完成	
138	20.4	搭六层塔	
139	20.5	兰色模板,放置六个模块	
140	21	指出五副画	
141	21.1	说出三物名	
142	21.2	勉强合格地安装破娃娃	
143	21.2	区别两物:杯、盘、盒	•
144	22.8	辨认钟表:第四张图 1 , 2 , 3 , 4 , 5	
145	22.9	说出三幅画名	
146	23.8	粉红模板(反转)	
147	24.3	近似地安装破娃娃	
148	24.6	区别三物:杯、盘、盒	
149	24.7	兰色模板,在150秒钟内完成	
150	25	搭八层塔	
151	25.1	指出七副画	
152	25.1	用方木搭火车	
153	25.7	说出五副画名	
154	26.3	模仿笔划:垂直线和水平线	

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			yright, i
155	27.1	辨认钟表:第2张图	ncludi
156	27.6	理解两个方位词	ng f
157	28	在 22 秒钟内插完桩钉	
158	28.5	兰色模板:90秒钟内完成	
159	29.5	折纸	signer te er
160	29.6	兰色模板:60秒钟内完成	d nent to t
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eTable 2 Psychomotor Development Index (Chinese version)

运动量表

(※可偶尔观察到,△可在施测智力量表时观察到)

序号	月龄	条目	计分
1	0.1	抱起靠肩时抬头	
2	0.1	抱起靠肩时调整姿势	
3	0.1	侧头	
4	0.1	爬起	
5	0.8	△保留红环	
6	0.8	※伸臂玩耍	
7	0.8	※踢腿玩耍	
8	0.8	头起竖起:垂直位	
9	1.6	头部稳定地竖起	
10	1.7	抬头(背悬位)	
11	1.8	由侧卧转向仰卧	
12	2.2	在俯卧位时用双臂撑起自己	
13	2.2	支撑下坐起	
14	2.5	保持头部稳定	
15	2.6	※双手张开占优势	
16	3.3	头平衡	
17	3.4	※尺侧一手掌抓握方木	



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[1	な 座土 ₩₩		
		轻度支撑坐位	3.5	18
		※由仰卧转向侧卧	4.3	19
		努力想坐起	4.7	20
		部分的拇指相对(桡侧一手掌)拾起方木	5.0	21
		独坐片刻	5.1	22
		※单手抽取	5.1	23
			5.2	24
		牵拉坐起△试图获取小糖丸	5.2	25
		独立 30 秒钟或以上	5.6	26
		由仰卧转向俯卧	5.7	27
		稳定地独坐	5.8	28
		· 独坐时协调好	6.2	29
1.	-6	※舀起小糖丸	6.5	30 31
		△完全的拇指相对拾起方木	6.6	32
0 _h		早期跨步运动	7	33
		牵拉站起	7.5	34
-		※不完全的拇指相对抓糖丸	7.6	35
		走路之前的行进方式(俯卧、手膝、手足、其他)	7.6	36
		使两个勺子或方木在中线相碰	8.3	37
		跨步运动	8.5	38
		自己坐起	8.6	39
		借助家具站起	8.6	40

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	8.9	精细地抓糖丸(灵巧地钳夹)		
41	9.6			
42		拍手(中线技巧)		
43	9.8	坐下		
44	10	扶助下行走		
45	11.1	独站		
46	12	投球		
47	12.1	独走		
48	12.4	起立」		
49	13.2	扶助下右足独站		
50	13.7	扶助下左足独站		
51	14.1	侧身走		
52	14.5	扶助上楼梯		
53	14.7	倒退走		
54	15.1	扶助下楼梯	C	
55	17.6	试图站在行木上		
56	18.7	左足独站		
57	19.3	单足踏在行木上走		
58	19.9	起立॥		
59	20.1	右足独站		
60	21.1	走直线:大致方向		
61	23.1	行木:双足站立		
62	24	踮脚走几步		
63	24.3	独自上楼梯:双足		

Page	43	of	58
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64	24.4	双足跳离地面	
65	25.3	独自下楼梯	<u>د</u>
66	25.6	行木:企图跨步	
67	25.6	倒行两米半	
68	25.7	自第一级台阶下跳下	
69	29.2	自第二级台阶下跳下	
70	29.8	踮脚走两米半	
71	29.9	跳远:10 至 35cm (记录距离)	
72	30+	起立: III	
73	30+	上楼梯:双足交替向前	
74	30+	行木:交替步伐走部分路程	 עיש
75	30+	保持双足走在直线上(两米半)	
76	30+	跳远:35cm 至 60cm	
77	30+	跳过:5cm 高的绳子	
78	30+	跳远:60cm 至 85cm	
79	30+	独脚跳两次以上	
80	30+	下楼梯:双足交替向前	
81	30+	跳过 20cm 高的绳子	

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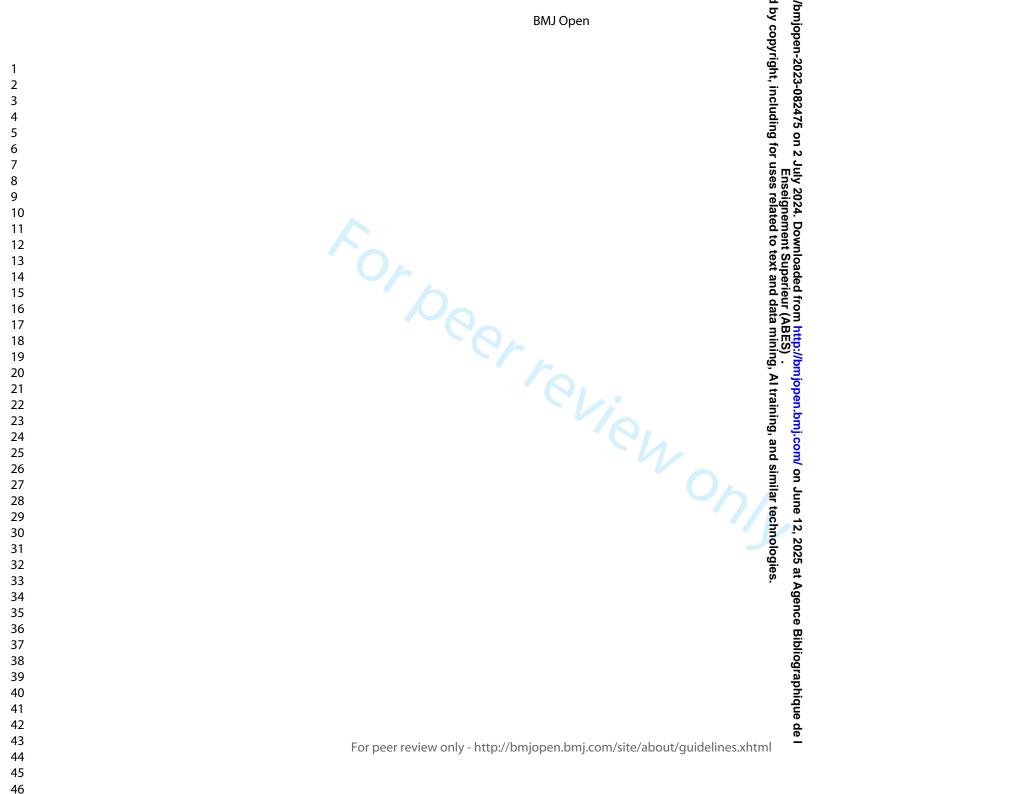
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eTable 3 Distributions of whole pregnancy period			evel in 90 days prior	to conception, each t	trimester (1 , 1 , 1 , 1 , 1 , 1 , 1 , 1 , 1 , 2 , and 1 , 1 , 1 , 1 , 1 , 1 , 1 , 1 , 1 , 1	1 T3) and combined	across
				Estimated ex	xposure (µg/mg)22		
	N	Minimum	25th percentile	Mean ± SD	Mediaed and by the second sec	75th percentile	Maximum
Estimated exposure to PM _{2.5}		`			o tex		
90 days prior to conception	1,174	38.17	44.00	52.91 ± 10.99	48.43 and 48.43	62.06	80.53
First trimester	1,174	37.26	43.77	52.07 ± 10.98	47.26	61.08	82.41
Second trimester	1,174	38.46	47.57	58.64 ± 12.21	57.97	67.19	90.02
Third trimester	1,174	37.03	47.25	61.83 ± 16.04		75.95	96.48
Total pregnancy	1,174	46.69	54.85	57.48 ± 3.97	57.3 lt 1 5776	60.61	66.98
Estimated exposure to NO ₂				VIA.	in		
90 days prior to conception	1,174	25.86	45.49	49.59 ± 6.34	49.94 8 ± 8 2 7	53.76	70.48
First trimester	1,174	20.81	44.60	48.8 ± 6.43	48.92 8 8 1	53.10	69.31
Second trimester	1,174	28.93	47.18	50.98 ± 6.23	48.92 48.92 48 51.20 2 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	54.90	70.42
Third trimester	1,174	20.57	47.20	51.79 ± 6.78	57 452 + 017	56.67	75.12
Total pregnancy	1,174	27.50	47.89	50.52 ± 5.08	50.4 content for the second se	53.40	67.53
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Page	45 of 58				В	MJ Open		/bmjope J by cop				
1 2 3 4 5 6 7 8		eTable 4 Pearson's correlation	ons of PM _{2.5} and	NO ₂ betwee	n each of th	e five differe	ent pregnancy	n-2023-082475 on 2 July 2 vright, including for uses	N = 1,174)			
9 10	Estimat	ted exposure to			PM _{2.5}			relat		NO ₂		
11 12 13			90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy	2 July 2024. Downloaded from h EnseignemenoSuperieur (AB 90 days potext and data n 90 days to concept and data n	First trimester	Second trimester	Third trimester	Total pregnancy
14	PM _{2.5}	90 days prior to conception	1	r .		1		uperi tt an	1	1		1
15 16		First trimester	-0.065	1				leur (<i>F</i> d data				
17 18		Second trimester	-0.779	-0.2012				http://BES				
19 20		Third trimester	0.288	-0.7613	-0.1688	1) . ing, /				
21 22		Total pregnancy	-0.534	-0.2709	0.6838	0.3858	1	hining, Al training, and a 0.5544				
23	NO ₂	90 days prior to conception	0.6383	0.0684	-0.4588	0.3714	0.0376	1 ning				
24 25		First trimester	0.1537	0.6352	-0.0159	-0.4927	-0.0633	0.554 5	1			
26 27		Second trimester	-0.431	0.0714	0.6269	-0.0133	0.7251	0.3345	0.5399	1		
28 29		Third trimester	0.3027	-0.5213	0.0528	0.6817	0.4432	0.7149 une	0.2159	0.5145	1	
30 31		Total pregnancy	0.0057	0.0781	0.2862	0.0737	0.4779	0.67860 12, 20	0.7435	0.8755	0.7331	1
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45			For pe	er review only	r - http://bmjo	pen.bmj.com/	site/about/guid	0.678000gies.				

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1						n-2023 yright,			
2 3 4	eŢ	Table 5 Associations between	n PM _{2.5} and NO ₂ exposi	ure in different pregnan	cy periods and adve		(unadjusted mode	ls)	
5 6			Mean c	difference			d ratios		
7 8 9			Birth weight, grams	Birth length, cm	PTB (case: 33)	LBW (cereigr	LGA (case: 108)	SGA (case: 84)	
10 11			99% CI	99% CI	99% CI	elated 99% CIdente	99% CI	99% CI	
12 13	!	Per IQR increase in	(N=1,165)	(N=1,149)	(N=1,174)	99% CIed to 7 99% Cled to 7 (N=1,17 eignement. Superie (N=1,17 ext and	(N=1,174)	(N=1,174)	
14 15 16	Estimated	90 days prior to conception	9.28 (-44.04, 62.60)	-0.09 (-0.32, 0.14)	0.98 (0.46, 2.09)	and de 1.35 (0.64⊈_25682)	1.2 (0.79, 1.81)	0.98 (0.60, 1.58)	
17 18	exposure	First trimester	21.95 (-29.14, 73.04)	0.14 (-0.09, 0.36)	0.98 (0.48, 2.02)		0.97 (0.64, 1.47)	0.78 (0.48, 1.27)	
19 20	to PM _{2.5}	Second trimester	-18.21 (-70.25, 33.84)	0.04 (-0.19, 0.27)	0.85 (0.40, 1.79)	0.61 (0.26, B 40)	0.92 (0.60, 1.40)	1.33 (0.84, 2.10)	
21 22 23			-37.38 (-95.31, 20.56)	-0.32 (-0.57, -0.07)	1.35 (0.61, 2.99)	1.51 (0.56, 347)	1.08 (0.68, 1.72)	1.12 (0.67, 1.88)	
24	Estimated		-20.02 (-66.93, 26.89)	-0.1 (-0.30, 0.10)	0.81 (0.42, 1.55)		1.00 (0.69, 1.46)	1.2 (0.78, 1.84)	
26 27	exposure		-13.23 (-55.66, 29.19)	-0.12 (-0.31, 0.06)	1.2 (0.65, 2.19)		1.21 (0.85, 1.70)	1.24 (0.84, 1.83)	
28 29	to NO ₂	Second trimester	0.3 (-42.65, 43.25)	0.08 (-0.11, 0.27)	1.01 (0.55, 1.85)	1.15 (0.61, 1, 1, 17)	1.17 (0.83, 1.66)	1.27 (0.86, 1.87)	
30 31 32		Third trimester	-22.85 (-63.02, 17.32)	-0.04 (-0.22, 0.13)	1.11 (0.63, 1.95)	1.08 (0.00, 295)	1.06 (0.77, 1.47)	1.46 (1.01, 2.11)	
32 33 34		Total pregnancy	-32.72 (-78.00, 12.57)	-0.16 (-0.36, 0.03)	1.13 (0.60, 2.16)	1.35 (0.88, 269)	1.24 (0.86, 1.80)	1.58 (1.03, 2.42)	
35 36			-16.58 (-51.79, 18.63)	-0.03 (-0.18, 0.12)	1.03 (0.63, 1.69)	1.13 (0.67, b 91) b	1.16 (0.87, 1.55)	1.44 (1.04, 2.00)	
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41 42 43			For peer review	only - http://bmjopen.bmj.		de			

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1 2 3 4 5	e	Table 6 Associations betwee	en PM _{2.5} and NO ₂ exposu Mean diffe		lverse birth and the second	s (co-exposure mod	lels)	
6 7			Birth weight, grams	Birth length, cm	PTB (case: 33)	or دي LBW (ca	LGA (case: 108)	SGA (case: 84)
8 9			99% CI	99% CI	99% CI	2024. 99% CI att	99% CI	99% CI
10 11						a a D		
12 13	ł	Per IQR increase in	(N=941)	(N=927)	(N=945)	(N=945) to the sub- text sub-	(N=945)	(N=945)
14 15	Estimated	90 days prior to conception	75.00 (-36.61, 186.61)	0.23 (-0.25, 0.71)	0.21 (0.04, 1.03)	0.41 (0.10) (0.10)	1.14 (0.43, 3.03)	1.18 (0.36, 3.87)
16 17	exposure	First trimester	19.59 (-99.85, 139.04)	0 (-0.52, 0.52)	0.97 (0.17, 5.55)		0.67 (0.25, 1.79)	0.73 (0.21, 2.61)
18 19	to PM _{2.5}	Second trimester	-25.62 (-129.13, 77.90)	0.08 (-0.36, 0.53)	1.34 (0.25, 7.29)		0.83 (0.34, 2.01)	0.69 (0.27, 1.75)
20 21		Third trimester	13.77 (-99.47, 127.00)	-0.2 (-0.69, 0.29)	1.12 (0.20, 6.12)	(0.18≥4.58)	1 (0.38, 2.68)	0.57 (0.21, 1.56)
22 23		Total pregnancy	21.13 (-54.55, 96.81)	0.02 (-0.31, 0.35)	0.73 (0.26, 2.07)	0.52 (0.18 1.48)	0.98 (0.51, 1.88)	0.55 (0.27, 1.15)
24 25	Estimated	90 days prior to conception	-18.63 (-78.33, 41.07)	-0.09 (-0.35, 0.17)	1.24 (0.49, 3.11)	1.3 (0.52, a).29	1.27 (0.74, 2.16)	1.39 (0.79, 2.46)
26 27	exposure	First trimester	-14.53 (-75.84, 46.78)	0.05 (-0.22, 0.31)	0.91 (0.36, 2.28)		1.33 (0.78, 2.27)	1.70 (0.93, 3.11)
28 29 30	to NO ₂	Second trimester	-14.46 (-71.01, 42.09)	-0.08 (-0.32, 0.17)	1.22 (0.51, 2.91)		1.27 (0.77, 2.10)	1.50 (0.88, 2.55)
30 31 32		Third trimester	-13.13 (-81.19, 54.93)	0.04 (-0.25, 0.34)	0.77 (0.28, 2.13)		1.41 (0.78, 2.57)	1.77 (0.92, 3.40)
33 34		Total pregnancy	-15.02 (-60.15, 30.11)	0 (-0.20, 0.19)	1.08 (0.55, 2.12)	1.28 (0.64, 2.3)	1.21 (0.81, 1.80)	1.60 (1.03, 2.48)
35	Models adj	usted for maternal age at enrol	ment, infant's sex, maternal	BMI at 11–14 weeks'	gestation, primiparit	y, monthly hous to de	income level, and sea	ason of births.
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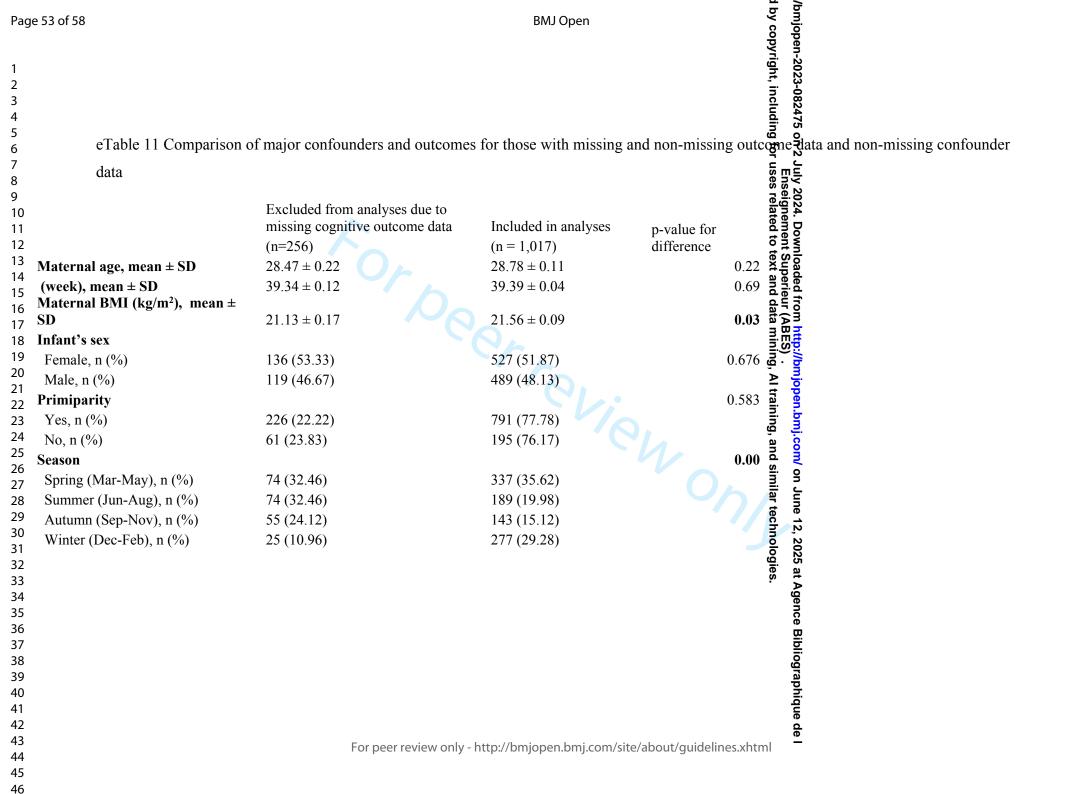
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sureFirst trimester $-1.07 (-3.51, 1.37)$ $0.04 (-2.01, 2.10)$ M2.5Second trimester $4.21 (1.87, 6.56)$ $2.63 (0.65, 4.61)$ Third trimester $-1.43 (-4.03, 1.17)$ $-1.76 (-3.94, 0.42)$ Total pregnancy $1.64 (-0.43, 3.71)$ $0.5 (-1.24, 2.25)$ nated90 days prior to conception $-1.90 (-3.82, 0.02)$ $-2.86 (-4.46, -1.26)$ sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$			
Per IQR increase in (N=946) (N=946) atacd 90 days prior to conception -3.54 (-5.94, -1.13) -3.42 (-5.44, -1.40) sure First trimester -1.07 (-3.51, 1.37) 0.04 (-2.01, 2.10) M2.5 Second trimester 4.21 (1.87, 6.56) 2.63 (0.65, 4.61) Third trimester -1.43 (-4.03, 1.17) -1.76 (-3.94, 0.42) Total pregnancy 1.64 (-0.43, 3.71) 0.5 (-1.24, 2.25) atacd 90 days prior to conception -1.90 (-3.82, 0.02) -2.86 (-4.46, -1.26) sure First trimester -0.08 (-2.05, 1.90) -1.17 (-2.83, 0.48) M2.5 Second trimester 0.04 (-2.04, 2.11) -1.97 (-3.70, -0.23)		Me	ean difference
nated90 days prior to conception-3.54 (-5.94, -1.13)-3.42 (-5.44, -1.40)sureFirst trimester-1.07 (-3.51, 1.37) 0.04 (-2.01, 2.10) $M_{2.5}$ Second trimester 4.21 (1.87, 6.56)2.63 (0.65, 4.61) Third trimester-1.43 (-4.03, 1.17)-1.76 (-3.94, 0.42)Total pregnancy1.64 (-0.43, 3.71) 0.5 (-1.24, 2.25)nated90 days prior to conception-1.90 (-3.82, 0.02) -2.86 (-4.46, -1.26) SureFirst trimester-0.08 (-2.05, 1.90)-1.17 (-2.83, 0.48) IO_2 Second trimester1.81 (-0.03, 3.66) 0 (-1.56, 1.55)Third trimester0.04 (-2.04, 2.11) -1.97 (-3.70, -0.23)		MDI 99% CI	PDI 99% CI
sureFirst trimester $-1.07 (-3.51, 1.37)$ $0.04 (-2.01, 2.10)$ M2.5Second trimester $4.21 (1.87, 6.56)$ $2.63 (0.65, 4.61)$ Third trimester $-1.43 (-4.03, 1.17)$ $-1.76 (-3.94, 0.42)$ Total pregnancy $1.64 (-0.43, 3.71)$ $0.5 (-1.24, 2.25)$ nated90 days prior to conception $-1.90 (-3.82, 0.02)$ $-2.86 (-4.46, -1.26)$ sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$ IO_2 Second trimester $1.81 (-0.03, 3.66)$ $0 (-1.56, 1.55)$ Third trimester $0.04 (-2.04, 2.11)$ $-1.97 (-3.70, -0.23)$	Per IQR increase in	n (N=946)	(N=946)
$M_{2.5}$ Second trimester 4.21 (1.87, 6.56)2.63 (0.65, 4.61) Third trimester $-1.43 (-4.03, 1.17)$ $-1.76 (-3.94, 0.42)$ Total pregnancy $1.64 (-0.43, 3.71)$ $0.5 (-1.24, 2.25)$ nated90 days prior to conception $-1.90 (-3.82, 0.02)$ $-2.86 (-4.46, -1.26)$ sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$ $M_{2.2}$ Second trimester $1.81 (-0.03, 3.66)$ $0 (-1.56, 1.55)$ Third trimester $0.04 (-2.04, 2.11)$ $-1.97 (-3.70, -0.23)$	mated 90 days prior to	conception -3.54 (-5.94, -1.13)	-3.42 (-5.44, -1.40)
Third trimester $-1.43 (-4.03, 1.17)$ $-1.76 (-3.94, 0.42)$ Total pregnancy $1.64 (-0.43, 3.71)$ $0.5 (-1.24, 2.25)$ nated90 days prior to conception $-1.90 (-3.82, 0.02)$ $-2.86 (-4.46, -1.26)$ sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$ MO_2 Second trimester $1.81 (-0.03, 3.66)$ $0 (-1.56, 1.55)$ Third trimester $0.04 (-2.04, 2.11)$ $-1.97 (-3.70, -0.23)$	osure First trimester	-1.07 (-3.51, 1.37)	0.04 (-2.01, 2.10)
Total pregnancy $1.64 (-0.43, 3.71)$ $0.5 (-1.24, 2.25)$ nated90 days prior to conception $-1.90 (-3.82, 0.02)$ $-2.86 (-4.46, -1.26)$ sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$ MO_2 Second trimester $1.81 (-0.03, 3.66)$ $0 (-1.56, 1.55)$ Third trimester $0.04 (-2.04, 2.11)$ $-1.97 (-3.70, -0.23)$	PM _{2.5} Second trimester	4.21 (1.87, 6.56)	2.63 (0.65, 4.61)
nated90 days prior to conception $-1.90 (-3.82, 0.02)$ $-2.86 (-4.46, -1.26)$ sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$ IO_2 Second trimester $1.81 (-0.03, 3.66)$ $0 (-1.56, 1.55)$ Third trimester $0.04 (-2.04, 2.11)$ $-1.97 (-3.70, -0.23)$	Third trimester	-1.43 (-4.03, 1.17)	-1.76 (-3.94, 0.42)
sureFirst trimester $-0.08 (-2.05, 1.90)$ $-1.17 (-2.83, 0.48)$ IO_2 Second trimester $1.81 (-0.03, 3.66)$ $0 (-1.56, 1.55)$ Third trimester $0.04 (-2.04, 2.11)$ $-1.97 (-3.70, -0.23)$	Total pregnancy	1.64 (-0.43, 3.71)	0.5 (-1.24, 2.25)
IO_2 Second trimester1.81 (-0.03, 3.66)0 (-1.56, 1.55)Third trimester0.04 (-2.04, 2.11)-1.97 (-3.70, -0.23)	mated 90 days prior to	conception -1.90 (-3.82, 0.02)	-2.86 (-4.46, -1.26)
Third trimester 0.04 (-2.04, 2.11) -1.97 (-3.70, -0.23)	osure First trimester	-0.08 (-2.05, 1.90)	-1.17 (-2.83, 0.48)
	NO ₂ Second trimester	n 1.81 (-0.03, 3.66)	0 (-1.56, 1.55)
Total pregnancy 0.67 (-0.95, 2.28) -1.08 (-2.44, 0.28)	Third trimester	0.04 (-2.04, 2.11)	-1.97 (-3.70, -0.23)
	Total pregnancy	0.67 (-0.95, 2.28)	-1.08 (-2.44, 0.28)

		BMJ Open and NO ₂ exposure in different pregnancy periods and BSID scores $\frac{1}{20}$							
eTable 8 Ass	ociations between PM _{2.5} and	d NO ₂ exposure in different	pregnancy periods and BSID scor	right, increased ing					
		Mean di	fference						
		MDI 99% CI	PDI 99% CI	uly 20 Ense uses r					
Р	er IQR increase in	(N=946)	(N=946)	n 2 July 2024. Do Enseignem for uses related					
Estimated	90 days prior to conception	-1.73 (-6.43, 2.98)	-4.74 (-8.67, -0.81)	to					
exposure to	First trimester	-2.84 (-7.85, 2.18)	-0.45 (-4.68, 3.77)	Downloaded ment Superie					
PM _{2.5}	Second trimester	4.19 (-0.15, 8.53)	5.51 (1.86, 9.16)	from data					
	Third trimester	-3.84 (-8.60, 0.93)	0.04 (-3.99, 4.06)	http:// BES)					
	Total pregnancy	-0.85 (-4.04, 2.33)	1.69 (-0.99, 4.37)	http://bmjopen.bmj.com/ on June 12, 2025 at A BES) . mining, Al training, and similar technologies.					
Estimated	90 days prior to conception	-0.31 (-2.83, 2.20)	-1.72 (-3.82, 0.38)	en.bm					
exposure to	First trimester	1.28 (-1.30, 3.86)	-1.80 (-3.98, 0.37)	y, and					
NO_2	Second trimester	-0.48 (-2.85, 1.90)	-2.11 (-4.11, -0.12)	on Ju					
	Third trimester	1.52 (-1.34, 4.38)	-1.92 (-4.34, 0.49)	ine 12 Ir tech					
	Total pregnancy	0.67 (-1.23, 2.57)	-1.68 (-3.28, -0.08)	, 2025 nolog					
Models adjus	sted for maternal age at enrolm	ent, infant's sex, maternal BM	I at 11–14 weeks' gestation,						
primiparity, 1	nonthly household income lev	el, and season of births.		ence					
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Page 51 of 58 1 2		ation effect of SGA on the assoc		BMJ Open		/bmjopen-2023-0 1 by copyright, in		
	eTable 9 Media	ation effect of SGA on the assoc	iations between PM	$_{2.5}$ and NO ₂ e	exposure in different p	82475 ଡୁମ 2 cludinୁଙ୍କfor reg⊈for	periods and MDI scor	res
7 8			Total Effect	P value	Direct Effect	은 Jue 기파 2 Pes -	Indirect Effect	P value
9 10	Estimated	90 days prior to conception	-3.54	0.000	-3.543	0 <u>40</u> 490 <u>6</u> 0	0.007	0.745
11	exposure to	First trimester	-1.07	0.259	-1.083		0.013	0.715
12 13	PM2.5	Second trimester	4.21	0.000	4.239	ૺૡૢૼૢૻૼઌ૽ૼૢૼ	0.024	0.599
14 15		Third trimester	-1.43	0.157	-1.422		-0.006	0.779
16		Total pregnancy	1.64	0.042	1.65	. Downboadsd from t emrentSuperieur(AE teo)to fext and data i	-0.012	0.695
17 18	Estimated	90 days prior to conception	-1.90	0.011	1.896	⇒ w <mark>-</mark>	0.007	0.799
19 20	exposure to	First trimester	-0.08	0.921	0.067	世紀//と明joとの. (19)3日の (19)3 (19)3日の (19)3	0.009	0.744
21 22	NO2	Second trimester	1.81	0.011	1.844	0an10a	-0.03	0.596
23		Third trimester	0.04	0.962	0.059		-0.021	0.728
24 25		Total pregnancy	0.67	0.288	0.686	0 ² 274	-0.021	0.672
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44		For peer	review only - http://bm	njopen.bmj.com	m/site/about/guidelines.xl	June 12, 2025 at Agence Bibliographique de ilar technologies.		

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eTable 10 Med	diation effect of SGA on the asso	ciations between P	$M_{2.5}$ and NO_2	exposure in differe	o23-08 ont pregnate ont pregnate ont pregnate official official of	periods and PDI sc	ores
		Total Effect	P value	Direct Effect	Povalize	Indirect Effect	P value
Estimated	90 days prior to conception	-3.422	0.000	-3.421	0ૡ૿ <u>ૼ</u> 0ૡ૽ૻૡૼ	0.001	0.931
exposure to	First trimester	0.045	0.955	0.049		-0.005	0.872
PM2.5	Second trimester	2.632	0.001	2.631	0 50 55	0.000	0.997
	Third trimester	-1.758	0.038	-1.762	05000	0.003	0.849
	Total pregnancy	0.504	0.456	0.501	4. Downloaded nethentSupprie ated to text and	0.003	0.894
Estimated	90 days prior to conception	-2.862	0.000	-2.869		0.007	0.762
exposure to	First trimester	-1.174	0.067	-1.179		0.005	0.826
NO2	Second trimester	-0.003	0.996	-0.010	0998	0.007	0.872
	Third trimester	-1.966	0.004	-1.985	≥ 0 g 00 <mark>%</mark>	0.018	0.711
	Total pregnancy	-1.079	0.041	-1.092		0.013	0.751
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Reporting checklist for cohort study.

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Title

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1 2 3	Abstract	<u>#1b</u>	Provide in the abstract an informative and balanced	2, 3	
4 5			summary of what was done and what was found		
6 7 8	Introduction				
9 10 11	Background /	<u>#2</u>	Explain the scientific background and rationale for the	4, 5	Pro
12 13	rationale		investigation being reported		ected b
14 15 16 17	Objectives	<u>#3</u>	State specific objectives, including any prespecified	5	Protected by copyright
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23 24 25	Study design	<u>#4</u>	Present key elements of study design early in the paper	5,6	uding for uses r
26 27 28	Setting	<u>#5</u>	Describe the setting, locations, and relevant dates,	5,6	elated t
29			including periods of recruitment, exposure, follow-up, and		o text
30 31 32 33			data collection		and data
34 35	Eligibility criteria	<u>#6a</u>	Give the eligibility criteria, and the sources and methods of	5,6	a mininé
36 37 38			selection of participants. Describe methods of follow-up.		g, Al tra
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41 42 43			exposed and unexposed		and simi
44 45 46	Variables	<u>#7</u>	Clearly define all outcomes, exposures, predictors,	6, 7, 8	similar technologies.
47 48			potential confounders, and effect modifiers. Give diagnostic		nologi
49 50 51			criteria, if applicable		es.
51 52 53	Data sources /	<u>#8</u>	For each variable of interest give sources of data and	6, 7, 8	
54 55 56	measurement		details of methods of assessment (measurement).		
57 58			Describe comparability of assessment methods if there is		
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1			more than one group. Give information separately for for		BMJ
2 3 4			exposed and unexposed groups if applicable.		Open: f
5 6 7	Bias	<u>#9</u>	Describe any efforts to address potential sources of bias	6, 7, 8	BMJ Open: first published as 10.1136/bmjopen-2023-082475 on 2 July 2024. Enseigne Protected by copyright, including for uses relat
8 9 10	Study size	<u>#10</u>	Explain how the study size was arrived at	6	ned as 1 Pr
11 12 13	Quantitative	<u>#11</u>	Explain how quantitative variables were handled in the	8, 9	0.1136/ otected
14 15	variables		analyses. If applicable, describe which groupings were		bmjop by cop
16 17 18			chosen, and why		s 10.1136/bmjopen-2023-082475 on 2 July 20 Ense Protected by copyright, including for uses r
19 20 21	Statistical	<u>#12a</u>	Describe all statistical methods, including those used to	8, 9	-082475 includi
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1			confirmed eligible, included in the study, completing follow-		
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6 7			exposed and unexposed groups if applicable.		
8 9 10	Participants	<u>#13b</u>	Give reasons for non-participation at each stage	10, 20	
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17 18	Descriptive data	<u>#14a</u>	Give characteristics of study participants (eg demographic,	10,22	
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42 43	Outcome data	<u>#15</u>	Report numbers of outcome events or summary measures	10,22	
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52 53	Main results	<u>#16a</u>	Give unadjusted estimates and, if applicable, confounder-	10, 11	
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			BMJ Open	Page	58 of 58
1			interval). Make clear which confounders were adjusted for		BMJ
2 3 4			and why they were included		Open: f
5 6 7	Main results	<u>#16b</u>	Report category boundaries when continuous variables	10, 11	BMJ Open: first published as 10.1136/bmjopen-2023-082475 on 2 July 2024. Enseigne Protected by copyright, including for uses relat
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24 25 26	Discussion				s 10.1136/bmjopen-2023-082475 on 2 July 2024. Dov Enseigneme Protected by copyright, including for uses related t
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30 31	Limitations	#19	Discuss limitations of the study, taking into account sources	14	Downloaded from ment Superieur (A d to text and data
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46 47 48	Generalisability	<u>#21</u>	Discuss the generalisability (external validity) of the study	14	<mark>p://bmjopen.bmj.com/</mark> on June 12, 2025 at Agence Bibliographique de S) . ning, Al training, and similar technologies.
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1 2	Funding	<u>#22</u>	Give the source of funding and the role of the funders for	18
3 4			the present study and, if applicable, for the original study	
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Associations of air pollution exposures in preconception and pregnancy with birth outcomes and infant neurocognitive development: analysis of the Complex Lipids in Mothers and Babies (CLIMB) prospective cohort in Chongqing, China

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BMJ Open

Associations of air pollution exposures in preconception and pregnancy with birth outcomes and infant neurocognitive development: analysis of the Complex Lipids in Mothers and Babies (CLIMB) prospective cohort in Chongging, China Yingxin Chen^{1,2}, Tao Kuang³, Ting Zhang⁴, Yutong Samuel Cai^{1,2,5}, John Colombo⁶, Alex Harper⁷, Ting-Li Han⁸, Yinyin Xia⁹, John Gulliver¹⁰, Anna L Hansell^{1,2,5}, Hua Zhang⁸, Philip N Baker^{7,8} 1: Centre for Environmental Health and Sustainability, University of Leicester, Leicester, UK 2: The National Institute of Health Research (NIHR) Health Protection Research Unit (HPRU) in Environmental Exposure and Health at the University of Leicester, Leicester, UK 3: Department of public health and management, Zunyi Medical and Pharmaceutical College, Zunyi, 563000, Guizhou, China 4. Stomatological Hospital of Chongqing Medical University, Chongqing, 401147, China 5: NIHR Leicester Biomedical Research Centre, Leicester General Hospital, Leicester, UK 6: Schiefelbusch Institute for Life Span Studies and Department of Psychology, University of Kansas, Lawrence, KS 66045, USA 7: College of Life Sciences, University of Leicester, Leicester, UK 8: Department of Obstetrics and Gynaecology, the First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China 9: School of Public Health, Chongqing Medical University, Chongqing, 400016, China 10: Environmental and Exposure Sciences, Population Health Research Institute, St George's, University of London, London, UK Correspondence to: Yinyin Xia. School of Public Health, Chongqing Medical University, Chongqing, 400016, China. Email: 100118@cqmu.edu.cn

Abstract

Objectives: to investigate the associations of traffic-related air pollution exposures in early pregnancy with birth outcomes and infant neurocognitive development

Design: cohort study

Setting: eligible women attended six visits in the maternity clinics of two centres (the First Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for Women and Children).

Participants: women who were between 20 and 40 years of age and were at 11–14 weeks gestation with a singleton pregnancy were eligible for participation. Women were excluded if they had a history of premature delivery before 32 weeks of gestation, maternal milk allergy or aversion, or severe lactose intolerance. 1,273 pregnant women enrolled in 2015-2016 and 1,174 live births were included in this analysis.

Exposures: Air pollution concentrations at their home addresses, including particulate matter (PM) with diameter $\leq 2.5 \mu m$ (PM_{2.5}) and nitrogen dioxide (NO₂), during pre-conception and each trimester period were estimated using land-use regression models.

Outcome measures: birth outcomes (i.e., birthweight, birth length, preterm birth (PTB), low birth weight (LBW), large for gestational age (LGA) and small for gestational age (SGA) status) and neurodevelopment outcomes measured by the Chinese version of Bayley Scales of Infant Development (CBSID).

Results: An association between SGA and per Interquartile range (IQR) increases in NO₂ was found in the first trimester (Odd ratio (OR): 1.57, 95% confidence interval (CI): 1.06, 2.32) and during the whole pregnancy (OR: 1.33, 99% CI: 1.01, 1.75). Both PM_{2.5} and NO₂ exposure in the 90 days prior to conception were associated with lower Psychomotor Development Index (PDI) scores (β : -6.15, 95% CI: -8.84, -3.46; β : -2.83, 95% CI: -4.27, -1.39, respectively). Increased NO₂ exposure was associated with an increased risk of psychomotor development delay (PDD) during different trimesters of pregnancy.

Conclusions: Increased exposure to NO_2 during pregnancy were associated with increased risk of SGA and psychomotor development delay, while increased exposure to both $PM_{2.5}$ and NO_2 pre-conception were associated with adverse psychomotor development outcomes at 12 months of age.

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Keywords: Air pollution; birth outcomes; child cognition

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Article summary

Strengths and limitations of this study

- We developed an LUR model to capture spatial and temporal variations of air pollution at individual level to reduce exposure misclassification.
- This study uniquely explored the impacts of both pre-conception and prenatal exposure to PM_{2.5} and NO₂ on neurodevelopmental outcomes in young infants, within an urban environment characterized by relatively high air pollution levels.
- Our sample size was relatively small, limiting the statistical power to assess several outcomes.
- We defined exposure windows for clinically-defined trimesters.

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Introduction

Air pollution is a major environmental factor that has been linked to a range of adverse health outcomes in children. Maternal exposure to air pollutants during pregnancy, especially particulate matter (PM) with diameter $\leq 2.5 \mu m$ (PM_{2.5}) and nitrogen dioxide (NO₂), has been found to be associated with adverse birth outcomes, including pre-term birth (PTB)(1), term low birth weight (TLBW) (2), and small for gestational age (SGA) status (3). According to the developmental origins of health and disease (DOHaD) hypothesis, prenatal exposures to air pollution may lead to adverse birth outcomes and subsequently increase the susceptibility to the development of certain diseases later in life (4). A number of epidemiological studies have linked prenatal air pollution exposure with neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and cognitive impairment (5). Although the underlying biological mechanisms are still unclear, some studies indicated that prenatal air pollution exposure may induce systemic oxidative stress that triggers intrauterine inflammation, leading to damage to several fetal organs, including the brain (6, 7).

It is also unclear that whether the adverse effects of air pollution may start earlier before conception. Three months before conception was considered as a critical developmental window for gametogenesis. Air pollution exposure during the three-month preconception period may have adverse effects on gametogenesis of sperm (8, 9) and ova cells (10). Exposures to PM_{2.5} in preconception period have been associated with various neurodevelopmental outcomes, such as neural tube defects (11), lower psychomotor development scores (12), higher risk of ASD (13, 14), and higher risk of intellectual disability (15). Further research is required due to inconsistencies across studies in terms of studied health outcomes and exposure levels of air pollution (12). Additionally, while there is growing evidence for the effects of preconception PM_{2.5} exposure on the risk of adverse neurodevelopmental outcomes, no study to date has examined the effects of preconception NO₂ exposure. Exposure to NO₂ during pregnancy may be linked to compromised neural development in children, particularly affecting fine psychomotor skills(16). Studying PM_{2.5} along with NO₂ may allow us to explore how multiple pollutants affect birth outcomes and infant neurocognitive development independently and jointly. Moreover, both PM2.5 and NO2 are regulated traffic-related air pollutants in many countries. Understanding their impacts on birth and infant neurocognitive development can provide valuable insights for policymakers and public health authorities to develop effective air quality regulations and interventions.

Many studies have reported the effects of prenatal exposure to air pollution on neurodevelopmental function in children. However, the reported associations vary, due to the heterogeneous assessments of air pollution and neurodevelopmental outcomes (5, 17).

The current study leveraged the Complex Lipids in Mothers and Babies (CLIMB) cohort, a prospective birth cohort recruited in Chongqing, China (18), with trimester-specific maternal $PM_{2.5}$ and NO_2 air pollution exposure derived from a spatio-temporal land use regression (LUR) model (19). The aim of this analysis was to examine the associations between $PM_{2.5}$ and NO_2 exposures during pre- and during pregnancy, with birth and infant neurocognitive development outcomes at 12 months of age.

A key aspect in all studies like this one is the accuracy of documenting exposure; a recent Chinese study determined air pollution exposure based on data from the nearest monitoring station (20) may not reflect the fine temporal and spatial variability of pollutant exposures among participants. Our study employed common air pollution exposure models based on advanced geographic information systems (GIS), to address some of the limitations of previous studies (21).

In addition, the timing of exposure is also critical in determining the effects of exposure on developmental outcomes. Indeed, the evidence from previous studies on the sensitive time windows for exposure pre- and during pregnancy remains inconclusive. Some studies have indicated that the early-to-mid pregnancy phase may be a critical period in terms of the impact of air pollution on neurodevelopment(22, 23). Early pregnancy is particularly important for neurogenesis and neuromigration, making it a susceptible period (24). However, some studies reported stronger associations for middle or late pregnancy (20, 25, 26). More studies identifying critical periods are needed to enhance our understanding of how pre-conception and prenatal air pollution exposure affect neurodevelopment. With this cohort, we are able to examine the effects of exposure pre-conception, at each trimester, and the entire pregnancy.

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Methods

Study population

Participant recruitment in the CLIMB cohort has been described previously (27). In brief, women who were between 20 and 40 years of age and were at 11–14 weeks gestation with a singleton pregnancy were eligible for participation. Women were excluded if they had a history of premature delivery before 32 weeks of gestation, maternal milk allergy or aversion, or severe lactose intolerance.

From September 2015 to November 2016, a total of 1,500 women were recruited into the cohort. Participants attended six visits at the First Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for Women and Children: 11–14 weeks' gestation (visit 1), 22–28 week's gestation (visit 2), 32–34 week's gestation (visit 3), at birth (visit 4), 6 weeks postnatal (visit 5), and 12 months postnatal (visit 6).

Women who withdrew from the study (n = 146), terminated their pregnancy (n = 29), miscarried (n = 12) or were lost to follow-up (n = 40) were excluded from the analysis, leaving a sample size of 1,273 women. Analyses were restricted to mothers whose detailed residential addresses during pregnancy were known (**Figure 1**). A total of 1,174 live births were thus included in the pregnancy and neonatal outcomes analysis. Subsequently, at 1 year follow-up, 946 children were included in the analysis of neurodevelopment outcomes.

Exposure assessment

The address of participants was collected at the first visit. Exposure assessment based on spatiotemporal land use regression (LUR) models for $PM_{2.5}$ and NO_2 were developed for the study region. The study area focused on the urban center of the Chinese municipality of Chongqing (**Figure 2**). A description of the methodology of exposure modelling has been reported previously (19). Briefly, the models included both spatial and temporal components of exposure. $PM_{2.5}$ and NO_2 concentration data were collected from 17 routine monitoring sites operated by the Chongqing Environmental Monitoring Center in 2015-2016. For the spatial component of models, we calculated annual average concentrations of each pollutant in 2015, and fit linear regression models using five groups of geographic data (road network, land use, topography, vegetation, and population density) as spatial predictor variables. For the temporal component at each

monitoring site on a daily basis by subtracting the predicted annual average concentration from the observed daily average concentrations measured in 2015 and 2016, and then fitted generalised additive models (GAM) using seven groups of meteorological data (temperature, amount of rainfall, rainfall events, relative humidity, horizontal visibility, wind direction and wind speed) as temporal predictor variables. The meteorological variables were used to account for the influence of weather on the change in air pollution concentration over time. To account for the remaining spatial autocorrelation, the smoothed terms of longitude and latitude were fit to spatiotemporal residuals which were calculated by subtracting the sum of the spatial temporal predictions from the measured daily average concentrations in 2015 and 2016. The performance of the $PM_{2.5}$ spatiotemporal models was good (Correlation (COR)-R²: 0.72) and the NO₂ spatiotemporal model was moderate (COR-R²: 0.39) when providing concentration estimates in absolute terms.

Combining the family address coordinates of each pregnant woman and the gestation period of the pregnancy (calculated from the date of last menstrual period to the date of delivery), we used this spatiotemporal model to estimate the average exposure of each pregnant woman in 90 days prior to pregnancy (90D), first trimester (T1), second trimester (T2), third trimester (T3) and whole pregnancy period (WP), respectively.

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Outcomes

Birth Outcomes

Birth outcomes were determined by experienced obstetricians and abstracted from the medical records. Birth outcomes included: birthweight (in grams), birth length (in centimetres), PTB, low birth weight (LBW), large for gestational age (LGA) and SGA status (28). PTB was defined as delivery before 37 weeks. LBW was defined as weighing less than 2500 g at birth. LGA and SGA were indicated by birth weight greater than and less than the 90th and 10th percentile within this study for the gestational age by sex respectively (29). Term low birth weight was not considered due to a small sample size of only 8 cases.

Neurodevelopment outcomes

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The Chinese version of Bayley Scales of Infant Development (CBSID) was used to assess mental and psychomotor development for infants in this study. The CBSID is appropriate for evaluation of infants from 2–30 months old (30) and takes into consideration each infant's age in days. Infants were assessed at around 12 months (range from 11 months and 15 days to 12 months and 15 days) by a trained examiner, with ages corrected for preterm birth. These scales have been formally adapted to the Chinese language and locally standardized to become culturally appropriate, with two main indexes: the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The MDI component comprised 163 items and assessed age-appropriate items related to cognitive functioning, personal and social development, and language development (see eTable 1 in the Supplement). The PDI component comprised 81 items and assessed age-appropriate fine and gross motor skills (see eTable 2 in the Supplement). The test provided raw scores for mental and psychomotor development that were converted to standardized (in terms of age in days) MDI and PDI scores, based on norms for the Chinese population. As with other forms of the Bayley test these index scores have a mean of 100, and a standard deviation of 15, with a lower score reflecting poorer performance (31). If an infant refused to cooperate with the examiners to finish the task, a second assessment was arranged within two weeks. If the infant could not cooperate at the second BSID assessment, their data were classified as missing. In addition to the continuous scores, we define mental developmental delay (MDD) and psychomotor developmental delay (PDD) if the score is less than 85(32).

Covariates

Socio-demographic data were collected through interviews by trained nurses. The following potential confounders were identified: maternal age at enrolment (in years), infant sex (male/female), maternal BMI at 11–14 weeks' gestation (kg/m²), parity (Yes/No), monthly household income level (categorized as: <2,000 yuan, 2,000–7,000 yuan, 7,000–10,000 yuan, or >10,000 yuan), season of birth (categorized as: Spring (Mar-May), Summer (Jun-Aug), Autumn (Sep-Nov) or Winter (Dec-Feb)). Marital status (single/married) and smoking or drinking during pregnancy (Yes/no) were not taken into account in this analysis because of the homogeneity of the study population (i.e., 98.6% women were married and 99.6% women reported not smoking or drinking alcohol during pregnancy). We did not adjust dietary

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supplements during pregnancy because all pregnant women routinely take folic acid in this cohort.

Statistical analyses

Data were described in terms of mean \pm SD or median (IQR) for continuous variables, or as percentages for categorical variables. Modelled PM_{2.5} and NO₂ exposure levels in 90D, T1, T2, T3 and WP were considered separately. We examined the Spearman correlation between each of the exposures in the different pregnancy periods. For birth outcomes, multivariable linear regression was used for continuous outcomes (e.g., birth weight and birth length) to estimate β coefficient and their 95% confidence intervals (CIs) and multivariable logistic regression for binary outcomes (e.g., PTB, LBW, LGA and SGA status) to estimate odds ratio (OR) and 95% CIs. For mental and psychomotor development (e.g., MDI and PDI scores), multivariable linear regression models were fit to estimate β coefficient and their 95% CIs. We also conducted multivariable logistic regression analysis for binary neurodevelopment outcomes (i.e., MDD and PDD). Models were adjusted for maternal age at enrolment, infant sex, maternal BMI at 11–14 weeks gestation, primiparity, monthly household income level, and season of birth. We also ran co-exposure models to estimate associations of one air pollutant whilst additionally adjusting for the other air pollutant (i.e., PM_{2.5} effects in T1 adjusted for NO₂ in T1). Effect estimates are reported for each IQR increase of PM2.5 and NO2. All analyses were performed using STATA version 17. A p-value of <0.05 was considered statistically significant to address multiple comparisons in the analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Results

Study Participants

Participant characteristics are presented in **Table 1**. Of those participating women, the mean age was 28.7 years and mean BMI was 21.5 kg/m². 98.0% of women were of Han ethnicity, 77.9% were primiparous, and 67.6% had completed tertiary education. 33 (2.8%), 30 (2.6%), 108 (9.2%), 84 (7.2%) of the 1,174 births considered in this analysis were classified as PTB, LBW, LGA and SGA, respectively. For those 946 children who completed the BSID test, the mean MDI score was 94.7 (SD: 17.7) and the mean PDI score was 87.4 (SD: 14.9). The proportions of participants with MDD (MDI <85) and PDD (PDI < 85) were 27.1% and 42.4%, respectively.

Exposure assessment

Median PM_{2.5} exposure concentrations were 57.31 μ g/m³ (IQR: 5.76) and median NO₂ exposure levels were 50.46 μ g/m³ (IQR: 5.51) during the whole pregnancy period (**eTable 3 in the Supplement**). For PM_{2.5}, the concentration in the pre-conception and T1 were considerably lower than other periods, close to 10 μ g/m³. The between-trimester and 90D values for NO₂ were generally moderately correlated (Pearson's r > 0.5). The correlation coefficients of PM_{2.5} were more variable between time periods reflecting the high variability of PM_{2.5} concentrations, with values ranging from -0.78 to +0.68. Correlations between PM_{2.5} and NO₂ in the same pregnancy period were moderately correlated (Pearson's r ~0.6, **eTable 4 in the Supplement**).

Table 1 Characteristics of study sample in the CLIMB cohort (N = 1,174)

Characteristic of mothers	Ν	n (%) / mean ± SD	Characteristic of child	Ν	n (%) /mean ± S
Maternal age (Years)	1,174	28.7 ± 3.5	Gestational week (week)	1,174	39.4 ± 1.5
BMI (kg/m ²)	1,174	21.5 ± 2.9	Birth weight (g)	1,165	3314.4 ± 428.8
Han ethnicity (%)	1,174		Birth length (cm)	1,149	49.7 ± 1.9
Yes		1,151 (98.0%)	New born sex	1,172	
No		23 (2.0%)	Female		561 (47.9%)
Marital status (%)	1,174	×	Male		611 (52.1%)
≨ ingle		16 (1.4%)	Birth outcomes		
Married		1,158 (98.6%)	Preterm birth (PTB)	1,174	
Primiparity (%)	1,174		Yes	,	33 (2.8%)
Yes	-,-,	914 (77.9%)	No		1,141 (97.2%)
8No		260 (22.1%)	Low birth weight (LBW)	1,174	, (, / •)
History of miscarriage or	1,174	200 (22.170)	Yes	-,-/	30 (2.6%)
abortion (%)	1,171				56 (2.070)
Ves		553 (47.1%)	No		1,141 (97.2%)
Yes No		621 (52.9%)	Large for gestational age	1,174	1,111 ()7.270)
3``		021(32.7/0)	(LGA)	1,1/4	
4 §moking/drinking during	1,174		Yes		108 (9.2%)
pregnancy (%)	1,1/4		105		108 (9.270)
		5 (0.4%)	No		1,066 (90.8%)
Yes		1,169 (99.6%)	Small for gestational age	1,174	1,000 (90.870)
8No		1,109 (99.0%)		1,1/4	
9 Education level	046		(SGA)		94(7,20/)
	946	20((22 20/)	Yes		84 (7.2%)
Low: High school or below		306 (32.3%)	No	0.16	1,090 (92.8%)
High: College/uni or above	0.1.6	640 (67.6%)	BSID test	946	
Job Full-time	946		MDI score		94.7 ± 17.7
Full-time		762 (80.5%)	PDI score		87.4 ± 14.9
Housewife		82 (8.7%)	Mental development	946	
Others		102 (10.8%)	Delay (MDI < 85)		276 (27.1%)
Household income (Monthly)	946		Normal (MDI \geq 85)		741 (72.9%)
92000 RMB		186 (19.7%)	Psychomotor Development	946	
2000-4000 RMB		329 (34.8%)	Delay (PDI < 85)		431 (42.4%)
4000-7000 RMB		292 (30.9%)	Normal (PDI \geq 85)		586 (57.6%)
≹000-10000 RMB		139 (14.7%)	Season of birth	1,174	
3		. ,	Spring (Mar-May)		411 (35.01%)
4			Summer (Jun-Aug)		263 (22.40%)
5			Autumn (Sep-Nov)		198 (16.87%)
6			Winter (Dec-Feb)		302 (25.72%)
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25 Association with birth outcomes

In the unadjusted models (eTable 5 in the Supplement), higher exposure concentrations of PM_{2.5} in T3 were significantly associated with lower birth length (β: -0.32, 95% CI: -0.51, -0.13; per IQR increase). We also observed increased NO₂ in T3 were significantly associated with lower birth length (β: -0.16, 95% CI: -0.32, -0.01; per IQR). A risk between SGA and increases in NO₂ (per IQR) was found in T2 (OR: 1.46, 95% CI: 1.10, 1.93), T3 (OR: 1.58, 95% CI: 1.14, 2.18) and in the whole pregnancy period (OR: 1.44, 95% CI: 1.13, 1.85). We observed no evidence of associations of NO₂ with overall birth weight, birth length and other adverse birth outcomes (e.g., PTB, LBW, and LGA).

In the adjusted models (**Table 2**), we found increased effect size for NO₂ and SGA in T2

35 (OR: 1.57, 95% CI: 1.06, 2.32), and slightly reduced effects size for NO_2 and SGA in the

36 whole pregnancy period (OR: 1.33, 95% CI: 1.01, 1.75) compared with the unadjusted

37 model. We observed no evidence of associations with birth length in the adjusted models.

38 After co-adjustment for $PM_{2.5}$ (see eTable 6 in the Supplement), the association of NO_2

39 with SGA was also found in T1 (OR: 1.70, 95% CI: 1.07, 2.69), T3 (OR: 1.77, 95% CI: 1.08,

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40 2.91) and in the whole pregnancy period (OR: 1.60, 95% CI: 1.15, 2.23).

Page 15 of 48	3		BMJ Open		/bmjopen-202 d by copyright		
1 2 3 41 4	Table 2 Associations bet	tween PM _{2.5} and NO ₂ exp	osure in different pregna	ncy periods and a	in o	mes (adjusted mod	lels)
6		Mean dit	fference		t S Odd	ratios	
9	Per IQR increase in	Birth weight, grams (95% CI) (N=941)	Birth length, cm (95% CI) (N=927)	PTB (case: 33) (95% CI) (N=945)	LBWG(255: 30) (98% 51) (1499 52)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
10 1 Estimated	90 days prior to conception	59.73 (-16.52, 135.98)	0.15 (-0.176, 0.48)	0.24 (0.06, 1.00)	0.49 (8.38, 1.29)	1.40 (0.72, 2.71)	1.66 (0.75, 3.68)
¹² exposure	First trimester	6.21 (-73.79, 86.20)	0.04 (-0.308, 0.388)	0.88 (0.28, 2.80)	0.76 (9.315 2.81)	0.86 (0.45, 1.67)	1.33 (0.58, 3.04)
-	Second trimester	-37.64 (-107.73, 32.44)	0.02 (-0.283, 0.326)	1.62 (0.53, 4.96)	1.34 (8, 8, 4.68)	1.00 (0.55, 1.83)	0.94 (0.50, 1.76)
14to PM _{2.5} 15	Third trimester	4.20 (-73.17, 81.57)	-0.17 (-0.509, 0.162)	0.92 (0.29, 2.90)	0.92 (2.85)	1.29 (0.65, 2.53)	0.83 (0.42, 1.66)
16	Total pregnancy	8.01 (-41.10, 57.11)	0.02 (-0.198, 0.230)	0.77 (0.38, 1.54)	0.62 (2 12 1.25)	1.15 (0.75, 1.77)	0.84 (0.52, 1.35)
¹ Estimated	90 days prior to conception	-1.03 (-41.88, 39.81)	-0.04 (-0.215, 0.139)	0.84 (0.45, 1.57)	1.04 (9.04 1.98)	1.31 (0.91, 1.88)	1.45 (0.99, 2.12)
18 19exposure	First trimester	-9.78 (-50.84, 31.28)	0.04 (-0.133, 0.223)	0.90 (0.49, 1.65)	1.03 (3.96 1.91)	1.21 (0.85, 1.72)	1.57 (1.06, 2.32)
$\frac{20}{21}$ to NO ₂	Second trimester	-20.82 (-59.11, 17.47)	-0.06 (-0.222, 0.112)	1.31 (0.73, 2.34)	1.34 (0.75 2.40)	1.21 (0.86, 1.70)	1.36 (0.95, 1.95)
	Third trimester	-9.50 (-56.00, 36.99)	-0.01 (-0.213, 0.191)	0.79 (0.40, 1.59)	0.95 (.47 1.94)	1.42 (0.94, 2.13)	1.51 (0.97, 2.36)
22 <u>23</u>	Total pregnancy	-8.45 (-37.73, 20.83)	0.00 (-0.125, 0.130)	0.97 (0.62, 1.51)	1.04 (9.66 1.64)	1.20 (0.93, 1.56)	1.33 (1.01, 1.75)
2All signific	cant findings in the table are bo	old.			<u> </u>		
	justed for maternal age at enrol	lment, infant's sex, maternal	BMI at 11–14 weeks' gestati	on, primiparity, mont	hly hous hous hous hous hous hous hous hous	e level, and season of	births.
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43 Association with infant neurodevelopment outcomes

In unadjusted models, PM_{2.5} exposure in the 90 days prior to conception was associated with lower MDI and PDI scores in offspring (β: -3.54, 95% CI: -5.37, -1.71; β: -3.42, 95% CI: -4.96, -1.89) (Table 3). We also observed an unexpected positive association between $PM_{2.5}$ exposures in second trimester with MDI (β: 4.21, 95% CI: 2.43, 6.00) and PDI (β: 2.63, 95% CI: 1.12, 4.14). Exposure to NO₂ was associated with lower MDI (-1.90, 95% CI: -3.36, -0.44) and PDI in the 90 days prior to conception (-2.86, 95% CI: -4.08, -1.65). NO₂ exposure was also associated with lower PDI scores in T3 (-1.97, 95% CI: -3.29, -0.65) and in the whole pregnancy periods (-1.08, 95% CI: -2.11, -0.05). We did not observe any association between NO₂ and MDI in any pregnancy periods.

In the adjusted models (Table 3), we found $PM_{2.5}$ exposure in the 90 days prior to conception was associated with lower PDI scores (β : -6.15, 95% CI: -8.84, -3.46). Similarly, there was also a significant association of increased NO₂ exposure and lower PDI score in the 90 days prior to conception (β : -2.83, 95% CI: -4.27, -1.39), T1 (β : -1.91, 95% CI: -3.37, -0.46), T3 (β : -1.92, 95% CI: -3.57, -0.26) and whole pregnancy period (β : -1.15, 95% CI: -2.19, -0.11). The positive association between PM_{2.5} exposures in second trimester with PDI (β : 3.76, 95% CI: 1.27, 6.24) remained. We did not observe any association with MDI in any pregnancy periods.

In the co-exposure models (**Table 3**), $PM_{2.5}$ exposure in the 90 days prior to conception was associated with lower PDI scores (β : -4.74, 95% CI: -7.73, -1.75). We also observed a positive association between $PM_{2.5}$ exposures in second trimester with PDI (β : 5.51, 95% CI:2.73, 8.28). Exposure to NO₂ was significantly associated with lower PDI in 90D (β : -1.72, 95% CI: -3.31, -0.12), T1 (β : -1.80, 95% CI: -3.46, -0.15), T2 (β : -2.11, 95% CI: -3.63, -0.60), T3 (β : -1.92, 95% CI: -3.76, -0.09) and whole pregnancy period (β : -1.68, 95% CI: -2.89, -0.46).

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66	Table 3 Associations between PM _{2.5} and NO ₂ exposure in different pregnancy periods and continuo	incendir	ය SID scores

5					n(
6		Crude models		Adjusted models*		Co-exposure models**		
7 8 Per IQR increase in		MDI (95% CI) (N=946)	PDI 95% CI (N=946)	MDI (95% CI) (N=945)	PDI 95% E Luy (N=945	MDI (95% CI) (N=945)	PDI 95% CI (N=945)	
10 ^{Estimated}	90 days prior to conception	-3.54 (-5.37, -1.71)	-3.42 (-4.96, -1.89)	-1.98 (-5.19, 1.23)	-6.15 (-8.84, 23746)	-1.73 (-5.30, 1.85)	-4.74 (-7.73, -1.75)	
¹ ¹ exposure	First trimester	-1.07 (-2.93, 0.79)	0.04 (-1.52, 1.61)	-1.66 (-5.02, 1.70)	-2.11 (-4.95, b , a)	-2.84 (-6.65, 0.97)	-0.45 (-3.67, 2.76)	
12 13to PM _{2.5}	Second trimester	4.21 (2.43, 6.00)	2.63 (1.12, 4.14)	3.79 (0.85, 6.73)	3.76 (1.27, 😴 🏹	4.19 (0.89, 7.49)	5.51 (2.73, 8.28)	
14	Third trimester	-1.43 (-3.41, 0.55)	-1.76 (-3.42, -0.10)	-2.73 (-5.99, 0.53)	-1.37 (-4.12, a 🛓	-3.84 (-7.46, -0.22)	0.04 (-3.02, 3.09)	
15	Total pregnancy	1.64 (0.06, 3.21)	0.5 (-0.82, 1.83)	-0.27 (-2.34, 1.80)	0.23 (-1.52, § . 2 8	-0.85 (-3.28, 1.57)	1.69 (-0.35, 3.73)	
¹⁶ Estimated	90 days prior to conception	-1.90 (-3.36, -0.44)	-2.86 (-4.08, -1.65)	-0.72 (-2.43, 1.00)	-2.83 (-4.27, a) (-2.83	-0.31 (-2.22, 1.60)	-1.72 (-3.31, -0.12)	
18exposure	First trimester	-0.08 (-1.57, 1.42)	-1.17 (-2.43, 0.08)	0.59 (-1.14, 2.32)	-1.91 (-3.37, Bras	1.28 (-0.68, 3.24)	-1.80 (-3.46, -0.15)	
19 20 to NO ₂	Second trimester	1.81 (0.41, 3.22)	0.00 (-1.18, 1.18)	0.56 (-1.05, 2.17)	-0.75 (-2.11, 3.6	-0.48 (-2.28, 1.33)	-2.11 (-3.63, -0.60)	
20 ¹⁰ 110 ₂ 21	Third trimester	0.04 (-1.54, 1.62)	-1.97 (-3.29, -0.65)	0.51 (-1.45, 2.47)	-1.92 (-3.57, 2 0.2 5)	1.52 (-0.66, 3.69)	-1.92 (-3.76, -0.09)	
<u>21</u> <u>22</u>	Total pregnancy	0.67 (-0.56, 1.89)	-1.08 (-2.11, -0.05)	0.41 (-0.83, 1.64)	-1.15 (-2.19, a).19	0.67 (-0.77, 2.12)	-1.68 (-2.89, -0.46)	

23 Il significant findings in the table are bold.
 24 Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income level, and season of births.

 $^{25}*$ Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income level, and season of births, and 25

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In the adjusted model, the risk of PDD was found to increase by 112% and 42% with each per-IQR increase in $PM_{2.5}$ (OR: 2.12, 95% CI: 1.45, 3.11) and NO₂ (OR: 1.42, 95% CI: 1.16, 1.75) in the 90 days prior to conception (**Table 4**). There was also a significant association between increased NO₂ exposure and the risk of PDD in T1 (OR: 1.29, 95% CI: 1.05, 1.58), T3 (OR: 1.27, 95% CI: 1.01, 1.60), and the whole pregnancy period (OR: 1.17, 95% CI: 1.02, 1.36). We did not observe any association with MDD in any pregnancy periods.

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Page 19 of 48 1 2 3 74 4	³ Table 4 Associations betw	ween PM _{2.5} and NO ₂ o	exposure in differe	BMJ Open ent pregnancy periods a	/bmjopen-2023-08露75 。 d by copyright, inc强ding and mental	chomotor developme	ental delay
6		Crude	models	Adjusted 1	models* to N	Co-exposure	e models**
7	Dar IOD ingraage in	MDD (95% CI)	PDD (95% CI)	MDD (95% CI)		MDD (95% CI)	PDD (95% CI)
8	Per IQR increase in	(N=946)	(N=946)	(N=945)		(N=945)	(N=945)
1 ^E stimated	90 days prior to conception	1.45 (1.16, 1.83)	1.49 (1.20, 1.83)	0.95 (0.64, 1.42)	2.12 (1.45, a g k)	0.97 (0.63, 1.51)	1.78 (1.17, 2.71)
¹ ¹ exposure	First trimester	1.05 (0.83, 1.33)	1.04 (0.84, 1.28)	1.14 (0.73, 1.79)	1.42 (0.96, 2,3 b	1.35 (0.80, 2.25)	1.16 (0.74, 1.82)
12 13to PM _{2.5}	Second trimester	0.63 (0.49, 0.80)	0.77 (0.63, 0.95)	0.81 (0.54, 1.22)	0.72 (0.51, 2 , 3 , 5 , 5 , 5 , 5 , 5 , 5 , 6 , 7	0.83 (0.52, 1.31)	0.57 (0.38, 0.85)
14	Third trimester	1.23 (0.96, 1.58)	1.19 (0.95, 1.49)	1.25 (0.82, 1.90)	1.17 (0.80, 🗍 🗟 👸	1.39 (0.87, 2.23)	0.98 (0.64, 1.49)
15	Total pregnancy	0.84 (0.69, 1.03)	0.98 (0.82, 1.18)	1.07 (0.82, 1.39)	1.07 (0.84, ā. š	1.17 (0.86, 1.59)	0.90 (0.68, 1.20)
¹ Estimated 17 18exposure	90 days prior to conception	1.20 (0.99, 1.45)	1.41 (1.19, 1.67)	0.97 (0.77, 1.21)	1.42 (1.16, 🖁 着 🗿	0.97 (0.76, 1.25)	1.24 (0.99, 1.56)
	First trimester	0.97 (0.80, 1.17)	1.18 (0.99, 1.40)	0.91 (0.72, 1.13)	1.29 (1.05, <u>a</u> , a	0.84 (0.65, 1.09)	1.24 (0.99, 1.57)
$\frac{19}{10}$ to NO ₂	Second trimester	0.79 (0.66, 0.95)	1.04 (0.88, 1.22)	0.94 (0.76, 1.15)	1.14 (0.95, jj	0.98 (0.77, 1.24)	1.31 (1.06, 1.63)
20 ^{10 NO₂}	Third trimester	1.04 (0.85, 1.28)	1.25 (1.04, 1.50)	0.94 (0.73, 1.21)	1.27 (1.01, 4 .6 6	0.86 (0.65, 1.14)	1.28 (0.99, 1.65)

22 All significant findings in the table are bold.

24 Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly hogsehold income level, and season of births.

1.16 (1.01, 1.33)

25*Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly hause old income level, and season of births, and

0.94 (0.80, 1.11)

1.21 (1.02, 1.43)

0.9 (0.75, 1.08)

1.17 (1.02, 🕽 .3 👸

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 $^{26}_{27}$ djusted for the other air pollutant.

Total pregnancy

²⁸ djusted for the other air pollutant.	•			simi	on	
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0.92 (0.79, 1.07)

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Discussion

We analyzed associations between modelled PM_{2.5} and NO₂ pre- and during pregnancy with birth and neurodevelopment outcomes in singleton children born in a south-western metropolis of China in 2015-16. We found the likelihood of SGA increased by 33% per IQR higher exposure to NO₂ in the whole pregnancy periods after adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11-14 weeks' gestation, primiparity, monthly household income level, and season of births and PM_{2.5}. For childhood cognitive development, increased exposure to PM_{2.5} and NO₂ in the 90 days prior to conception were both associated with lower PDI scores, with the effect size per IQR being higher for PM_{2.5} than for NO₂. Increased NO₂ exposure was associated with an increased risk of PDD during different trimesters of pregnancy.

Many studies from other geographic areas, including Europe (33-35), the United States (22, 26), and Asia (23, 36-38) have found that prenatal air pollution exposure has a negative impact on a variety of neurodevelopmental outcomes. Our finding of a negative association between prenatal NO₂ air pollution exposure and infant neurocognitive development is consistent with these reports. A recent Chinese birth cohort study of 15,778 child-mother pairs in Foshan reported that maternal NO₂ exposure during pregnancy was associated with an increased risk of suspected developmental delay (OR: 1.06, 95% CI: 0.94, 1.19) measured by a five-domain scale and developmental quotient (DQ) (23). A birth cohort study of 520 mother-child pairs in South Korea reported that maternal NO₂ exposure during pregnancy was associated with impairment of psychomotor development ($\beta = -1.30$, p = 0.05) but – as in the present study -not with cognitive function ($\beta = -0.84$, p = 0.20) (36). However, results from previous research varied by air pollutants. For example, a Chinese study of 1193 mother-newborn pairs in Changsha found significant associations between PM_{2.5} exposure in trimester two and lower neurobehavioral developmental scores, while other air pollutants such as PM₁₀, carbon monoxide (CO), and Sulfur dioxide (SO₂) had null or even reverse associations. In this study, we observed that the negative effect of NO₂ exposure during pregnancy on PDI is significant at 5% level; this negative effect of NO2 still remained after adjustment for PM2.5. This heterogeneity may relate to the temporality of exposure assessment, types of outcome assessment instruments or evaluators, and the levels of air pollution. In addition, air pollution mixtures may have differed among the study regions, thus there are several potential explanations for the heterogeneity of the findings. We also observed negative correlations between certain exposures, indicating the need to consider potential collinearity in our two-pollutant models. In Chongqing, a major industrial city in southwest China, air pollution may

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come from industrial and traffic emissions, construction activities, and dust, and negative correlations may occur if different sources contribute disproportionately to each pollutant. Their correlations may also be affected by seasonal changes and variations in weather patterns. Future research should also explore the impact of source-specific air pollution on children's cognitive health.

To date, most studies on prenatal air pollution exposure and child neurodevelopment have been conducted in developed countries with relatively low levels of air pollution. In this study, the level of air pollution was higher (median PM_{2.5}: 57.31 µg/m³, IQR: 5.76; median NO₂: $50.46 \,\mu\text{g/m}^3$, IQR: 5.51) compared to studies in developed countries such as Europe and the United States. In a multi-centre European cohort, the mean PM2.5 and NO2 exposure concentration during pregnancy were 13.4 μ g/m³ and 11.5 μ g/m³ (33). Researchers found that the psychomotor development score significantly decreased by 0.68 points (95% CI: -1.25, -0.11) for every 10 μ g/m³ increase in NO₂, and there was also a non-significant decrease of 1.64 points (95% CI: -3.47, 0.18) for every 5 µg/m³ increase in PM_{2.5} during pregnancy (33). Factors such as the types of pollutants and concentrations may differ between China and other regions with a lower air pollution level, leading to variations in the observed effects.

Contrary to expectations, we found significant positive associations between prenatal exposure to PM_{2.5} air pollution in the second trimester and PDI. However, no association was observed between PM_{2.5} exposures in the second trimester and the risk of PDD. Given the existing literature and the conflicted observation here, we believe that this is likely to be spurious/sample specific. Some plausible explanations include the uneven distribution of PDI scores, the potentially inappropriate selection of the cut-off value of 85 (which may not effectively discriminate between groups), or the possibility that the observed outcome occurred by chance. Several epidemiological studies have reported associations between prenatal exposure to high levels of PM_{2.5} and lower neurodevelopment in children ranging in age from 6 months to 6 years (12, 34, 39-41). In agreement with our findings, a multi-centre cohort study from six European countries investigated the effects of prenatal exposure to multiple air pollutants including PM_{2.5}, PM₁₀, coarse particles, NO₂ and nitrogen oxides (NOx) among 9482 children between 1 and 6 years; the authors found nonsignificant positive associations between prenatal $PM_{2.5}$ exposure and normal neurodevelopment (β : 1.64, 95% CI: –3.47, 0.18; per 5 $\mu g/m^3$ increase in PM_{2.5}) (33). Similarly, another study examining the effects of multiple pollutant exposures on early childhood cognition at 40 days of age in a highly exposed area of Spain also found PM₁₀, PM_{coarse}, PM_{2.5absorbance}, NO₂, NO_x, and Ozone (O₃) were linked to lower

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142 motor function in children, except for $PM_{2.5}$ (42). The inconsistent findings could be because 143 of heterogeneity between studies in terms of exposure (e.g., exposure assessment methods used, 144 $PM_{2.5}$ exposure levels, or composition of $PM_{2.5}$).

Aside from the conflicting findings regarding prenatal $PM_{2.5}$ exposure and neurodevelopmental outcomes, results regarding the most potential sensitive time windows before and during pregnancy are also inconclusive. Some studies suggested that early-to-mid pregnancy might be a potential sensitive period (22, 23), while other studies found stronger associations for middleto- late pregnancy, thus results are equivocal (20, 25, 26).

The potential biological mechanisms by which air pollution could affect neurodevelopment are not yet clearly understood. There is evidence suggesting that exposure to prenatal PM_{2.5} could potentially induce maternal immune activation during pregnancy (43). Higher levels of cytokines or reactive oxygen species may potentially interfere fetal neurodevelopment through three mechanisms: crossing the placental barrier into the fetal body, inducing fetal immune dysregulation, and contributing to inadequate placental perfusion that affects nutritional processes and oxygenation of maternal blood(44). More research is needed to investigate trimester effects of air pollution on neurodevelopment and provide better understanding on the underlying biological mechanisms. Our study is the first to consider an exposure window 90 days prior to conception for NO₂. A novel observation is that effects of NO₂ or PM_{2.5} air pollution on child cognition can be seen at least 90 days prior to conception, representing a potentially vulnerable periods in relation to air pollution on neurodevelopment. Similar results were found in previous study recruited 1329 mother-child pairs in Wuhan, China (12). This study reported a higher level of PM_{2.5} during preconception (Median: 76.1 μ g/m³) and in the first trimester (Median: 82.3 μ g/m³). This study found for each doubling of PM_{2.5} exposure during preconception, children's PDI scores was reduced by 6.15 (95% CI: -8.84, -3.46) points. A potential explanation is that preconception air pollution exposures induce genetic and epigenetic alterations in sperm, that increase the risk of adverse health outcomes in offspring (45, 46). To date, all studies examined the effect of maternal preconception exposure while omitting paternal exposures (17). Future studies should consider the effect of preconception paternal exposure in relation to childhood health outcomes.

This study has several strengths. We developed an LUR model to capture spatial and temporal
 variations of air pollution at individual level to reduce exposure misclassification if using
 monitoring stations. This is an novel study to investigate both pre-conception and prenatal

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PM_{2.5} and NO₂ exposure with neurodevelopment outcomes among young infants, in the context of a relatively high air pollution urban environment. The exposure levels in our study were similar as those in comparable urban areas in Chinese cities. A study in Shanghai, China reported an average NO₂ exposure during pregnancy from 2014 to 2015, predicted by the LUR model, of 48.23 μ g/m³ (Mean PM_{2.5} in our study: 50.52 μ g/m³) (47). Similarly, a study in Tianjin found the annual average $PM_{2.5}$ exposure to be 62 µg/m³ in 2017 (Mean NO₂ in our study: 57.48 μ g/m³) (48). Wu et al. developed a LUR model for PM_{2.5} in the main urban area of Chongqing (49). This model predicted an annual average PM_{2.5} concentration of 40.6 µg/m³ (49), whereas our prediction is higher at 55.9 μ g/m³ (19). This difference can be attributed to the temporal variations. Wu et al. used monitoring data from 2013, while we utilized data from 2015. It could be considered that our GAM model, with its temporal component, could explain temporal variations and is more suitable for pregnancy-specific exposure estimates.

A major limitation of this study was that our sample size was relatively small, limiting the statistical power to assess several outcomes, although the higher exposures in Chongqing than in some other studies may increase probability of detecting effects. In terms of limitations, due to a lack of information on participant time-activity patterns, exposure estimates in this study refer only to ambient concentrations at home addresses, and no other activity spaces (e.g., indoor, workplace, commuting) were considered. We may have thus underestimated total air pollution exposure. Second, we defined exposure windows for clinically-defined trimesters; sensitive periods may be shorter or longer than 3 months, or they may exist in the overlap of multiple trimesters. However, we were unable to investigate the sensitive time windows using established methods such as distributed lag non-linear models due to the lack of highly time-resolved air pollution estimates. Third, the performance of the NO₂ spatiotemporal model was moderate (COR-R²: 0.39), which may introduce exposure misclassification and therefore bias in the coefficients. Finally, we were unable to include some other air pollutants such as polycyclic aromatic hydrocarbons (PAH), black carbon (BC) and Ozone, which have bene found particular harmful to neurodevelopment in children (50). Although we have accounted for most of the important confounders in this study, unfortunately, we did not collect information on the feeding patterns of infants. This may undermine the validity and reliability of our findings.

Conclusion

This study provides evidence for an association between NO_2 exposure prior to- and during pregnancy with birth and neurodevelopmental outcomes in a birth cohort in Chongqing, China. Exposure to NO_2 and $PM_{2.5}$ exposure before pregnancy was associated with a lower psychomotor development score. Increased NO_2 exposure was linked to a risk of psychomotor development delay during various pregnancy trimesters.

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212 List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
BMI	Body mass index
BSID	Bayley Scales of Infant Development
CBSID	Chinese version of Bayley Scales of Infant Development
CI	Confidence interval
CLIMB	Complex Lipids in Mothers and Babies
СО	Carbon monoxide
COR	Correlation
DOHaD	Developmental origins of health and disease
DQ	Developmental quotient
GIS	Geographic information systems
IQR	Interquartile range
LBW	Low birth weight
LGA	Large for gestational age
LUR	Land-use Regression
MDD	Mental Developmental Delay
MDI	Mental Development Index
NO _x	Nitrogen oxides
NO ₂	Nitrogen dioxide
OR	Odd ratio
O ₃	Ozone

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PDD	Psychomotor Developmental Delay
PDI	Psychomotor Development Index
PM	Particulate matter
PM _{2.5}	Particulate matter with diameter ≤2.5µm
РТВ	Preterm birth
SGA	Small for gestational age
SO ₂	Sulfur dioxide
TLBW	Term low birth weight
T1	First trimester
T2	Second trimester
T3	Third trimester
WP	Whole pregnancy period
90D	90 days prior to pregnancy

Declarations

4 5 6 7	215	Ethics approval and consent to participate
8	216	Ethical approval for this study was granted by the Ethics Committee of Chongqing Medical
9 10	217	University (#2014034). The participants provided their written informed consent to
11 12	218	participate in this study. Written informed consent was obtained from the individual(s) for the
13 14	219	publication of any potentially identifiable images or data included in this article.
15 16 17	220	Data availability statement
18	221	The data that support the findings of this study are available from Chongqing Medical
19 20	222	University but restrictions apply to the availability of these data, which were used under
21 22	223	license for the current study, and so are not publicly available. Data are however available
23 24	224	from the authors upon reasonable request and with permission of Chongqing Medical
25	225	University.
26 27 28	226	Competing interests
29 30	227	The authors declare that they have no conflicts of interests.
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48 49	237	and the University of Leicester and by the NIHR Leicester Biomedical Research Centre (BRC).
50	238	The views expressed are those of the author(s) and not necessarily those of the NIHR, the
51 52	239	Department of Health and Social Care or UK Health Security Agency.
53 54 55	240	Contributors
56 57	241	Y. X., T.L.H., H.Z. and P.B. conceived and designed research; T.Z., Y.X. and H.Z. recruited
58 59	242	the patients and collected the samples; T.K., A.H., and J.G. constructed the air pollution
60	243	model; Y.C. analyzed, interpreted the data and prepared the figures; Y.C and T.K were major

contributors in writing the manuscript text; YSC, JC, TLH, YX, ALH, and PNB substantively
revised the manuscript; All authors read and approved the final manuscript.

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1 2		
3 4	251	Reference
5 6	252	1. Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iniguez C. Preterm birth
7 8	253	and exposure to air pollutants during pregnancy. Environmental Research. 2010;110(8):778-
9	254	85.
10 11	255	2. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). The
12 13	256	Lancet Respiratory Medicine. 2013;1(9):695-704.
14 15	257	3. Stieb DM, Chen L, Hystad P, Beckerman BS, Jerrett M, Tjepkema M, et al. A
16	258	national study of the association between traffic-related air pollution and adverse pregnancy
17 18	259	outcomes in Canada, 1999–2008. Environmental Research. 2016.
19 20	260	4. Barker DJ. The origins of the developmental origins theory. Journal of internal
21 22	261	medicine. 2007;261(5):412-7.
23	262	5. Volk HE, Perera F, Braun JM, Kingsley SL, Gray K, Buckley J, et al. Prenatal air
24 25	263	pollution exposure and neurodevelopment: A review and blueprint for a harmonized
26 27	264	approach within ECHO. Environmental research. 2021;196:110320.
28 29	265	6. Feng S, Dan G, Liao F, Zhou F, Wang X. The health effects of ambient PM2.5 and
30	266	potential mechanisms. Ecotoxicology and Environmental Safety. 2016;128:67-74.
31 32	267	7. Massa NR, Guangyun M, Xingyou Z, Xiumei H, Zhu C, Sampankanpanich SC, et al.
33 34	268	Intrauterine Inflammation and Maternal Exposure to Ambient PM2.5 during Preconception
35 36	269	and Specific Periods of Pregnancy: The Boston Birth Cohort. Environ Health Perspect.
37	270	2016;124(10):1608-15.
38 39	271	8. Vecoli C, Montano L, Andreassi MG. Environmental pollutants: genetic damage and
40 41	272	epigenetic changes in male germ cells. Environmental Science and Pollution Research.
42	273	2016;23:23339-48.
43 44	274	9. Marcho C, Oluwayiose OA, Pilsner JR. The preconception environment and sperm
45 46	275	epigenetics. Andrology. 2020;8(4):924-42.
47 48	276	10. Udagawa O, Furuyama A, Imai K, Fujitani Y, Hirano S. Effects of diesel exhaust-
49	277	derived secondary organic aerosol (SOA) on oocytes: Potential risks to meiotic maturation.
50 51	278	Reproductive Toxicology. 2018;75:56-64.
52 53	279	11. Zhang J-Y, Wu Q-J, Huang Y-H, Li J, Liu S, Chen Y-L, et al. Association between
54 55	280	maternal exposure to ambient PM10 and neural tube defects: a case-control study in Liaoning
56	281	Province, China. International Journal of Hygiene and Environmental Health.
57 58	282	2020;225:113453.
59 60		

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

1 2		
- 3 4	283	12. Li J, Liao J, Hu C, Bao S, Mahai G, Cao Z, et al. Preconceptional and the first
5	284	trimester exposure to PM2. 5 and offspring neurodevelopment at 24 months of age:
6 7 8 9	285	Examining mediation by maternal thyroid hormones in a birth cohort study. Environmental
	286	Pollution. 2021;284:117133.
10 11	287	13. Jo H, Eckel SP, Chen J-C, Cockburn M, Martinez MP, Chow T, et al. Gestational
11 12 13 14 15 16 17 18 19	288	diabetes mellitus, prenatal air pollution exposure, and autism spectrum disorder. Environment
	289	international. 2019;133:105110.
	290	14. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism spectrum
	291	disorder and particulate matter air pollution before, during, and after pregnancy: a nested
	292	case-control analysis within the Nurses' Health Study II cohort. Environmental health
20 21	293	perspectives. 2015;123(3):264-70.
22 23	294	15. Grineski S, Alexander C, Renteria R, Collins TW, Bilder D, VanDerslice J, et al.
24	295	Trimester-specific ambient PM2.5 exposures and risk of intellectual disability in Utah.
25 26	296	Environmental Research. 2023;218:115009.
27 28 29 30 31	297	16. Shang L, Yang L, Yang W, Huang L, Qi C, Yang Z, et al. Effects of prenatal
	298	exposure to NO(2) on children's neurodevelopment: a systematic review and meta-analysis.
	299	Environ Sci Pollut Res Int. 2020;27(20):24786-98.
32 33	300	17. Blanc N, Liao J, Gilliland F, Zhang JJ, Berhane K, Huang G, et al. A systematic
34 35	301	review of evidence for maternal preconception exposure to outdoor air pollution on
36	302	Children's health. Environmental Pollution. 2022:120850.
37 38	303	18. Huang S, Mo T-T, Norris T, Sun S, Zhang T, Han T-L, et al. The CLIMB (Complex
39 40	304	Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel
41 42	305	randomised controlled trial to investigate the effect of supplementation of complex lipids in
43	306	pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the
44 45	307	offspring. BMJ open. 2017;7(10):e016637.
46 47	308	19. Harper A, Baker PN, Xia Y, Kuang T, Zhang H, Chen Y, et al. Development of
48	309	spatiotemporal land use regression models for PM2. 5 and NO2 in Chongqing, China, and
49 50	310	exposure assessment for the CLIMB study. Atmospheric Pollution Research.
51 52	311	2021;12(7):101096.
53 54	312	20. Chen B, Huang S, He J, He Q, Chen S, Liu X, et al. Sex-specific influence of prenatal
55	313	air pollutant exposure on neonatal neurobehavioral development and the sensitive window.
56 57	314	Chemosphere. 2020;254:126824.
58 59		
60		

Page 31 of 48

BMJ Open

1 2		
3 4	315	21. Volk HE, Perera F, Braun JM, Kingsley SL, Gray K, Buckley J, et al. Prenatal air
5	316	pollution exposure and neurodevelopment: A review and blueprint for a harmonized
6 7	317	approach within ECHO. Environ Res. 2021;196:110320.
8 9	318	22. Ha S, Yeung E, Bell E, Insaf T, Ghassabian A, Bell G, et al. Prenatal and early life
10 11	319	exposures to ambient air pollution and development. Environmental research. 2019;174:170-
12	320	5.
13 14	321	23. Su X, Zhang S, Lin Q, Wu Y, Yang Y, Yu H, et al. Prenatal exposure to air pollution
15 16	322	and neurodevelopmental delay in children: A birth cohort study in Foshan, China. Science of
17	323	The Total Environment. 2022;816:151658.
18 19	324	24. Bennet L, Walker DW, Horne RS. Waking up too early-the consequences of preterm
20 21	325	birth on sleep development. The Journal of physiology. 2018;596(23):5687-708.
22 23	326	25. Wang P, Zhao Y, Li J, Zhou Y, Luo R, Meng X, et al. Prenatal exposure to ambient
24	327	fine particulate matter and early childhood neurodevelopment: A population-based birth
25 26	328	cohort study. Science of The Total Environment. 2021;785:147334.
27 28	329	26. Chiu Y-HM, Hsu H-HL, Coull BA, Bellinger DC, Kloog I, Schwartz J, et al. Prenatal
29	330	particulate air pollution and neurodevelopment in urban children: examining sensitive
30 31	331	windows and sex-specific associations. Environment international. 2016;87:56-65.
32 33	332	27. Huang S, Mo T-T, Norris T, Sun S, Zhang T, Han T-L, et al. The CLIMB (Complex
34 35	333	Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel
36	334	randomised controlled trial to investigate the effect of supplementation of complex lipids in
37 38	335	pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the
39 40	336	offspring. BMJ Open. 2017;7(10):e016637.
41 42	337	28. Albert BB, Derraik JG, Xia Y-Y, Norris T, Zhang T, Han T-L, et al. Supplementation
43	338	with milk enriched with complex lipids during pregnancy: a double-blind randomized
44 45	339	controlled trial. Plos one. 2021;16(2):e0244916.
46 47	340	29. Zhao X, Xia Y, Zhang H, Baker PN, Norris T. Birth weight charts for a Chinese
48	341	population: an observational study of routine newborn weight data from Chongqing. BMC
49 50	342	Pediatr. 2019;19(1):426.
51 52	343	30. Shourong Y, Xuerong L, Zhiwei Y. The revising of the bayley scales of infant
53 54	344	development (BSID) in China. Chin J Clin Psychol. 1993;2:71-5.
55	345	31. Chen Y-T, Zhang T, Chen C, Xia Y-Y, Han T-L, Chen X-Y, et al. Associations of
56 57	346	early pregnancy BMI with adverse pregnancy outcomes and infant neurocognitive
58 59 60	347	development. Scientific Reports. 2021;11(1):1-8.

BMJ Open

2		
3 4	348	32. Çelik P, Sucakli IA, Yakut HI. Which Bayley-III cut-off values should be used in
5 6	349	different developmental levels? Turkish journal of medical sciences. 2020;50(4):764-70.
7	350	33. Guxens M, Garcia-Esteban R, Giorgis-Allemand L, Forns J, Badaloni C, Ballester F,
8 9	351	et al. Air pollution during pregnancy and childhood cognitive and psychomotor development:
10 11	352	six European birth cohorts. Epidemiology. 2014:636-47.
12	353	34. Lertxundi A, Baccini M, Lertxundi N, Fano E, Aranbarri A, Martínez MD, et al.
13 14	354	Exposure to fine particle matter, nitrogen dioxide and benzene during pregnancy and
15 16	355	cognitive and psychomotor developments in children at 15 months of age. Environment
17	356	international. 2015;80:33-40.
18 19	357	35. Porta D, Narduzzi S, Badaloni C, Bucci S, Cesaroni G, Colelli V, et al. Air pollution
20 21	358	and cognitive development at age 7 in a prospective Italian birth cohort. Epidemiology.
22 23	359	2016;27(2):228-36.
24	360	36. Kim E, Park H, Hong Y-C, Ha M, Kim Y, Kim B-N, et al. Prenatal exposure to PM10
25 26	361	and NO2 and children's neurodevelopment from birth to 24 months of age: Mothers and
27 28	362	Children's Environmental Health (MOCEH) study. Science of the Total Environment.
29 30	363	2014;481:439-45.
31	364	37. Lin C-C, Yang S-K, Lin K-C, Ho W-C, Hsieh W-S, Shu B-C, et al. Multilevel
32 33	365	analysis of air pollution and early childhood neurobehavioral development. International
34 35	366	journal of environmental research and public health. 2014;11(7):6827-41.
36	367	38. Yorifuji T, Kashima S, Diez MH, Kado Y, Sanada S, Doi H. Prenatal exposure to
37 38	368	traffic-related air pollution and child behavioral development milestone delays in Japan.
39 40	369	Epidemiology. 2016;27(1):57-65.
41 42	370	39. Tozzi V, Lertxundi A, Ibarluzea JM, Baccini M. Causal effects of prenatal exposure
43	371	to PM2. 5 on child development and the role of unobserved confounding. International
44 45	372	Journal of Environmental Research and Public Health. 2019;16(22):4381.
46 47	373	40. Hurtado-Díaz M, Riojas-Rodríguez H, Rothenberg SJ, Schnaas-Arrieta L, Kloog I,
48	374	Just A, et al. Prenatal PM2. 5 exposure and neurodevelopment at 2 years of age in a birth
49 50	375	cohort from Mexico city. International journal of hygiene and environmental health.
51 52	376	2021;233:113695.
53	377	41. Lertxundi A, Andiarena A, Martínez MD, Ayerdi M, Murcia M, Estarlich M, et al.
54 55	378	Prenatal exposure to PM2.5 and NO2 and sex-dependent infant cognitive and motor
56 57	379	development. Environmental Research. 2019;174:114-21.
58 59 60		

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2 3	200		
4	380	42. Iglesias-Vázquez L, Binter A-C, Canals J, Hernández-Martínez C, Voltas N, Ambros	
5 6	381	A, et al. Maternal exposure to air pollution during pregnancy and child's cognitive, language,	
7 8	382	and motor function: ECLIPSES study. Environmental Research. 2022;212:113501.	
9	383	43. Umezawa M, Onoda A, Korshunova I, Jensen AC, Koponen IK, Jensen KA, et al.	
10 11	384	Maternal inhalation of carbon black nanoparticles induces neurodevelopmental changes in	
12 13	385	mouse offspring. Particle and Fibre Toxicology. 2018;15:1-18.	
14	386	44. Monk C, Lugo-Candelas C, Trumpff C. Prenatal developmental origins of future	
15 16	387	psychopathology: mechanisms and pathways. Annual review of clinical psychology.	
17 18	388	2019;15:317-44.	
19	389	45. Xu R, Zhong Y, Li R, Li Y, Zhong Z, Liu T, et al. Association between exposure to	
20 21	390	ambient air pollution and semen quality: A systematic review and meta-analysis. Science of	
22 23	391	The Total Environment. 2023;870:161892.	
24	392	46. Braun JM, Messerlian C, Hauser R. Fathers matter: why it's time to consider the	
25 26	393	impact of paternal environmental exposures on children's health. Current epidemiology	
27 28	394	reports. 2017;4:46-55.	
29	395	47. Ji X, Meng X, Liu C, Chen R, Ge Y, Kan L, et al. Nitrogen dioxide air pollution and	
30 31	396	preterm birth in Shanghai, China. Environmental research. 2019;169:79-85.	
32 33	397	48. Zhang Y, Wang J, Chen L, Yang H, Zhang B, Wang Q, et al. Ambient PM2. 5 and	
34 35	398	clinically recognized early pregnancy loss: A case-control study with spatiotemporal	
36	399	exposure predictions. Environment International. 2019;126:422-9.	
37 38	400	49. Wu J-S, Liao X, Peng J, Huang X-L. Simulation and influencing factors of spatial	
39 40	401	distribution of PM2. 5 concentrations in Chongqing. Huan Jing ke Xue= Huanjing Kexue.	
41	402	2015;36(3):759-67.	
42 43	403	50. Lopuszanska U, Samardakiewicz M. The relationship between air pollution and	
44 45	404	cognitive functions in children and adolescents: a systematic review. Cognitive and	
46 47	405	Behavioral Neurology. 2020;33(3):157-78.	
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7 8	410	Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors,
9 10	411	2015; https://data.nextgis.com/en/region/CN-50/).
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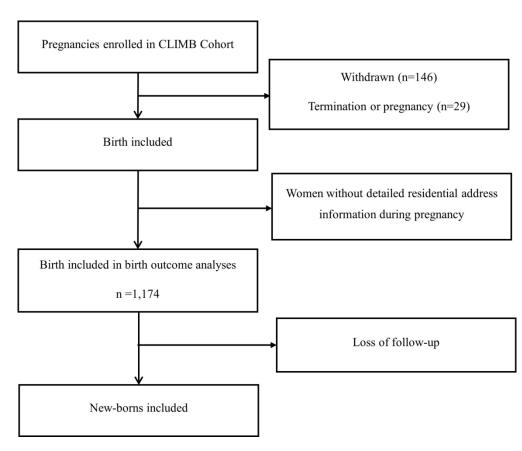
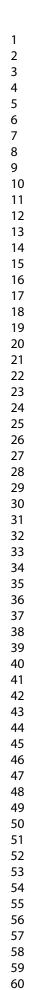


Figure 1 Flow chart of the study population in CLIMB

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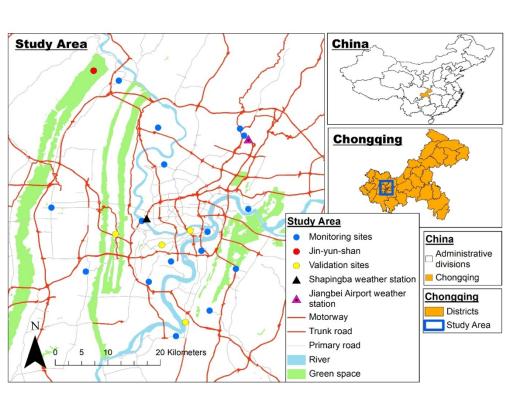


Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors, 2015; https://data.nextgis.com/en/region/CN-50/).

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Associations of air pollution exposures in preconception and pregnancy with birth outcomes and infant neurocognitive development: analysis of the Complex Lipids in Mothers and Babies (CLIMB) prospective cohort in Chongqing, China

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Supplement

eTable 1 Mental Development Index (Chinese version)

智力量表

(*可偶尔观察到)

序号	月龄	条目	计分
1	0.1	对铃声反应	
2	0.1	抱起时安静	
3	0.1	对摇鼓声反应	
4	0.1	对尖声反应: (电灯开关)	
5	0.1	短暂地注视红环	
6	0.2	短暂地注视人	
7	0.4	稍长时间地注视红环	
8	0.5	眼的水平协调活动(红环)	
9	0.7	眼的水平向天活动 (光)	
10	0.7	眼睛追随移动的人	
11	0.7	对说话声反应	
12	0.8	眼的垂直协调活动(光)	
13	0.9	发声一至两次	
14	1	眼的垂直协调活动(红环)	
15	1.2	眼的旋转协调活动(光)	
16	1.2	眼的旋转细条活动(光环)	
17	1.3	*自由环视周围	
18	1.5	社交笑:测试者谈话与微笑时	
19	1.6	眼转向红环	
20	1.6	眼转向光	
21	1.6	*发声至少四次	
22	1.7	期待性兴奋	
23	1.7	对面部的纸有反应	
24	1.9	能用视觉辨认母亲	
25	1.9	社交笑:测试者微笑与安静时	
26	2	*对测试者的微笑和说话有发声反应	
27	2.1	*用眼睛寻找声源(详细说明)	
28	2.2	*发出两种不同的声音	
29	2.2	对手的遮蔽眨眼	
30	2.2	对面孔的消失有反应	
31	2.4	注视方木	
32	2.6	从一物转看另一物	
33	2.6	眼睛追随铅笔	
34	2.7	对抱起有预感性的调节反应	
35	2.9	目光追随横过桌面的球	
36	2.9	头追随悬摆的环	

37	3.1	头追随逐渐消失的勺子	
38	3.2	操作红环	
39	3.3	简单地玩摇鼓	
40	3.4	*轻轻地抚摸桌沿	
41	3.4	*意识到陌生环境	
42	3.5	头转向铃声	
43	3.6	头转向摇鼓声	
44	3.6	*手碰手的玩耍	
45	3.6	将红环送入口中	
46	3.7	伸手够悬环	
47	3.8	看自己的手	
48	4.2	接近悬环 (优势手)	
49	4.4	*发声时的姿态(描述)	
50	4.4	*主动抚摸桌沿	
51	4.4	接近镜像	
52	4.4	注意小糖丸	
53	4.6	伸手取方木	
54	4.7	喜欢嬉戏 🔍	
55	4.9	伸手时眼手协调	
56	4.9	拾起方木 (优势手)	
57	5	保持两块方木	
58	5	持久地看红环	
59	5	头部跟着掉下的勺转动	
60	5	探索性地玩纸	
61	5	对镜像微笑	
62	5	坚持够东西	
63	5.1	在小床内重新找到摇鼓	
64	5.1	*辨别生人	
65	5.4	举起倒扣的茶杯	
66	5.5	*敲打玩耍	
67	5.5	探索性地玩细绳	
68	5.5	伸手取第二块方木	
69	5.6	*由一手向另一手传递物体	
70	5.8	*对产生响声感兴趣	
71	5.9	灵巧而直接地拾起方木	
72	6	*对镜像开玩笑	
73	6	用把柄举起茶杯	
74	6	寻找掉落的勺子	
75	6.1	牵拉细绳获取红环	
76	6.1	保留三块方木中的两块	
77	6.6	*发出四个不同的音节	
78	6.8	能配合玩游戏	
79	7	恰当地牵拉细绳获取红环	
80	7.1	玩摇铃,对细节感兴趣	
81	7.4	企图获得三块方木	

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82	7.4	有目的地摇铃
83	7.5	*选择性地倾听熟悉的词语
84	8	*对 da-da 或类同词
85	8.1	暴露玩具
86	8.2	注意测试者的乱写
87	8.3	将手指插入桩板洞中
88	8.6	观看书中图画
89	8.9	对他人的言语要求有反应
90	9.1	拿起茶杯获得方木
91	9.8	寻找盒子里面的东西
92	10.3	遵照命令将方木放入茶杯(放入数)
93	10.7	企图模仿乱写
94	10.8	模仿用勺子搅拌
95	10.9	遵照命令停止
96	10.9	推动小汽车
97	11	模仿地拍打哨娃
98	11.1	*重复引入发笑的把戏
99	11.2	解开裹着的方木
100	11.2	将三块方木放入杯中
101	11.4	*快速而不清的表达
102	11.4	揭开兰盒子的盖
103	11.5	翻开书页
104	11.5	摇晃悬环的
105	11.8	将骰子放入盒中(6个)
106	12	恰当地握持画笔
107	12.2	模仿说单词(记录用过的词)
108	12.4	重复地插一根桩钉
109	12.5	用手势表达想要的东西
110	12.9	自动乱写
111	12.9	能说两个词
112	13	搭两层塔
113	13.1	出示鞋子或其他衣服或自己的玩具
114	13.2	从瓶中移出小糖丸
115	13.3	掺九块方木放入杯中
116	14.3	*盖上圆盒
117	14.4	兰曲工商曲 兰色模板: 放置一个圆形模块
118	14.8	用棍子够取玩具
119	15.4	搭三层塔
120	15.7	在 70 秒钟内插完桩钉
120	16.1	指出娃娃身体的各部分:三个部位以上
121	16.3	粉红模板:放置圆形模块
122	16.6	兰色模板:放置两个圆形模块
123	17.2	用笔模仿画一划
124	17.2	在 42 秒钟内插完桩钉
125	17.5	<u> </u>

127	17.7	对娃娃执行指令(在通过部位打钩:椅、杯、鼻)
128	18.1	用语言表达要求
129	18.6	不用于一划的乱写?
130	18.8	兰色模板: 放置两个圆快和方块
131	18.8	指出三幅画
132	19.1	能说两个单词的句子
133	19.2	说出一副画名
134	19.2	说出两幅画名
135	19.3	找出两物
136	19.8	在 30 秒钟内插完桩钉
137	20.4	粉红模板:完成
138	20.4	搭六层塔
139	20.5	兰色模板,放置六个模块
140	21	指出五副画
141	21.1	说出三物名
142	21.2	勉强合格地安装破娃娃
143	21.2	区别两物:杯、盘、盒
144	22.8	辨认钟表: 第四张图 1, 2, 3, 4, 5
145	22.9	说出三幅画名 🔨
146	23.8	粉红模板(反转)
147	24.3	近似地安装破娃娃
148	24.6	区别三物:杯、盘、盒
149	24.7	兰色模板,在150秒钟内完成
150	25	搭八层塔
151	25.1	指出七副画
152	25.1	用方木搭火车
153	25.7	说出五副画名
154	26.3	模仿笔划:垂直线和水平线
155	27.1	辨认钟表:第2张图
156	27.6	理解两个方位词
157	28	在 22 秒钟内插完桩钉
158	28.5	兰色模板: 90 秒钟内完成
159	29.5	折纸
160	29.6	兰色模板: 60秒钟内完成
161	30+	正确安装破娃娃
162	30+	"—"的概念
163	30+	理解三个方位词

eTable 2 Psychomotor Development Index (Chinese version)

运动量表

(*可偶尔观察到, △可在施测智力量表时观察到)

序号	月龄	条目	计分
1	0.1	抱起靠肩时抬头	
2	0.1	抱起靠肩时调整姿势	
3	0.1	侧头	
4	0.1	爬起	
5	0.8	△保留红环	
6	0.8	*伸臂玩耍	
7	0.8	*踢腿玩耍	
8	0.8	头起竖起:垂直位	
9	1.6	头部稳定地竖起	
10	1.7	抬头 (背悬位)	
11	1.8	由侧卧转向仰卧	
12	2.2	在俯卧位时用双臂撑起自己	
13	2.2	支撑下坐起 🔨	
14	2.5	保持头部稳定	
15	2.6	*双手张开占优势	
16	3.3	头平衡	
17	3.4	*尺侧一手掌抓握方木	
18	3.5	轻度支撑坐位	
19	4.3	*由仰卧转向侧卧	
20	4.7	努力想坐起	
21	5.0	部分的拇指相对(桡侧一手掌)拾起方木	
22	5.1	独坐片刻	
23	5.1	*单手抽取	
24	5.2	*转腕	
25	5.2	牵拉坐起	
26	5.6	△试图获取小糖丸	
27	5.7	独立 30 秒钟或以上	
28	5.8	由仰卧转向俯卧	
29	6.2	稳定地独坐	
30	6.5	独坐时协调好	
31	6.6	*舀起小糖丸	
32	6.6	△完全的拇指相对拾起方木	
33	7	早期跨步运动	
34	7.5	牵拉站起	
35	7.6	*不完全的拇指相对抓糖丸	
36	7.6	走路之前的行进方式(俯卧、手膝、手足、其他)	
37	8.3	使两个勺子或方木在中线相碰	
38	8.5	跨步运动	

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39	8.6	自己坐起
40	8.6	借助家具站起
41	8.9	精细地抓糖丸(灵巧地钳夹)
42	9.6	拍手(中线技巧)
43	9.8	坐下
44	10	扶助下行走
45	11.1	独站
46	12	投球
47	12.1	独走
48	12.4	起立丨
49	13.2	扶助下右足独站
50	13.7	扶助下左足独站
51	14.1	侧身走
52	14.5	扶助上楼梯
53	14.7	倒退走
54	15.1	扶助下楼梯
55	17.6	试图站在行木上
56	18.7	左足独站 💦
57	19.3	单足踏在行木上走
58	19.9	起立Ⅱ
59	20.1	右足独站
60	21.1	走直线:大致方向
61	23.1	行木:双足站立
62	24	踮脚走几步
63	24.3	独自上楼梯:双足
64	24.4	双足跳离地面
65	25.3	独自下楼梯
66	25.6	行木:企图跨步
67	25.6	倒行两米半
68	25.7	自第一级台阶下跳下
69	29.2	自第二级台阶下跳下
70	29.8	踮脚走两米半
71	29.9	跳远: 10 至 35cm (记录距离)
72	30+	起立:
73	30+	上楼梯:双足交替向前
74	30+	行木: 交替步伐走部分路程
75	30+	保持双足走在直线上(两米半)
76	30+	跳远: 35cm 至 60cm
77	30+	跳过: 5cm 高的绳子
78	30+	跳远: 60cm 至 85cm
79	30+	独脚跳两次以上
80	30+	下楼梯:双足交替向前
81	30+	跳过 20cm 高的绳子

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Estimated exposure to PM _{2.5}					ownloa lent Su I to text		
90 days prior to conception	1,174	38.17	44.00	52.91 ± 10.99	48.4 3 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	62.06	80.53
First trimester	1,174	37.26	43.77	52.07 ± 10.98	47.2 🙀 🛱 .31	61.08	82.41
Second trimester	1,174	38.46	47.57	58.64 ± 12.21	\$\$ 62 57.9 2 57.9 2	67.19	90.02
Third trimester	1,174	37.03	47.25	61.83 ± 16.04	58.82 ± 28.7	75.95	96.48
Total pregnancy	1,174	46.69	54.85	57.48 ± 3.97	57.3 ± ± = 57.3	60.61	66.98
Estimated exposure to NO ₂				Via	ainin bn		
90 days prior to conception	1,174	25.86	45.49	49.59 ± 6.34	49.9 4 ± 8.27	53.76	70.48
First trimester	1,174	20.81	44.60	48.8 ± 6.43	48.9% ± 8.51	53.10	69.31
Second trimester	1,174	28.93	47.18	50.98 ± 6.23	51 2 9 + € 72	54.90	70.42
Third trimester	1,174	20.57	47.20	51.79 ± 6.78	52.45 ± \$47	56.67	75.12
Total pregnancy	1,174	27.50	47.89	50.52 ± 5.08	50.48 ± \$51	53.40	67.53
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	BMJ Open eTable 4 Pearson's correlations of PM _{2.5} and NO ₂ between each of the five different pregnancy time periods (N = 1,174)									Page 46 of 48		
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eTable 4 Pearson's correlations of PM _{2.5} and NO ₂ between each of the five different pregnancy time between each of the five different pregnancy time between the second seco												
Estimated exposure to		PM _{2.5}					ng for					
		90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy	90 days provident	First trimester	Second trimester	Third trimester	Total pregnancy	
PM _{2.5}	90 days prior to conception	1					<u> </u>					
	First trimester	-0.065	1				Downloaded from ment Superieur (A ed to text and data					
	Second trimester	-0.779	-0.2012	1			aded uperior t and					
	Third trimester	0.288	-0.7613	-0.1688	1		∣ from d data					
	Total pregnancy	-0.534	-0.2709	0.6838	0.3858	1	a min					
NO ₂	90 days prior to conception	0.6383	0.0684	-0.4588	0.3714	0.0376	1 g,					
	First trimester	0.1537	0.6352	-0.0159	-0.4927	-0.0633	0.55454rai	1				
	Second trimester	-0.431	0.0714	0.6269	-0.0133	0.7251	1 0.554 Straining, Alstraining, O.554 Straining, O.334 March 10, 2000 March 20000 March 20000 March 20000 Marc	0.5399	1			
	Third trimester	0.3027	-0.5213	0.0528	0.6817	0.4432	0.714920 O	0.2159	0.5145	1		
	Total pregnancy	0.0057	0.0781	0.2862	0.0737	0.4779	0.678 Si on	0.7435	0.8755	0.7331	1	
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Page 47 of 48	3		BMJ Open	1	/bmjopen-2023 d by copyright,		
1 2 3 4 5	eTable 5 Associations be	etween PM2.5 and NO2 expo	sure in different preg	nancy periods and ac	-2023-0; right, in	mes (unadjusted m	nodels)
6 7		Mean di	fference		for (Odd ratios	
7 8 F 9 10	Per IQR increase in	Birth weight, grams (95% CI) (N=941)	Birth length, cm (95% CI) (N=927)	PTB (case: 33) (95% CI) (N=945)	LB \$ 555 (2010) (1979) (2010) (1970) (2010) (2010) (1970) (2010) (2010) (1970) (2010)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
Estimated	90 days prior to conception	9.28 (-31.26, 49.83)	-0.09 (-0.27, 0.09)	0.98 (0.56, 1.74)	1.35	1.2 (0.87, 1.64)	0.98 (0.68, 1.41)
12 13exposure	First trimester	21.95 (-16.90, 60.80)	0.14 (-0.03, 0.31)	0.98 (0.57, 1.70)	1 (6 . 5 . 5 . 1.77)	0.97 (0.71, 1.33)	0.78 (0.54, 1.13)
14 15 ^{to} PM _{2.5}	Second trimester	-18.21 (-57.78, 21.37)	0.04 (-0.13, 0.21)	0.85 (0.48, 1.50)	0.61 g (kg 2, 1.15)	0.92 (0.67, 1.27)	1.33 (0.94, 1.89)
15 ^{60 1} 1912.5 16	Third trimester	-37.38 (-81.43, 6.68)	-0.32 (-0.51, -0.13)	1.35 (0.74, 2.47)	1.51 2 (2.85)	1.08 (0.76, 1.54)	1.12 (0.76, 1.66)
16 <u>17</u>	Total pregnancy	-20.02 (-55.69, 15.65)	-0.1 (-0.26, 0.05)	0.81 (0.49, 1.33)	0.69 a (54 , 1.16)	1 (0.75, 1.34)	1.2 (0.87, 1.66)
1 Estimated	90 days prior to conception	-13.23 (-45.50, 19.03)	-0.12 (-0.26, 0.02)	1.2 (0.76, 1.89)	1.62 3 (758) , 2.65)	1.21 (0.93, 1.57)	1.24 (0.92, 1.66)
19 20 exposure	First trimester	0.3 (-32.36, 32.96)	0.08 (-0.06, 0.22)	1.01 (0.64, 1.60)	1.15 3 0.73, 1.86)	1.17 (0.90, 1.52)	1.27 (0.94, 1.71)
20^{-1} 21 to NO ₂	Second trimester	-22.85 (-53.39, 7.70)	-0.04 (-0.17, 0.09)	1.11 (0.72, 1.70)	1.08 2 0.67, 1.69)	1.06 (0.83, 1.36)	1.46 (1.10, 1.93)
22	Third trimester	-32.72 (-67.16, 1.72)	-0.16 (-0.32, -0.01)	1.13 (0.69, 1.85)	1.35 4.0.8, 2.28)	1.24 (0.94, 1.65)	1.58 (1.14, 2.18)
23	Total pregnancy	-16.58 (-43.35, 10.20)	-0.03 (-0.15, 0.09)	1.03 (0.71, 1.50)	1.13 (0. 3), 1.69)	1.16 (0.93, 1.44)	1.44 (1.13, 1.85)
²⁴ All signific	cant findings in the table are be	old.			, an		
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1 2 3 4 5	eTable 6 Associations be	etween PM2.5 and NO2 exp	osure in different preg	gnancy periods and a	adverseebingh outc	omes (co-exposure	models)
6		Mean d	ifference		fon 2 Odd	l ratios	
7 8 I 9 10	Per IQR increase in	Birth weight, grams (95% CI) (N=941)	Birth length, cm (95% CI) (N=927)	PTB (case: 33) (95% CI) (N=945)	LBW派(音歌: 30) (995号)[[20] (哈雪雪拉)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
1Estimated	90 days prior to conception	75.00 (-9.86, 159.86)	0.23 (-0.14, 0.60)	0.98 (0.56, 1.89)	0.41 (8.3471.22)	1.14 (0.55, 2.40)	1.18 (0.48, 2.92)
12 exposure	First trimester	19.59 (-71.23, 110.41)	0.00 (-0.40, 0.39)	0.97 (0.26, 3.65)	0.66 (0.745 3.05)	0.67 (0.32, 1.42)	0.73 (0.28, 1.93)
13 ¹¹ 14to PM _{2.5}	Second trimester	-25.62 (-104.32, 53.09)	0.08 (-0.26, 0.42)	1.34 (0.37, 4.86)	0.94 (4.21)	0.83 (0.42, 1.62)	0.69 (0.34, 1.40)
1410 PM _{2.5}	Third trimester	13.77 (-72.33, 99.86)	-0.2 (-0.58, 0.17)	1.12 (0.31, 4.07)	0.94 (a) 2 0 0 3.35)	1.00 (0.48, 2.12)	0.57 (0.26, 1.23)
16	Total pregnancy	21.13 (-36.41, 78.67)	0.02 (-0.23, 0.27)	0.73 (0.33, 1.61)	0.52 (24) 24 2 1.15)	0.98 (0.60, 1.61)	0.55 (0.32, 0.96)
¹ Estimated	90 days prior to conception	-18.63 (-64.02, 26.76)	-0.09 (-0.29, 0.10)	1.24 (0.61, 2.49)	1.3 (2.64)	1.27 (0.84, 1.90)	1.39 (0.90, 2.15)
18 19exposure	First trimester	-14.53 (-61.15, 32.09)	0.05 (-0.16, 0.25)	0.91 (0.45, 1.83)	1.14 🔁 🥰 2.37)	1.33 (0.89, 2.00)	1.70 (1.07, 2.69)
$\frac{20}{21}$ to NO ₂	Second trimester	-14.46 (-57.45, 28.54)	-0.08 (-0.26, 0.11)	1.22 (0.63, 2.36)	1.36 (0.68 2.71)	1.27 (0.87, 1.87)	1.50 (1.00, 2.24)
21	Third trimester	-13.13 (-64.87, 38.62)	0.04 (-0.18, 0.27)	0.77 (0.35, 1.67)	0.97 (1.41 (0.90, 2.23)	1.77 (1.08, 2.91)
22 23	Total pregnancy	-15.02 (-49.33, 19.30)	0.00 (-0.15, 0.15)	1.08 (0.64, 1.80)	1.28 (2.18)	1.21 (0.90, 1.63)	1.60 (1.15, 2.23)
	cant findings in the table are bo	ld.		101	<u> </u>		
	justed for maternal age at enrol	lment, infant's sex, maternal H	3MI at 11–14 weeks' gesta	ation, primiparity, mont	hly hou 🗟 ho	e level, and season of	births, and adjusted
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eTable 7 Comparison of major confounders and outcomes for those with missing and

non-missing outcome data and non-missing confounder data

$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Excluded from analyses*	Included in analyses	p-value
Maternal age, mean \pm SD 28.47 ± 0.22 28.78 ± 0.11 0.22 Gestational week, mean \pm SD 39.34 ± 0.12 39.39 ± 0.04 0.69 Maternal BMI (kg/m²), mean \pm SD 21.13 ± 0.17 21.56 ± 0.09 0.03 Infant's sex $136 (53.33)$ $527 (51.87)$ 0.676 Male, n (%) $119 (46.67)$ $489 (48.13)$ 0.583 Primiparity 0.583 0.583 0.583 Yes, n (%) $226 (22.22)$ $791 (77.78)$ 0.600 Spring (Mar-May), n (%) $74 (32.46)$ $337 (35.62)$ 0.000 Summer (Jun-Aug), n (%) $74 (32.46)$ $189 (19.98)$ 0.000 Autumn (Sep-Nov), n (%) $25 (24.12)$ $143 (15.12)$ $0.577 (29.28)$		•	•	r
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Maternal BMI (kg/m²), mean \pm SD 21.13 ± 0.17 21.56 ± 0.09 0.03 Infant's sex136 (53.33) $527 (51.87)$ 0.676 Male, n (%)119 (46.67)489 (48.13)Primiparity0.583Yes, n (%) $226 (22.22)$ $791 (77.78)$ No, n (%) $61 (23.83)$ $195 (76.17)$ Season0.00Spring (Mar-May), n (%) $74 (32.46)$ $337 (35.62)$ Summer (Jun-Aug), n (%) $74 (32.46)$ $189 (19.98)$ Autumn (Sep-Nov), n (%) $25 (10.96)$ $277 (29.28)$				
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Associations of air pollution exposures in preconception and pregnancy with birth outcomes and infant neurocognitive development: analysis of the Complex Lipids in Mothers and Babies (CLIMB) prospective cohort in Chongqing, China

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Associations of air pollution exposures in preconception and pregnancy with birth
 outcomes and infant neurocognitive development: analysis of the Complex Lipids in
 Mothers and Babies (CLIMB) prospective cohort in Chongqing, China

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27	Abstract
28 29	Objectives: To investigate the associations of traffic-related air pollution exposures in early pregnancy with birth outcomes and infant neurocognitive development.
30	Design: Cohort study.
31 32 33	Setting: Eligible women attended six visits in the maternity clinics of two centres, the First Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for Women and Children.
34 35 36 37 38	Participants: Women who were between 20 and 40 years of age and were at 11–14 weeks gestation with a singleton pregnancy were eligible for participation. Women were excluded if they had a history of premature delivery before 32 weeks of gestation, maternal milk allergy or aversion, or severe lactose intolerance. 1,273 pregnant women enrolled in 2015-2016 and 1,174 live births were included in this analysis.
39 40 41	Exposures: Air pollution concentrations at their home addresses, including particulate matter (PM) with diameter $\leq 2.5 \mu m$ (PM _{2.5}) and nitrogen dioxide (NO ₂), during pre-conception and each trimester period were estimated using land-use regression models.
42 43 44 45	Outcome measures: Birth outcomes (i.e., birthweight, birth length, preterm birth (PTB), low birth weight (LBW), large for gestational age (LGA) and small for gestational age (SGA) status) and neurodevelopment outcomes measured by the Chinese version of Bayley Scales of Infant Development (CBSID).
46 47 48 49 50 51 52	Results: An association between SGA and per-interquartile range (IQR) increases in NO ₂ was found in the first trimester (odds ratio (OR): 1.57, 95% confidence interval (CI): 1.06, 2.32) and during the whole pregnancy (OR: 1.33, 99% CI: 1.01, 1.75). Both PM _{2.5} and NO ₂ exposure in the 90 days prior to conception were associated with lower Psychomotor Development Index (PDI) scores (β : -6.15, 95% CI: -8.84, -3.46; β : -2.83, 95% CI: -4.27, -1.39, respectively). Increased NO ₂ exposure was associated with an increased risk of psychomotor development delay (PDD) during different trimesters of pregnancy.
53 54 55 56	Conclusions: Increased exposures to NO_2 during pregnancy were associated with increased risks of SGA and psychomotor development delay, while increased exposures to both $PM_{2,5}$ and NO_2 pre-conception were associated with adverse psychomotor development outcomes at 12 months of age.

1 2 3 4	57	
5 6 7	58	Keywords: Air pollution; birth outcomes; child cognition
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1 2 3 59	Article summary
4 5 5 60	Strengths and limitations of this study
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9	• This study uniquely explored the impacts of both pre-conception and prenatal exposure
$ \begin{array}{cccc} 10 & 62 \\ 11 & 62 \end{array} $	to $PM_{2.5}$ and NO_2 on neurodevelopmental outcomes in young infants, within an urban
12 63 13 64	environment characterized by relatively high air pollution levels.
14 04	• We developed an LUR model to capture spatial and temporal variations of air pollution
16	at individual level to reduce exposure misclassification.
17 66 18 19 67	• Our sample size was relatively small, limiting the statistical power to assess several outcomes.
19 67 20 68	 We defined exposure windows for clinically-defined trimesters; sensitive periods may
21 ⁰⁸ 22 69	
22 69 23 70 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 59	be shorter or longer than 3 months, or may exist in the overlap of multiple trimesters.

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71 INTRODUCTION

Air pollution is a major environmental factor that has been linked to a range of adverse health outcomes in children. Maternal exposure to air pollutants during pregnancy, especially particulate matter (PM) with diameter $\leq 2.5 \mu m$ (PM_{2.5}) and nitrogen dioxide (NO₂), has been found to be associated with adverse birth outcomes, including pre-term birth (PTB)(1), term low birth weight (TLBW) (2), and small for gestational age (SGA) status (3). According to the developmental origins of health and disease (DOHaD) hypothesis, prenatal exposures to air pollution may lead to adverse birth outcomes and subsequently increase the susceptibility to the development of certain diseases later in life (4). A number of epidemiological studies have linked prenatal air pollution exposure with neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and cognitive impairment (5). Although the underlying biological mechanisms are still unclear, some studies indicated that prenatal air pollution exposure may induce systemic oxidative stress that triggers intrauterine inflammation, leading to damage to several fetal organs, including the brain (6, 7).

It is also unclear that whether the adverse effects of air pollution may start earlier before conception. Three months before conception was considered as a critical developmental window for gametogenesis. Air pollution exposure during the three-month preconception period may have adverse effects on gametogenesis of sperm (8, 9) and ova cells (10). Exposures to PM_{2.5} in preconception period have been associated with various neurodevelopmental outcomes, such as neural tube defects (11), lower psychomotor development scores (12), higher risk of ASD (13, 14), and higher risk of intellectual disability (15). Further research is required due to inconsistencies across studies in terms of studied health outcomes and exposure levels of air pollution (12). Additionally, while there is growing evidence for the effects of preconception PM_{2.5} exposure on the risk of adverse neurodevelopmental outcomes, no study to date has examined the effects of preconception NO₂ exposure. Exposure to NO₂ during pregnancy may be linked to compromised neural development in children, particularly affecting fine psychomotor skills (16). Studying PM_{2.5} along with NO₂ may allow us to explore how multiple pollutants affect birth outcomes and infant neurocognitive development independently and jointly. Moreover, both PM2.5 and NO2 are regulated traffic-related air pollutants in many countries. Understanding their impacts on birth and infant neurocognitive development can provide valuable insights for policymakers and public health authorities to develop effective air quality regulations and interventions.

103 Many studies have reported the effects of prenatal exposure to air pollution on 104 neurodevelopmental function in children. However, the reported associations vary, due to the 105 heterogeneous assessments of air pollution and neurodevelopmental outcomes (5, 17).

106 The current study leveraged the Complex Lipids in Mothers and Babies (CLIMB) cohort, a 107 prospective birth cohort recruited in Chongqing, China (18), with trimester-specific maternal 108 $PM_{2.5}$ and NO_2 air pollution exposure derived from a spatio-temporal land use regression (LUR) 109 model (19). The aim of this analysis was to examine the associations between $PM_{2.5}$ and NO_2 100 exposures during pre- and during pregnancy, with birth and infant neurocognitive development 111 outcomes at 12 months of age.

A key aspect in all studies like this one is the accuracy of documenting exposure; a recent Chinese study determined air pollution exposure based on data from the nearest monitoring station (20) may not reflect the fine temporal and spatial variability of pollutant exposures among participants. Our study employed common air pollution exposure models based on advanced geographic information systems (GIS), to address some of the limitations of previous studies (21).

In addition, the timing of exposure is also critical in determining the effects of exposure on developmental outcomes. Indeed, the evidence from previous studies on the sensitive time windows for exposure pre- and during pregnancy remains inconclusive. Some studies have indicated that the early-to-mid pregnancy phase may be a critical period in terms of the impact of air pollution on neurodevelopment(22, 23). Early pregnancy is particularly important for neurogenesis and neuromigration, making it a susceptible period (24). However, some studies reported stronger associations for middle or late pregnancy (20, 25, 26). More studies identifying critical periods are needed to enhance our understanding of how pre-conception and prenatal air pollution exposure affect neurodevelopment. With this cohort, we are able to examine the effects of exposure pre-conception, at each trimester, and the entire pregnancy.

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129 METHODS

130 Study population

Participant recruitment in the CLIMB cohort has been described previously (27). In brief, women who were between 20 and 40 years of age and were at 11–14 weeks gestation with a singleton pregnancy were eligible for participation. Women were excluded if they had a selfstated history of premature delivery before 32 weeks of gestation, maternal milk allergy or aversion, or severe lactose intolerance.

From September 2015 to November 2016, a total of 1,500 women were recruited into the cohort.
Participants attended six visits at the First Affiliated Hospital of Chongqing Medical University
and Chongqing Health Centre for Women and Children: 11–14 weeks' gestation (visit 1), 22–
28 week's gestation (visit 2), 32–34 week's gestation (visit 3), at birth (visit 4), 6 weeks
postnatal (visit 5), and 12 months postnatal (visit 6).

Women who withdrew from the study (n = 146), terminated their pregnancy (n = 29), miscarried (n = 12) or were lost to follow-up (n = 40) were excluded from the analysis, leaving a sample size of 1,273 women. Analyses were restricted to mothers whose detailed residential addresses during pregnancy were known (**Figure 1**). A total of 1,174 live births were thus included in the pregnancy and neonatal outcomes analysis. Subsequently, at 1 year follow-up, 946 children were included in the analysis of neurodevelopment outcomes.

3 147 Study setting

The study area focused on the urban center of the Chinese municipality of Chongqing (Figure 2). The terrain of Chongqing is predominantly hilly and mountainous, with the core area located in a synclinal valley at the confluence of the Yangtze River and the Jialing River (28). The urban core of Chongqing, our study area, has a population of approximately 6.52 million people, a land area of 5,472 square kilometers, and 4.62 million vehicles (29). It shows a higher population density of approximately 1,191 people per square kilometer and a lower number of motor vehicles of 0.71 per capita. The urban core of Chongqing used to have multiple old industries with higher NO₂ and PM_{2.5} emissions, including the Chongqing Iron and Steel Company in Dadukou District and the Chongqing Thermal Power Plant in Jiulongpo District, both of which have been relocated to rural areas in Chongging. The main sources of pollution in the area now include traffic-related emissions, construction activities, and anthropogenic sources such as outdoor grilling and emissions from food establishments (30). The coverage

rate of urban population with access to gas in Chongqing was 95.34% (29), suggesting a low reliance on biomass cookstoves in urban areas.

Exposure assessment

The address of participants was collected at the first visit. Exposure assessment based on spatiotemporal land use regression (LUR) models for PM_{2.5} and NO₂ were developed for the study region. A description of the methodology of exposure modelling has been reported previously (19). Briefly, the models included both spatial and temporal components of exposure. PM_{2.5} and NO₂ concentration data were collected from 17 routine monitoring sites operated by the Chongqing Environmental Monitoring Center in 2015-2016. For the spatial component of models, we calculated annual average concentrations of each pollutant in 2015, and fit linear regression models using five groups of geographic data (road network, land use, topography, vegetation, and population density) as spatial predictor variables. For the temporal component of models, we calculated the residuals from the spatial component at each monitoring site on a daily basis by subtracting the predicted annual average concentration from the observed daily average concentrations measured in 2015 and 2016, and then fitted generalised additive models (GAM) using seven groups of meteorological data (temperature, amount of rainfall, rainfall events, relative humidity, horizontal visibility, wind direction and wind speed) as temporal predictor variables. The meteorological variables were used to account for the influence of weather on the change in air pollution concentration over time. To account for the remaining spatial autocorrelation, the smoothed terms of longitude and latitude were fit to spatiotemporal residuals which were calculated by subtracting the sum of the spatial temporal predictions from the measured daily average concentrations in 2015 and 2016. The performance of the PM_{2.5} spatiotemporal models was good (Correlation (COR)-R²: 0.72) and the NO₂ spatiotemporal model was low (COR- R^2 : 0.39) when providing concentration estimates in absolute terms.

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Combining the family address coordinates of each pregnant woman and the gestation period of the pregnancy (calculated from the date of last menstrual period to the date of delivery), we used this spatiotemporal model to estimate the average exposure of each pregnant woman in 90 days prior to pregnancy (90D), first trimester (T1), second trimester (T2), third trimester (T3) and whole pregnancy period (WP), respectively.

Outcomes

Birth outcomes

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 Birth outcomes were determined by experienced obstetricians and abstracted from the medical
records. Birth outcomes included: birthweight (in grams), birth length (in centimetres), PTB,
low birth weight (LBW), large for gestational age (LGA) and SGA status (31). PTB was
defined as delivery before 37 weeks. LBW was defined as weighing less than 2500 g at birth.
LGA and SGA were indicated by birth weight greater than and less than the 90th and 10th
percentile within this study for the gestational age by sex respectively (32). Term low birth
weight was not considered due to a small sample size of only 8 cases.

199 Neurodevelopment outcomes

The Chinese version of Bayley Scales of Infant Development (CBSID) was used to assess mental and psychomotor development for infants in this study. The CBSID is appropriate for evaluation of infants from 2–30 months old (33) and takes into consideration each infant's age in days. Infants were assessed at around 12 months (range from 11 months and 15 days to 12 months and 15 days) by a trained examiner, with ages corrected for preterm birth. These scales have been formally adapted to the Chinese language and locally standardized to become culturally appropriate, with two main indexes: the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The MDI component comprised 163 items and assessed age-appropriate items related to cognitive functioning, personal and social development, and language development (see eTable 1 in the Supplement). The PDI component comprised 81 items and assessed age-appropriate fine and gross motor skills (see eTable 2 in the Supplement). The test provided raw scores for mental and psychomotor development that were converted to standardized (in terms of age in days) MDI and PDI scores, based on norms for the Chinese population. As with other forms of the Bayley test these index scores have a mean of 100, and a standard deviation of 15, with a lower score reflecting poorer performance (34). If an infant refused to cooperate with the examiners to finish the task, a second assessment was arranged within two weeks. If the infant could not cooperate at the second BSID assessment, their data were classified as missing. In addition to the continuous scores, we define mental developmental delay (MDD) and psychomotor developmental delay (PDD) if the score is less than 85 (35).

55 220 Covariates

Socio-demographic data were collected through interviews by trained nurses. The following potential confounders were identified: maternal age at enrolment (in years), infant sex (male/female), maternal BMI at 11–14 weeks' gestation (kg/m²), parity (Yes/No), monthly

household income level (categorized as: <2,000 yuan, 2,000-7,000 yuan, 7,000-10,000 yuan, or >10,000 yuan), season of birth (categorized as: Spring (Mar-May), Summer (Jun-Aug), Autumn (Sep-Nov) or Winter (Dec-Feb)). Season of birth was taken into consideration because air pollution and related environmental factors, such as temperature and humidity, may vary across different seasons (i.e., air pollution levels tend to be higher during winter). Some studies suggest that the season of birth may indirectly influence cognitive function through factors such as seasonal differences in food availability affecting maternal nutrition during pregnancy, sunlight exposure impacting maternal vitamin D levels, and children's early-life indoor and outdoor activities. Marital status (Single/married) and smoking or drinking during pregnancy (Yes/no) were not taken into account in this analysis because of the homogeneity of the study population (i.e., 98.6% women were married and 99.6% women reported not smoking or drinking alcohol during pregnancy). We did not adjust dietary supplements during pregnancy because all pregnant women routinely take folic acid in this cohort.

237 Statistical analyses

Data were described in terms of mean \pm SD or median (IQR) for continuous variables, or as percentages for categorical variables. Modelled PM_{2.5} and NO₂ exposure levels in 90D, T1, T2, T3 and WP were considered separately. We examined the Spearman correlation between each of the exposures in the different pregnancy periods. For birth outcomes, multivariable linear regression was used for continuous outcomes (e.g., birth weight and birth length) to estimate β coefficient and their 95% confidence intervals (CIs) and multivariable logistic regression for binary outcomes (e.g., PTB, LBW, LGA and SGA status) to estimate odds ratio (OR) and 95% CIs. For mental and psychomotor development (e.g., MDI and PDI scores), multivariable linear regression models were fit to estimate β coefficient and their 95% CIs. We also conducted multivariable logistic regression analysis for binary neurodevelopment outcomes (i.e., MDD and PDD). Models were adjusted for maternal age at enrolment, infant sex, maternal BMI at 11–14 weeks gestation, primiparity, monthly household income level, and season of birth. We also ran co-exposure models to estimate associations of one air pollutant whilst additionally adjusting for the other air pollutant (i.e., PM_{2.5} effects in T1 adjusted for NO₂ in T1). Effect estimates are reported for each IQR increase of PM2.5 and NO2. All analyses were performed using STATA version 17. A p-value of <0.05 was considered statistically significant to address multiple comparisons in the analyses.

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255 Patient and public involvement

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2 3 4	257	RESULTS
5 6 7	258	Study participants
8	259	Participant characteristics are presented in Table 1. Of those participating women, the mean
9 10	260	age was 28.7 years and mean BMI was 21.5 kg/m ² . 98.0% of women were of Han ethnicity,
11 12	261	77.9% were primiparous, and 67.6% had completed tertiary education. 33 (2.8%), 30 (2.6%),
13 14	262	108 (9.2%), 84 (7.2%) of the 1,174 births considered in this analysis were classified as PTB,
15	263	LBW, LGA and SGA, respectively. For those 946 children who completed the BSID test, the
16 17	264	mean MDI score was 94.7 (SD: 17.7) and the mean PDI score was 87.4 (SD: 14.9). The
18 19	265	proportions of participants with MDD (MDI <85) and PDD (PDI < 85) were 27.1% and 42.4%,
20 21	266	respectively.
22 23	267	Exposure assessment
24 25	268	Median PM _{2.5} exposure concentrations were 57.31 μ g/m ³ (IQR: 5.76) and median NO ₂
26 27	269	exposure levels were 50.46 μ g/m ³ (IQR: 5.51) during the whole pregnancy period (eTable 3
28 29	270	in the Supplement). For PM _{2.5} , the concentration in the pre-conception and T1 were
30	271	considerably lower than other periods, close to 10 μ g/m ³ . The between-trimester and 90D
31 32	272	values for NO ₂ were generally moderately correlated (Pearson's $r > 0.5$). The correlation
33 34	273	coefficients of PM _{2.5} were more variable between time periods reflecting the high variability
35 36	274	of $PM_{2.5}$ concentrations, with values ranging from -0.78 to +0.68. Correlations between $PM_{2.5}$
37	275	and NO ₂ in the same pregnancy period were moderately correlated (Pearson's r \sim 0.6, eTable
38 39	276	4 in the Supplement).
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Characteristic of mother	Ν	n (%) / mean ± SD	Characteristic of child	Ν	n (%) /mean ± S
Maternal age (Years)	1,174	28.7 ± 3.5	Gestational week (week)	1,174	39.4 ± 1.5
$BMI (kg/m^2)$	1,174	21.5 ± 2.9	Birth weight (g)	1,165	3314.4 ± 428.8
Han ethnicity (%)	1,174		Birth length (cm)	1,149	49.7 ± 1.9
Yes		1,151 (98.0%)	New born sex	1,172	
No		23 (2.0%)	Female		561 (47.9%)
Marital status (%)	1,174		Male		611 (52.1%)
Single		16 (1.4%)	Birth outcomes		
Married		1,158 (98.6%)	Preterm birth (PTB)	1,174	
Primiparity (%)	1,174		Yes		33 (2.8%)
Yes		914 (77.9%)	No		1,141 (97.2%)
No		260 (22.1%)	Low birth weight (LBW)	1,174	
History of miscarriage or	1,174		Yes		30 (2.6%)
abortion (%)					
Ves		553 (47.1%)	No		1,141 (97.2%)
No 3		621 (52.9%)	Large for gestational age	1,174	
			(LGA)		
4 Şmoking/drinking during	1,174		Yes		108 (9.2%)
pregnancy (%)					
Yes		5 (0.4%)	No		1,066 (90.8%)
No		1,169 (99.6%)	Small for gestational age	1,174	
9			(SGA)		
Education level	946		Yes		84 (7.2%)
Low: High school or below		306 (32.3%)	No		1,090 (92.8%)
High: College/uni or above		640 (67.6%)	BSID test	946	
Job Full-time	946		MDI score		94.7 ± 17.7
Eull-time		762 (80.5%)	PDI score		87.4 ± 14.9
Housewife		82 (8.7%)	Mental development	946	
Others		102 (10.8%)	Delay (MDI < 85)		276 (27.1%)
Household income (Monthly)	946		Normal (MDI \geq 85)		741 (72.9%)
92000 RMB		186 (19.7%)	Psychomotor Development	946	
2000-4000 RMB		329 (34.8%)	Delay (PDI < 85)		431 (42.4%)
4000-7000 RMB		292 (30.9%)	Normal (PDI ≥ 85)		586 (57.6%)
7000-10000 RMB		139 (14.7%)	Season of birth	1,174	
3			Spring (Mar-May)		411 (35.01%)
4 5			Summer (Jun-Aug)		263 (22.40%)
5			Autumn (Sep-Nov)		198 (16.87%)
7			Winter (Dec-Feb)		302 (25.72%)
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0 281 Association with	birth out	comes			
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$\frac{2}{2}$ 282 In the unadjusted	models (Tabla 5 in the Sun	plement), higher exposure c		

279 Table 1. Characteristics of study sample in the CLIMB cohort (N = 1,174)

PM_{2.5} in T3 were significantly associated with lower birth length (β: -0.32, 95% CI: -0.51, -0.13; per IQR increase). We also observed increased NO₂ in T3 were significantly associated with lower birth length (β : -0.16, 95% CI: -0.32, -0.01; per IQR). A risk between SGA and increases in NO2 (per IQR) was found in T2 (OR: 1.46, 95% CI: 1.10, 1.93), T3 (OR: 1.58,

- 95% CI: 1.14, 2.18) and in the whole pregnancy period (OR: 1.44, 95% CI: 1.13, 1.85). We observed no evidence of associations of NO2 with overall birth weight, birth length and other adverse birth outcomes (e.g., PTB, LBW, and LGA). In the adjusted models (Table 2), we found increased effect size for NO₂ and SGA in T2 (OR: 1.57, 95% CI: 1.06, 2.32), and slightly reduced effects size for NO₂ and SGA in the whole pregnancy period (OR: 1.33, 95% CI: 1.01, 1.75) compared with the unadjusted model. We observed no evidence of associations with birth length in the adjusted models. After co-adjustment for PM_{2.5} (see eTable 6 in the Supplement), the association of NO₂ with SGA was also found in T1 (OR: 1.70, 95% CI: 1.07, 2.69), T3 (OR: 1.77, 95% CI: 1.08, pregu 2.91) and in the whole pregnancy period (OR: 1.60, 95% CI: 1.15, 2.23).

6		Mean di	fference		for N. Odds	s ratios	
7 r	Der IOD in graage in	Birth weight, grams	Birth length, cm	PTB (case: 33)	LBWg(case: 30)	LGA (case: 108)	SGA (case: 84)
5	Per IQR increase in	(95% CI)	(95% CI)	(95% CI)	(98% x I)	(95% CI)	(95% CI)
9 10		(N=941)	(N=927)	(N=945)		(N=945)	(N=945)
Estimated	90 days prior to conception	59.73 (-16.52, 135.98)	0.15 (-0.176, 0.48)	0.24 (0.06, 1.00)	0.49 (8.38, 1.29)	1.40 (0.72, 2.71)	1.66 (0.75, 3.68)
2 exposure	First trimester	6.21 (-73.79, 86.20)	0.04 (-0.308, 0.388)	0.88 (0.28, 2.80)	0.76 (9.315 2.81)	0.86 (0.45, 1.67)	1.33 (0.58, 3.04)
	Second trimester	-37.64 (-107.73, 32.44)	0.02 (-0.283, 0.326)	1.62 (0.53, 4.96)	1.34 (8, 8, 4.68)	1.00 (0.55, 1.83)	0.94 (0.50, 1.76)
4to PM _{2.5}	Third trimester	4.20 (-73.17, 81.57)	-0.17 (-0.509, 0.162)	0.92 (0.29, 2.90)	0.92 (2.85)	1.29 (0.65, 2.53)	0.83 (0.42, 1.66)
16	Total pregnancy	8.01 (-41.10, 57.11)	0.02 (-0.198, 0.230)	0.77 (0.38, 1.54)	0.62 (2 1.25)	1.15 (0.75, 1.77)	0.84 (0.52, 1.35)
Estimated	90 days prior to conception	-1.03 (-41.88, 39.81)	-0.04 (-0.215, 0.139)	0.84 (0.45, 1.57)	1.04 (9.04 1.98)	1.31 (0.91, 1.88)	1.45 (0.99, 2.12)
8 9exposure	First trimester	-9.78 (-50.84, 31.28)	0.04 (-0.133, 0.223)	0.90 (0.49, 1.65)	1.03 (2.36 1.91)	1.21 (0.85, 1.72)	1.57 (1.06, 2.32)
0	Second trimester	-20.82 (-59.11, 17.47)	-0.06 (-0.222, 0.112)	1.31 (0.73, 2.34)	1.34 (0.75 2.40)	1.21 (0.86, 1.70)	1.36 (0.95, 1.95)
21^{10} NO_2	Third trimester	-9.50 (-56.00, 36.99)	-0.01 (-0.213, 0.191)	0.79 (0.40, 1.59)	0.95 (9.47 1.94)	1.42 (0.94, 2.13)	1.51 (0.97, 2.36)
22 23	Total pregnancy	-8.45 (-37.73, 20.83)	0.00 (-0.125, 0.130)	0.97 (0.62, 1.51)	1.04 (9.66-1.64)	1.20 (0.93, 1.56)	1.33 (1.01, 1.75)
All signific	ant findings in the table are bo	old.			<u> </u>		,
2 Models adj	usted for maternal age at enrol	ment, infant's sex, maternal	BMI at 11-14 weeks' gestat	ion, primiparity, mont	hly hous houd incom	e level, and season of	births.
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Association with infant neurodevelopment outcomes

In unadjusted models, PM_{2.5} exposure in the 90 days prior to conception was associated with lower MDI and PDI scores in offspring (β: -3.54, 95% CI: -5.37, -1.71; β: -3.42, 95% CI: -4.96, -1.89) (Table 3). We also observed an unexpected positive association between $PM_{2.5}$ exposures in second trimester with MDI (β: 4.21, 95% CI: 2.43, 6.00) and PDI (β: 2.63, 95% CI: 1.12, 4.14). Exposure to NO₂ was associated with lower MDI (-1.90, 95% CI: -3.36, -0.44) and PDI in the 90 days prior to conception (-2.86, 95% CI: -4.08, -1.65). NO₂ exposure was also associated with lower PDI scores in T3 (-1.97, 95% CI: -3.29, -0.65) and in the whole pregnancy periods (-1.08, 95% CI: -2.11, -0.05). We did not observe any association between NO₂ and MDI in any pregnancy periods.

In the adjusted models (Table 3), we found PM_{25} exposure in the 90 days prior to conception was associated with lower PDI scores (β : -6.15, 95% CI: -8.84, -3.46). Similarly, there was also a significant association of increased NO₂ exposure and lower PDI score in the 90 days prior to conception (β: -2.83, 95% CI: -4.27, -1.39), T1 (β: -1.91, 95% CI: -3.37, -0.46), T3 (β: -1.92, 95% CI: -3.57, -0.26) and whole pregnancy period (β: -1.15, 95% CI: -2.19, -0.11). The positive association between $PM_{2.5}$ exposures in second trimester with PDI (β : 3.76, 95% CI: 1.27, 6.24) remained. We did not observe any association with MDI in any pregnancy periods.

In the co-exposure models (**Table 3**), $PM_{2.5}$ exposure in the 90 days prior to conception was associated with lower PDI scores (β : -4.74, 95% CI: -7.73, -1.75). We also observed a positive association between PM_{2.5} exposures in second trimester with PDI (β : 5.51, 95% CI:2.73, 8.28). Exposure to NO₂ was significantly associated with lower PDI in 90D (β : -1.72, 95% CI: -3.31, -0.12), T1 (β: -1.80, 95% CI: -3.46, -0.15), T2 (β: -2.11, 95% CI: -3.63, -0.60), T3 (β: -1.92, 95% CI: -3.76, -0.09) and whole pregnancy period (β: -1.68, 95% CI: -2.89, -0.46).

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322	Table 3. Associations between PM _{2.5} and NO ₂ exposure in different pregnancy periods and contir	t, inceus	SID scores

5					ing 5		
6		Crude n	nodels	Adjusted	l models* of N	Co-expos	ure models**
7 8 []]	Per IQR increase in	MDI (95% CI) (N=946)	PDI 95% CI (N=946)	MDI (95% CI) (N=945)	PDI 95% & Luy (N=945% & Second	MDI (95% CI) (N=945)	PDI 95% CI (N=945)
10 ^{Estimated}	90 days prior to conception	-3.54 (-5.37, -1.71)	-3.42 (-4.96, -1.89)	-1.98 (-5.19, 1.23)	-6.15 (-8.84, 23746)	-1.73 (-5.30, 1.85)	-4.74 (-7.73, -1.75)
¹ ¹ exposure	First trimester	-1.07 (-2.93, 0.79)	0.04 (-1.52, 1.61)	-1.66 (-5.02, 1.70)	-2.11 (-4.95, 8 , 8 , 9	-2.84 (-6.65, 0.97)	-0.45 (-3.67, 2.76)
12 13to PM _{2.5}	Second trimester	4.21 (2.43, 6.00)	2.63 (1.12, 4.14)	3.79 (0.85, 6.73)	3.76 (1.27, 😋 🎜	4.19 (0.89, 7.49)	5.51 (2.73, 8.28)
14	Third trimester	-1.43 (-3.41, 0.55)	-1.76 (-3.42, -0.10)	-2.73 (-5.99, 0.53)	-1.37 (-4.12, 🗐 🖉	-3.84 (-7.46, -0.22)	0.04 (-3.02, 3.09)
15	Total pregnancy	1.64 (0.06, 3.21)	0.5 (-0.82, 1.83)	-0.27 (-2.34, 1.80)	0.23 (-1.52, 5 .28)	-0.85 (-3.28, 1.57)	1.69 (-0.35, 3.73)
¹⁶ ¹ Estimated	90 days prior to conception	-1.90 (-3.36, -0.44)	-2.86 (-4.08, -1.65)	-0.72 (-2.43, 1.00)	-2.83 (-4.27, 🖬 🛐 🧐	-0.31 (-2.22, 1.60)	-1.72 (-3.31, -0.12)
1&exposure	First trimester	-0.08 (-1.57, 1.42)	-1.17 (-2.43, 0.08)	0.59 (-1.14, 2.32)	-1.91 (-3.37, Bras	1.28 (-0.68, 3.24)	-1.80 (-3.46, -0.15)
$\frac{19}{20}$ to NO ₂	Second trimester	1.81 (0.41, 3.22)	0.00 (-1.18, 1.18)	0.56 (-1.05, 2.17)	-0.75 (-2.11, 3.6	-0.48 (-2.28, 1.33)	-2.11 (-3.63, -0.60)
20 ¹⁰ 110 ² 21	Third trimester	0.04 (-1.54, 1.62)	-1.97 (-3.29, -0.65)	0.51 (-1.45, 2.47)	-1.92 (-3.57, 🖄 .26)	1.52 (-0.66, 3.69)	-1.92 (-3.76, -0.09)
21 22	Total pregnancy	0.67 (-0.56, 1.89)	-1.08 (-2.11, -0.05)	0.41 (-0.83, 1.64)	-1.15 (-2.19, a).19	0.67 (-0.77, 2.12)	-1.68 (-2.89, -0.46)

23All significant findings in the table are bold.
 24 Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income level, and season of births.

 $^{25}*$ Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income level, and season of births, and 25

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42% with each per- 95% CI: 1.16, 1.75) association between .05, 1.58), T3 (OR: CI: 1.02, 1.36). We	
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In the adjusted model, the risk of PDD was found to increase by 112% and 4 IQR increase in PM_{2.5} (OR: 2.12, 95% CI: 1.45, 3.11) and NO₂ (OR: 1.42, 9

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 in the 90 days prior to conception (Table 4). There was also a significant as increased NO₂ exposure and the risk of PDD in T1 (OR: 1.29, 95% CI: 1. 1.27, 95% CI: 1.01, 1.60), and the whole pregnancy period (OR: 1.17, 95% did not observe any association with MDD in any pregnancy periods.

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1 2 3 330 4 5 331 6	Table 4. Associations bet delay	tween PM _{2.5} and NO		MJ Open nt pregnancy periods	/bmjopen-2023-082475 on 2. 1 by copyright, incaders for and mental and and	chomotor developm	Page 20 of 45 ental
7 8		Cruc	le models	Adjusted 1	nodels*	Co-exposure	e models**
9		MDD (95% CI)	PDD (95% CI)	MDD (95% CI)	PDD (95% @12	MDD (95% CI)	PDD (95% CI)
10	Per IQR increase in	(N=946)	(N=946)	(N=945)	(N=94) [24]	(N=945)	(N=945)
¹ Estimated	90 days prior to conception	1.45 (1.16, 1.83)	1.49 (1.20, 1.83)	0.95 (0.64, 1.42)	2.12 (1.45, 2 4 4	0.97 (0.63, 1.51)	1.78 (1.17, 2.71)
12 13exposure	First trimester	1.05 (0.83, 1.33)	1.04 (0.84, 1.28)	1.14 (0.73, 1.79)	1.42 (0.96, g . b	1.35 (0.80, 2.25)	1.16 (0.74, 1.82)
14 15 ^{to} PM _{2.5}	Second trimester	0.63 (0.49, 0.80)	0.77 (0.63, 0.95)	0.81 (0.54, 1.22)	0.72 (0.51, a) (0.51	0.83 (0.52, 1.31)	0.57 (0.38, 0.85)
	Third trimester	1.23 (0.96, 1.58)	1.19 (0.95, 1.49)	1.25 (0.82, 1.90)	1.17 (0.80, a a	1.39 (0.87, 2.23)	0.98 (0.64, 1.49)
16 17	Total pregnancy	0.84 (0.69, 1.03)	0.98 (0.82, 1.18)	1.07 (0.82, 1.39)	1.07 (0.84, a 2	1.17 (0.86, 1.59)	0.90 (0.68, 1.20)
1 & stimated	90 days prior to conception	1.20 (0.99, 1.45)	1.41 (1.19, 1.67)	0.97 (0.77, 1.21)	1.42 (1.16,	0.97 (0.76, 1.25)	1.24 (0.99, 1.56)
19 20 ^{exposure}	First trimester	0.97 (0.80, 1.17)	1.18 (0.99, 1.40)	0.91 (0.72, 1.13)	1.29 (1.05, ā .58	0.84 (0.65, 1.09)	1.24 (0.99, 1.57)
20^{-1} to NO ₂	Second trimester	0.79 (0.66, 0.95)	1.04 (0.88, 1.22)	0.94 (0.76, 1.15)	1.14 (0.95, 복 .3👼	0.98 (0.77, 1.24)	1.31 (1.06, 1.63)
21 to NO ₂ 22	Third trimester	1.04 (0.85, 1.28)	1.25 (1.04, 1.50)	0.94 (0.73, 1.21)	1.27 (1.01,a. 60)	0.86 (0.65, 1.14)	1.28 (0.99, 1.65)
23	Total pregnancy	0.92 (0.79, 1.07)	1.16 (1.01, 1.33)	0.94 (0.80, 1.11)	1.17 (1.02, ā .3 👼	0.9 (0.75, 1.08)	1.21 (1.02, 1.43)
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All significant findings in the table are bold. ²⁵ ²⁶Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income level, and season of births. 27*Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly hause fold income level, and season of births, and ar t lune 28 djusted for the other air pollutant.

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333 DISCUSSION

We analyzed associations between modelled PM_{2.5} and NO₂ pre- and during pregnancy with birth and neurodevelopment outcomes in singleton children born in a south-western metropolis of China in 2015-16. We found the likelihood of SGA increased by 33% per IQR higher exposure to NO₂ in the whole pregnancy periods after adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11-14 weeks' gestation, primiparity, monthly household income level, and season of births and PM_{2.5}. For childhood cognitive development, increased exposure to PM_{2.5} and NO₂ in the 90 days prior to conception were both associated with lower PDI scores, with the effect size per IQR being higher for PM_{2.5} than for NO₂. Increased NO₂ exposure was associated with an increased risk of PDD during different trimesters of pregnancy.

Many studies from other geographic areas, including Europe (36-38), the United States (22, 26), and Asia (23, 39-41), have found significant associations between prenatal air pollution exposure and a variety of adverse neurodevelopmental outcomes. Our finding of a negative association between prenatal NO₂ air pollution exposure and infant neurocognitive development is consistent with these reports. A recent Chinese birth cohort study of 15,778 child-mother pairs in Foshan reported that maternal NO₂ exposure during pregnancy was associated with an increased risk of suspected developmental delay (OR: 1.06, 95% CI: 0.94, 1.19) measured by a five-domain scale and developmental quotient (DQ) (23). A birth cohort study of 520 mother-child pairs in South Korea reported that maternal NO₂ exposure during pregnancy was associated with impairment of psychomotor development ($\beta = -1.30$, p = 0.05) but – as in the present study - not with cognitive function ($\beta = -0.84$, p = 0.20) (39). However, results from previous research varied by air pollutants. For example, a Chinese study of 1193 mother-newborn pairs in Changsha found significant associations between PM_{2.5} exposure in trimester two and lower neurobehavioral developmental scores, while other air pollutants such as PM₁₀, carbon monoxide (CO), and Sulfur dioxide (SO₂) had null or even reverse associations. In this study, we observed that the negative effect of NO₂ exposure during pregnancy on PDI is significant at 5% level; this negative effect of NO₂ still remained after adjustment for PM_{2.5}. This heterogeneity may relate to the temporality of exposure assessment, types of outcome assessment instruments or evaluators, and the levels of air pollution. In addition, air pollution mixtures may have differed among the study regions, thus there are several potential explanations for the heterogeneity of the findings. We also observed negative correlations between certain exposures, indicating the need to consider potential collinearity in our two-pollutant models. In Chongqing, a major industrial city in southwest China, air pollution may

come from industrial and traffic emissions, construction activities, and dust, and negative correlations may occur if different sources contribute disproportionately to each pollutant. Their correlations may also be affected by seasonal changes and variations in weather patterns. Future research should also explore the impact of source-specific air pollution on children's cognitive health.

To date, most studies on prenatal air pollution exposure and child neurodevelopment have been conducted in developed countries with relatively low levels of air pollution. In this study, the level of air pollution was higher (median PM_{2.5}: 57.31 µg/m³, IQR: 5.76; median NO₂: $50.46 \,\mu\text{g/m}^3$, IQR: 5.51) compared to studies in developed countries such as Europe and the United States. In a multi-centre European cohort, the mean PM2.5 and NO2 exposure concentration during pregnancy were 13.4 μ g/m³ and 11.5 μ g/m³ (36). Researchers found that the psychomotor development score significantly decreased by 0.68 points (95% CI: -1.25, -0.11) for every 10 μ g/m³ increase in NO₂, and there was also a non-significant decrease of 1.64 points (95% CI: -3.47, 0.18) for every 5 µg/m³ increase in PM_{2.5} during pregnancy (36). Factors such as the types of pollutants and concentrations may differ between China and other regions with a lower air pollution level, leading to variations in the observed effects.

Contrary to expectations, we found significant positive associations between prenatal exposure to PM_{2.5} air pollution in the second trimester and PDI. However, no association was observed between PM_{2.5} exposures in the second trimester and the risk of PDD. Given the existing literature and the conflicted observation here, we believe that this is likely to be spurious/sample specific. Some plausible explanations include the uneven distribution of PDI scores, the potentially inappropriate selection of the cut-off value of 85 (which may not effectively discriminate between groups), or the possibility that the observed outcome occurred by chance. Several epidemiological studies have reported associations between prenatal exposure to high levels of PM_{2.5} and lower neurodevelopment in children ranging in age from 6 months to 6 years (12, 37, 42-44). In agreement with our findings, a multi-centre cohort study from six European countries investigated the effects of prenatal exposure to multiple air pollutants including PM_{2.5}, PM₁₀, coarse particles, NO₂ and nitrogen oxides (NOx) among 9482 children between 1 and 6 years; the authors found nonsignificant positive associations between prenatal $PM_{2.5}$ exposure and normal neurodevelopment (β : 1.64, 95% CI: –3.47, 0.18; per 5 $\mu g/m^3$ increase in PM_{2.5}) (36). Similarly, another study examining the effects of multiple pollutant exposures on early childhood cognition at 40 days of age in a highly exposed area of Spain also found PM₁₀, PM_{coarse}, PM_{2.5absorbance}, NO₂, NO_x, and Ozone (O₃) were linked to lower

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motor function in children, except for PM_{2.5} (45). The inconsistent findings could be because
of heterogeneity between studies in terms of exposure (e.g., exposure assessment methods used,
PM_{2.5} exposure levels, or composition of PM_{2.5}).

The prevalence of MDD and PDD in our study is higher than in other studies that also used the CBSID to report developmental delay rates, which were at 17% (46), 15.78% (47), and 13.68% (48). This may be attributed to the younger age of infants in our study, which were assessed at around 12 months, compared to most studies assessed at around 24 months. A Chinese study and a South Korean study also found lower scores on the MDI and PDI in 1-year-old children (49, 50). Aside from the conflicting findings regarding prenatal PM_{2.5} exposure and neurodevelopmental outcomes, results regarding the most potential sensitive time windows before and during pregnancy are also inconclusive. Some studies suggested that early-to-mid pregnancy might be a potential sensitive period (22, 23), while other studies found stronger associations for middle-to- late pregnancy, thus results are equivocal (20, 25, 26).

The potential biological mechanisms by which air pollution could affect neurodevelopment are not yet clearly understood. There is evidence suggesting that exposure to prenatal PM_{2.5} could potentially induce maternal immune activation during pregnancy (51). Higher levels of cytokines or reactive oxygen species may potentially interfere fetal neurodevelopment through three mechanisms: crossing the placental barrier into the fetal body, inducing fetal immune dysregulation, and contributing to inadequate placental perfusion that affects nutritional processes and oxygenation of maternal blood (52). More research is needed to investigate trimester effects of air pollution on neurodevelopment and provide better understanding on the underlying biological mechanisms. Our study is the first to consider an exposure window 90 days prior to conception for NO₂. A novel observation is that effects of NO₂ or PM_{2.5} air pollution on child cognition can be seen at least 90 days prior to conception, representing a potentially vulnerable periods in relation to air pollution on neurodevelopment. Similar results were found in previous study recruited 1329 mother-child pairs in Wuhan, China (12). This study reported a higher level of $PM_{2.5}$ during preconception (Median: 76.1 μ g/m³) and in the first trimester (Median: 82.3 μ g/m³). This study found for each doubling of PM_{2.5} exposure during preconception, children's PDI scores was reduced by 6.15 (95% CI: -8.84, -3.46) points. A potential explanation is that preconception air pollution exposures induce genetic and epigenetic alterations in sperm, that increase the risk of adverse health outcomes in offspring (53, 54). To date, all studies examined the effect of maternal preconception exposure while

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431 omitting paternal exposures (17). Future studies should consider the effect of preconception
432 paternal exposure in relation to childhood health outcomes.

This study has several strengths. We developed an LUR model to capture spatial and temporal variations of air pollution at individual level to reduce exposure misclassification if using monitoring stations. This is a novel study to investigate both pre-conception and prenatal PM_{2.5} and NO₂ exposure with neurodevelopment outcomes among young infants, in the context of a relatively high air pollution urban environment. The exposure levels in our study were similar as those in comparable urban areas in Chinese cities. A study in Shanghai, China reported an average NO₂ exposure during pregnancy from 2014 to 2015, predicted by the LUR model, of 48.23 μg/m³ (Mean PM_{2.5} in our study: 50.52 μg/m³) (55). Similarly, a study in Tianjin found the annual average $PM_{2.5}$ exposure to be 62 µg/m³ in 2017 (Mean NO₂ in our study: 57.48 $\mu g/m^3$) (56). Wu et al. developed a LUR model for PM_{2.5} in the main urban area of Chongqing (57). This model predicted an annual average $PM_{2.5}$ concentration of 40.6 µg/m³ (57), whereas our prediction is higher at 55.9 μ g/m³ (19). This difference can be attributed to the temporal variations. Wu et al. used monitoring data from 2013, while we utilized data from 2015. It could be considered that our GAM model, with its temporal component, could explain temporal variations and is more suitable for pregnancy-specific exposure estimates.

A major limitation of this study was that our sample size was relatively small, limiting the statistical power to assess several outcomes, although the higher exposures in Chongqing than in some other studies may increase probability of detecting effects. In terms of limitations, due to a lack of information on participant time-activity patterns, exposure estimates in this study refer only to ambient concentrations at home addresses, and no other activity spaces (e.g., indoor, workplace, commuting) were considered. We may have thus underestimated total air pollution exposure. Second, we defined exposure windows for clinically-defined trimesters; sensitive periods may be shorter or longer than 3 months, or they may exist in the overlap of multiple trimesters. However, we were unable to investigate the sensitive time windows using established methods such as distributed lag non-linear models due to the lack of highly time-resolved air pollution estimates. Third, the performance of the NO₂ spatiotemporal model was low (COR-R²: 0.39), which may introduce exposure misclassification and therefore bias in the coefficients. It may lead to underestimation of the association if the NO₂ spatiotemporal model inadequately represents the true variability in NO₂ levels. Or conversely, it could overestimate the association between NO₂ exposure and the outcome if the model fails to account for certain factors or inaccurately estimates NO₂ levels. Finally, we were unable to include some other air

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pollutants such as polycyclic aromatic hydrocarbons (PAH), black carbon (BC) and Ozone,
which have bene found particular harmful to neurodevelopment in children (58). Although we
have accounted for most of the important confounders in this study, unfortunately, we did not
collect information on the feeding patterns of infants. This may undermine the validity and
reliability of our findings.

5 470 CONCLUSION

471 This study provides evidence for an association between NO_2 exposure prior to- and during 472 pregnancy with birth and neurodevelopmental outcomes in a birth cohort in Chongqing, China. 473 Exposure to NO_2 and $PM_{2.5}$ exposure before pregnancy was associated with a lower 474 psychomotor development score. Increased NO_2 exposure was linked to a risk of psychomotor 475 development delay during various pregnancy trimesters.

Declarations

478 Ethics approval and consent to participate

479 Ethical approval for this study was granted by the Ethics Committee of Chongqing Medical
480 University (#2014034). The participants provided their written informed consent to
481 participate in this study. Written informed consent was obtained from the individual(s) for the
482 publication of any potentially identifiable images or data included in this article.

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Data availability statement

4 484 The data that support the findings of this study are available from Chongqing Medical
485 University but restrictions apply to the availability of these data, which were used under
486 license for the current study, and so are not publicly available. Data are however available
487 from the authors upon reasonable request and with permission of Chongqing Medical
488 University.

3Competing interests

 $\frac{2}{5}$ 490 The authors declare that they have no conflicts of interests.

8 491 Funding

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Contributors

Y. X., T.L.H., H.Z. and PNB. conceived and designed research; T.Z., Y.X. and H.Z. recruited the patients and collected the samples; T.K., A.H., and J.G. constructed the air pollution model; Y.C. analyzed, interpreted the data and prepared the figures; Y.C and T.K were major contributors in writing the manuscript text; YSC, JC, TLH, YX, ALH, and PNB substantively revised the manuscript; All authors read and approved the final manuscript.

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References

Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iniguez C. Preterm birth 1. and exposure to air pollutants during pregnancy. Environmental Research. 2010;110(8):778-85.

- 2. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). The Lancet Respiratory Medicine. 2013;1(9):695-704.
- 3. Stieb DM, Chen L, Hystad P, Beckerman BS, Jerrett M, Tjepkema M, et al. A national study of the association between traffic-related air pollution and adverse pregnancy outcomes in Canada, 1999-2008. Environmental Research. 2016.

BMJ Open

523	4. Barker DJ. The origins of the developmental origins theory. Journal of internal
524	medicine. 2007;261(5):412-7.
525	5. Volk HE, Perera F, Braun JM, Kingsley SL, Gray K, Buckley J, et al. Prenatal air
526	pollution exposure and neurodevelopment: A review and blueprint for a harmonized approach
527	within ECHO. Environmental research. 2021;196:110320.
528	6. Feng S, Dan G, Liao F, Zhou F, Wang X. The health effects of ambient PM2.5 and
529	potential mechanisms. Ecotoxicology and Environmental Safety. 2016;128:67-74.
530	7. Massa NR, Guangyun M, Xingyou Z, Xiumei H, Zhu C, Sampankanpanich SC, et al.
531	Intrauterine Inflammation and Maternal Exposure to Ambient PM2.5 during Preconception and
532	Specific Periods of Pregnancy: The Boston Birth Cohort. Environ Health Perspect.
533	2016;124(10):1608-15.
534	8. Vecoli C, Montano L, Andreassi MG. Environmental pollutants: genetic damage and
535	epigenetic changes in male germ cells. Environmental Science and Pollution Research.
536	2016;23:23339-48.
537	9. Marcho C, Oluwayiose OA, Pilsner JR. The preconception environment and sperm
538	epigenetics. Andrology. 2020;8(4):924-42.
539	10. Udagawa O, Furuyama A, Imai K, Fujitani Y, Hirano S. Effects of diesel exhaust-
540	derived secondary organic aerosol (SOA) on oocytes: Potential risks to meiotic maturation.
541	Reproductive Toxicology. 2018;75:56-64.
542	11. Zhang J-Y, Wu Q-J, Huang Y-H, Li J, Liu S, Chen Y-L, et al. Association between
543	maternal exposure to ambient PM10 and neural tube defects: a case-control study in Liaoning
544	Province, China. International Journal of Hygiene and Environmental Health.
545	2020;225:113453.
546	12. Li J, Liao J, Hu C, Bao S, Mahai G, Cao Z, et al. Preconceptional and the first trimester
547	exposure to PM2. 5 and offspring neurodevelopment at 24 months of age: Examining
548	mediation by maternal thyroid hormones in a birth cohort study. Environmental Pollution.
549	2021;284:117133.
550	13. Jo H, Eckel SP, Chen J-C, Cockburn M, Martinez MP, Chow T, et al. Gestational
551	diabetes mellitus, prenatal air pollution exposure, and autism spectrum disorder. Environment
552	international. 2019;133:105110.
553	14. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism spectrum disorder
554	and particulate matter air pollution before, during, and after pregnancy: a nested case-control
555	analysis within the Nurses' Health Study II cohort. Environmental health perspectives.
556	2015;123(3):264-70.
	26
	525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 544 545 546 547 548 549 550 551 552 553

- 557 15. Grineski S, Alexander C, Renteria R, Collins TW, Bilder D, VanDerslice J, et al.
 558 Trimester-specific ambient PM2.5 exposures and risk of intellectual disability in Utah.
 559 Environmental Research. 2023;218:115009.
- ⁸/₉ 560 16. Shang L, Yang L, Yang W, Huang L, Qi C, Yang Z, et al. Effects of prenatal exposure
 ¹⁰/₁₁ 561 to NO(2) on children's neurodevelopment: a systematic review and meta-analysis. Environ Sci
 ¹² 562 Pollut Res Int. 2020;27(20):24786-98.
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 ¹⁷
 ¹⁸
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 <li
- 566 Huang S, Mo T-T, Norris T, Sun S, Zhang T, Han T-L, et al. The CLIMB (Complex 18. 19 20 567 Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel 21 22 568 randomised controlled trial to investigate the effect of supplementation of complex lipids in 23 569 pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring. 24 25 BMJ open. 2017;7(10):e016637. 570 26
- 27 Harper A, Baker PN, Xia Y, Kuang T, Zhang H, Chen Y, et al. Development of 571 19. 28 29 572 spatiotemporal land use regression models for PM2. 5 and NO2 in Chongqing, China, and 30 573 exposure assessment for the CLIMB study. Atmospheric Pollution Research. 31 32 574 2021;12(7):101096. 33
- 575 20. Chen B, Huang S, He J, He Q, Chen S, Liu X, et al. Sex-specific influence of prenatal
 576 air pollutant exposure on neonatal neurobehavioral development and the sensitive window.
 577 Chemosphere. 2020;254:126824.
- 578 21. Volk HE, Perera F, Braun JM, Kingsley SL, Gray K, Buckley J, et al. Prenatal air
 579 pollution exposure and neurodevelopment: A review and blueprint for a harmonized approach
 43 580 within ECHO. Environ Res. 2021;196:110320.
- 581 22. Ha S, Yeung E, Bell E, Insaf T, Ghassabian A, Bell G, et al. Prenatal and early life
 582 exposures to ambient air pollution and development. Environmental research. 2019;174:170583 5.
- 584 23. Su X, Zhang S, Lin Q, Wu Y, Yang Y, Yu H, et al. Prenatal exposure to air pollution
 585 and neurodevelopmental delay in children: A birth cohort study in Foshan, China. Science of
 586 The Total Environment. 2022;816:151658.
- 55 587 24. Bennet L, Walker DW, Horne RS. Waking up too early-the consequences of preterm
 56 57 588 birth on sleep development. The Journal of physiology. 2018;596(23):5687-708.
- 58 59 60

Page 29 of 45

1

BMJ Open

2 3	500	
4	589	25. Wang P, Zhao Y, Li J, Zhou Y, Luo R, Meng X, et al. Prenatal exposure to ambient
5 6 7	590	fine particulate matter and early childhood neurodevelopment: A population-based birth cohort
	591	study. Science of The Total Environment. 2021;785:147334.
8 9	592	26. Chiu Y-HM, Hsu H-HL, Coull BA, Bellinger DC, Kloog I, Schwartz J, et al. Prenatal
10 11 12 13 14 15 16	593	particulate air pollution and neurodevelopment in urban children: examining sensitive windows
	594	and sex-specific associations. Environment international. 2016;87:56-65.
	595	27. Huang S, Mo T-T, Norris T, Sun S, Zhang T, Han T-L, et al. The CLIMB (Complex
	596	Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel
17	597	randomised controlled trial to investigate the effect of supplementation of complex lipids in
18 19	598	pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring.
20 21	599	BMJ Open. 2017;7(10):e016637.
22 23	600	28. Liu Y, Zhong M, Sun Q, Zhong B, Luo K. Temporal and spatial variations of
24	601	atmospheric pollutants in Chongqing metropolitan area during autumn. Huanjing Kexue
25 26	602	Xuebao/Acta Scientiae Circumstantiae. 2016;36:2344-54.
27 28	603	29. Statistics CMBo. Chongqing Statistical Yearbook 2015. 2015.
28 29 30 31	604	30. Jiaojiao L, Si C, Jie Z, Di Y. Characteristic Analysis of PM2. 5 and Evaluation of
	605	Forecast Results in Chongqing. Environmental Science & Technology (10036504). 2020;43(6).
32 33	606	31. Albert BB, Derraik JG, Xia Y-Y, Norris T, Zhang T, Han T-L, et al. Supplementation
33 34 35	607	with milk enriched with complex lipids during pregnancy: a double-blind randomized
36	608	controlled trial. Plos one. 2021;16(2):e0244916.
37 38	609	32. Zhao X, Xia Y, Zhang H, Baker PN, Norris T. Birth weight charts for a Chinese
39 40	610	population: an observational study of routine newborn weight data from Chongqing. BMC
41	611	Pediatr. 2019;19(1):426.
42 43	612	33. Shourong Y, Xuerong L, Zhiwei Y. The revising of the bayley scales of infant
44 45	613	development (BSID) in China. Chin J Clin Psychol. 1993;2:71-5.
46 47	614	34. Chen Y-T, Zhang T, Chen C, Xia Y-Y, Han T-L, Chen X-Y, et al. Associations of early
48	615	pregnancy BMI with adverse pregnancy outcomes and infant neurocognitive development.
49 50 51 52	616	Scientific Reports. 2021;11(1):1-8.
	617	35. Çelik P, Sucakli IA, Yakut HI. Which Bayley-III cut-off values should be used in
53	618	different developmental levels? Turkish journal of medical sciences. 2020;50(4):764-70.
54 55	619	36. Guxens M, Garcia-Esteban R, Giorgis-Allemand L, Forns J, Badaloni C, Ballester F, et
56 57	620	al. Air pollution during pregnancy and childhood cognitive and psychomotor development: six
58	621	European birth cohorts. Epidemiology. 2014:636-47.
59 60		

2 3 622 37. Lertxundi A, Baccini M, Lertxundi N, Fano E, Aranbarri A, Martínez MD, et al. 4 5 623 Exposure to fine particle matter, nitrogen dioxide and benzene during pregnancy and cognitive 6 624 and psychomotor developments in children at 15 months of age. Environment international. 7 8 625 2015;80:33-40. 9 10 626 Porta D, Narduzzi S, Badaloni C, Bucci S, Cesaroni G, Colelli V, et al. Air pollution 38.

1

and cognitive development at age 7 in a prospective Italian birth cohort. Epidemiology.
 2016;27(2):228-36.

15 629 Kim E, Park H, Hong Y-C, Ha M, Kim Y, Kim B-N, et al. Prenatal exposure to PM10 39. 16 17 630 and NO2 and children's neurodevelopment from birth to 24 months of age: Mothers and 18 Children's Environmental Health (MOCEH) study. Science of the Total Environment. 631 19 20 632 2014;481:439-45. 21

633 40. Lin C-C, Yang S-K, Lin K-C, Ho W-C, Hsieh W-S, Shu B-C, et al. Multilevel analysis
634 of air pollution and early childhood neurobehavioral development. International journal of
635 environmental research and public health. 2014;11(7):6827-41.

636 41. Yorifuji T, Kashima S, Diez MH, Kado Y, Sanada S, Doi H. Prenatal exposure to
637 traffic-related air pollution and child behavioral development milestone delays in Japan.
638 Epidemiology. 2016;27(1):57-65.

639
 639
 42. Tozzi V, Lertxundi A, Ibarluzea JM, Baccini M. Causal effects of prenatal exposure to
 640
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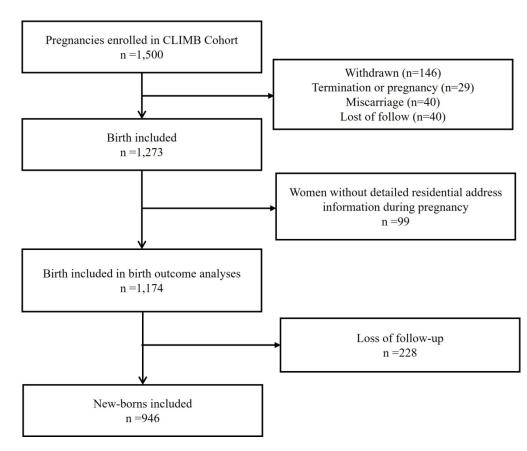
37 642 43. Hurtado-Díaz M, Riojas-Rodríguez H, Rothenberg SJ, Schnaas-Arrieta L, Kloog I, Just 38 39 643 A, et al. Prenatal PM2. 5 exposure and neurodevelopment at 2 years of age in a birth cohort 40 41 644 from Mexico city. International journal of hygiene and environmental health. 2021;233:113695. 42 645 44. Lertxundi A, Andiarena A, Martínez MD, Ayerdi M, Murcia M, Estarlich M, et al. 43 44 646 Prenatal exposure to PM2.5 and NO2 and sex-dependent infant cognitive and motor 45 46 647 development. Environmental Research. 2019;174:114-21. 47

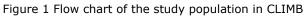
- ⁴⁸ 648 45. Iglesias-Vázquez L, Binter A-C, Canals J, Hernández-Martínez C, Voltas N, Ambros
 ⁵⁰ 649 A, et al. Maternal exposure to air pollution during pregnancy and child's cognitive, language,
 ⁵¹ and motor function: ECLIPSES study. Environmental Research. 2022;212:113501.
- 651 46. Wang H, Zhang H, Li J, Liao J, Liu J, Hu C, et al. Prenatal and early postnatal exposure
 652 to ambient particulate matter and early childhood neurodevelopment: A birth cohort study.
 653 Environmental Research. 2022;210:112946.
- ⁵⁸ 654 47. Zhu Y, Li X, Chen J, Gong W. Perinatal depression trajectories and child development
 ⁶⁰ 655 at one year: a study in China. BMC pregnancy and childbirth. 2024;24(1):176.

BMJ Open

2		
3 4	656	48. Wang A, Qi W, Liu H, Wan Y, Xu S, Xia W. Association of maternal exposure to
5	657	chlorpyrifos during pregnancy with neurodevelopmental abnormality in two-year-old children:
6 7	658	a survey in Wuhan city. Chinese Journal of Public Health. 2023;39(12):1590-5.
8 9	659	49. 谢松敏, 王鲜艳, 姚英民. 贝利婴幼儿发展量表在婴幼儿保健中的应用. 护理学报.
10 11	660	2006;13(4):76-7.
12 13	661	50. Kim E, Park H, Hong Y-C, Ha M, Kim Y, Kim B-N, et al. Prenatal exposure to PM10
14	662	and NO2 and children's neurodevelopment from birth to 24months of age: Mothers and
15 16	663	Children's Environmental Health (MOCEH) study. Science of The Total Environment.
17 18	664	2014;481:439-45.
19	665	51. Umezawa M, Onoda A, Korshunova I, Jensen AC, Koponen IK, Jensen KA, et al.
20 21	666	Maternal inhalation of carbon black nanoparticles induces neurodevelopmental changes in
22 23	667	mouse offspring. Particle and Fibre Toxicology. 2018;15:1-18.
24 25	668	52. Monk C, Lugo-Candelas C, Trumpff C. Prenatal developmental origins of future
26	669	psychopathology: mechanisms and pathways. Annual review of clinical psychology.
27 28	670	2019;15:317-44.
29 30	671	53. Xu R, Zhong Y, Li R, Li Y, Zhong Z, Liu T, et al. Association between exposure to
31	672	ambient air pollution and semen quality: A systematic review and meta-analysis. Science of
32 33	673	The Total Environment. 2023;870:161892.
34 35	674	54. Braun JM, Messerlian C, Hauser R. Fathers matter: why it's time to consider the impact
36 37	675	of paternal environmental exposures on children's health. Current epidemiology reports.
38	676	2017;4:46-55.
39 40	677	55. Ji X, Meng X, Liu C, Chen R, Ge Y, Kan L, et al. Nitrogen dioxide air pollution and
41 42	678	preterm birth in Shanghai, China. Environmental research. 2019;169:79-85.
43 44	679	56. Zhang Y, Wang J, Chen L, Yang H, Zhang B, Wang Q, et al. Ambient PM2. 5 and
45	680	clinically recognized early pregnancy loss: A case-control study with spatiotemporal exposure
46 47	681	predictions. Environment International. 2019;126:422-9.
48 49	682	57. Wu J-S, Liao X, Peng J, Huang X-L. Simulation and influencing factors of spatial
50	683	distribution of PM2. 5 concentrations in Chongqing. Huan Jing ke Xue= Huanjing Kexue.
	684	2015;36(3):759-67.
53 54	685	58. Lopuszanska U, Samardakiewicz M. The relationship between air pollution and
55 56	686	cognitive functions in children and adolescents: a systematic review. Cognitive and Behavioral
57	687	Neurology. 2020;33(3):157-78.
58 59 60	688	

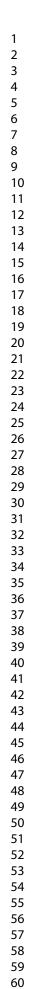
689	FIGURES
690	Figure 1. Flow chart of the study population in CLIMB
691	Figure 2. Study area and location of monitoring sites (OpenStreetMap contributors,
692	2015; https://data.nextgis.com/en/region/CN-50/)





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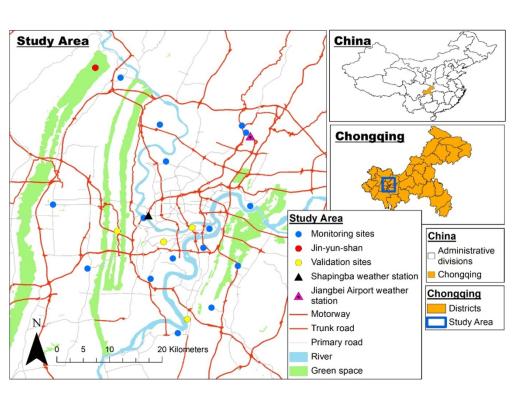


Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors, 2015; https://data.nextgis.com/en/region/CN-50/).

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Associations of air pollution exposures in preconception and pregnancy with birth outcomes and infant neurocognitive development: analysis of the Complex Lipids in Mothers and Babies (CLIMB) prospective cohort in Chongqing, China

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Supplement

eTable 1 Mental Development Index (Chinese version)

智力量表

(*可偶尔观察到)

序号	月龄	条目	计分
1	0.1	对铃声反应	
2	0.1	抱起时安静	
3	0.1	对摇鼓声反应	
4	0.1	对尖声反应: (电灯开关)	
5	0.1	短暂地注视红环	
6	0.2	短暂地注视人	
7	0.4	稍长时间地注视红环	
8	0.5	眼的水平协调活动(红环)	
9	0.7	眼的水平向天活动 (光)	
10	0.7	眼睛追随移动的人	
11	0.7	对说话声反应	
12	0.8	眼的垂直协调活动(光)	
13	0.9	发声一至两次 人名英格兰人 人名法格尔 人名法格尔 人名法格尔 人名法格尔 发展 人名法格尔 人名法格尔人名 人名法格尔人名 人名法格尔人名 人名法格尔人名 人名法格尔人名 人名法格尔人名 人名英格尔人名 人名法格尔人名 人名人名人名人名人名人名人名人名人名人名人名人名英格尔人名	
14	1	眼的垂直协调活动(红环)	
15	1.2	眼的旋转协调活动(光)	
16	1.2	眼的旋转细条活动(光环)	
17	1.3	*自由环视周围	
18	1.5	社交笑:测试者谈话与微笑时	
19	1.6	眼转向红环	
20	1.6	眼转向光	
21	1.6	*发声至少四次	
22	1.7	期待性兴奋	
23	1.7	对面部的纸有反应	
24	1.9	能用视觉辨认母亲	
25	1.9	社交笑:测试者微笑与安静时	
26	2	*对测试者的微笑和说话有发声反应	
27	2.1	*用眼睛寻找声源(详细说明)	
28	2.2	*发出两种不同的声音	
29	2.2	对手的遮蔽眨眼	
30	2.2	对面孔的消失有反应	
31	2.4	注视方木	
32	2.6	从一物转看另一物	
33	2.6	眼睛追随铅笔	
34	2.7	对抱起有预感性的调节反应	
35	2.9	目光追随横过桌面的球	
36	2.9	头追随悬摆的环	

37	3.1	头追随逐渐消失的勺子
38	3.2	操作红环
39	3.3	简单地玩摇鼓
40	3.4	高早地坑街鉄 *轻轻地抚摸桌沿
	3.4	* 老 年 地 仍 侯 未 加 () () () () () () () () () (
41		
42	3.5	→
43	3.6	→ 头转向摇鼓声
44	3.6	*手碰手的玩耍
45	3.6	将红环送入口中
46	3.7	伸手够悬环
47	3.8	看自己的手
48	4.2	接近悬环 (优势手)
49	4.4	*发声时的姿态(描述)
50	4.4	*主动抚摸桌沿
51	4.4	接近镜像
52	4.4	注意小糖丸
53	4.6	伸手取方木
54	4.7	喜欢嬉戏 🔨
55	4.9	伸手时眼手协调
56	4.9	拾起方木(优势手)
57	5	保持两块方木
58	5	持久地看红环
59	5	头部跟着掉下的勺转动
60	5	探索性地玩纸
61	5	对镜像微笑
62	5	坚持够东西
63	5.1	在小床内重新找到摇鼓
64	5.1	*辨别生人
65	5.4	举起倒扣的茶杯
66	5.5	*敲打玩耍
67	5.5	探索性地玩细绳
68	5.5	伸手取第二块方木
69	5.6	*由一手向另一手传递物体
70	5.8	*对产生响声感兴趣
71	5.9	灵巧而直接地拾起方木
72	6	*对镜像开玩笑
73	6	用把柄举起茶杯
74	6	寻找掉落的勺子
75	6.1	牵拉细绳获取红环
76	6.1	保留三块方木中的两块
77	6.6	*发出四个不同的音节
78	6.8	能配合玩游戏
10		恰当地牵拉细绳获取红环
70	/	
79 80	7 7.1	「山当地军拉圳绳获取红圻 玩摇铃,对细节感兴趣

82	7.4	有目的地摇铃
83	7.5	*选择性地倾听熟悉的词语
84	8	*对 da-da 或类同词
85	8.1	暴露玩具
86	8.2	注意测试者的乱写
87	8.3	将手指插入桩板洞中
88	8.6	观看书中图画
89	8.9	对他人的言语要求有反应
90	9.1	拿起茶杯获得方木
91	9.8	寻找盒子里面的东西
92	10.3	遵照命令将方木放入茶杯(放入数)
93	10.7	企图模仿乱写
94	10.8	模仿用勺子搅拌
95	10.9	遵照命令停止
96	10.9	推动小汽车
97	11	模仿地拍打哨娃
98	11.1	*重复引入发笑的把戏
99	11.2	解开裹着的方木
100	11.2	将三块方木放入杯中
101	11.4	*快速而不清的表达
102	11.4	揭开兰盒子的盖
103	11.5	翻开书页
104	11.5	摇晃悬环的
105	11.8	将骰子放入盒中(6个)
106	12	
107	12.2	模仿说单词(记录用过的词)
108	12.4	重复地插一根桩钉
109	12.5	用手势表达想要的东西
110	12.0	自动乱写
111	12.9	
112	13	搭两层塔
113	13.1	出示鞋子或其他衣服或自己的玩具
114	13.2	从瓶中移出小糖丸
115	13.3	掺九块方木放入杯中
116	14.3	*盖上圆盒
117	14.4	
118	14.8	用棍子够取玩具
119	15.4	搭三层塔
119	15.4	
120	16.1	指出娃娃身体的各部分:三个部位以上
121	16.3	新红模板:放置圆形模块
122	16.6	初红候做: 放置两个圆形模块
	10.0	
124		用笔模仿画一划
125	17.5	在 42 秒钟内插完桩钉

127	17.7	对娃娃执行指令(在通过部位打钩:椅、杯、鼻)
128	18.1	用语言表达要求
129	18.6	不用于一划的乱写?
130	18.8	兰色模板: 放置两个圆快和方块
131	18.8	指出三幅画
132	19.1	能说两个单词的句子
133	19.2	说出一副画名
134	19.2	说出两幅画名
135	19.3	找出两物
136	19.8	在 30 秒钟内插完桩钉
137	20.4	粉红模板:完成
138	20.4	搭六层塔
139	20.5	兰色模板,放置六个模块
140	21	指出五副画
141	21.1	说出三物名
142	21.2	勉强合格地安装破娃娃
143	21.2	区别两物:杯、盘、盒
144	22.8	辨认钟表: 第四张图 1, 2, 3, 4, 5
145	22.9	说出三幅画名
146	23.8	粉红模板(反转)
147	24.3	近似地安装破娃娃
148	24.6	区别三物:杯、盘、盒
149	24.7	兰色模板,在150秒钟内完成
150	25	搭八层塔
151	25.1	指出七副画
152	25.1	用方木搭火车
153	25.7	说出五副画名
154	26.3	模仿笔划:垂直线和水平线
155	27.1	辨认钟表:第2张图
156	27.6	理解两个方位词
157	28	在 22 秒钟内插完桩钉
158	28.5	兰色模板: 90秒钟内完成
159	29.5	折纸
160	29.6	兰色模板: 60秒钟内完成
161	30+	正确安装破娃娃
162	30+	"—"的概念
163	30+	理解三个方位词

eTable 2 Psychomotor Development Index (Chinese version)

运动量表

(*可偶尔观察到, △可在施测智力量表时观察到)

序号	月龄	条目	计分
1	0.1	抱起靠肩时抬头	
2	0.1	抱起靠肩时调整姿势	
3	0.1	侧头	
4	0.1	爬起	
5	0.8	△保留红环	
6	0.8	*伸臂玩耍	
7	0.8	*踢腿玩耍	
8	0.8	头起竖起:垂直位	
9	1.6	头部稳定地竖起	
10	1.7	抬头 (背悬位)	
11	1.8	由侧卧转向仰卧	
12	2.2	在俯卧位时用双臂撑起自己	
13	2.2	支撑下坐起	
14	2.5	保持头部稳定	
15	2.6	*双手张开占优势	
16	3.3	头平衡	
17	3.4	*尺侧一手掌抓握方木	
18	3.5	轻度支撑坐位	
19	4.3	*由仰卧转向侧卧	
20	4.7	努力想坐起	
21	5.0	部分的拇指相对(桡侧一手掌)拾起方木	
22	5.1	独坐片刻	
23	5.1	*单手抽取	
24	5.2	*转腕	
25	5.2	牵拉坐起	
26	5.6	△试图获取小糖丸	
27	5.7	独立 30 秒钟或以上	
28	5.8	由仰卧转向俯卧	
29	6.2	稳定地独坐	
30	6.5	独坐时协调好	
31	6.6	*舀起小糖丸	
32	6.6	△完全的拇指相对拾起方木	Ī
33	7	早期跨步运动	
34	7.5	牵拉站起	
35	7.6	*不完全的拇指相对抓糖丸	
36	7.6	走路之前的行进方式(俯卧、手膝、手足、其他)	
37	8.3	使两个勺子或方木在中线相碰	
38	8.5	跨步运动	

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39	8.6	自己坐起
40	8.6	借助家具站起
41	8.9	精细地抓糖丸(灵巧地钳夹)
42	9.6	拍手(中线技巧)
43	9.8	坐下
44	10	扶助下行走
45	11.1	独站
46	12	投球
47	12.1	独走
48	12.4	起立
49	13.2	扶助下右足独站
50	13.7	扶助下左足独站
51	14.1	侧身走
52	14.5	扶助上楼梯
53	14.7	倒退走
54	15.1	扶助下楼梯
55	17.6	试图站在行木上
56	18.7	左足独站 🚫
57	19.3	单足踏在行木上走
58	19.9	起立Ⅱ
59	20.1	右足独站
60	21.1	走直线:大致方向
61	23.1	行木:双足站立
62	24	踮脚走几步
63	24.3	独自上楼梯:双足
64	24.4	双足跳离地面
65	25.3	独自下楼梯
66	25.6	行木:企图跨步
67	25.6	倒行两米半
68	25.7	自第一级台阶下跳下
69	29.2	自第二级台阶下跳下
70	29.8	踮脚走两米半
71	29.9	跳远: 10 至 35cm (记录距离)
72	30+	起立: Ш
73	30+	上楼梯: 双足交替向前
74	30+	行木: 交替步伐走部分路程
75	30+	保持双足走在直线上(两米半)
76	30+	跳远: 35cm 至 60cm
77	30+	跳过: 5cm 高的绳子
78	30+	跳远: 60cm 至 85cm
79	30+	独脚跳两次以上
80	30+	下楼梯:双足交替向前
81	30+	跳过 20cm 高的绳子

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	Estimated exposure (µဋ/ฏิ)								
)									
	Ν	Minimum	25 th percentile	Mean ± SD	Mediang+JQR	75 th percentile	Maximum		
Estimated exposure to PM _{2.5}					to te				
90 days prior to conception	1,174	38.17	44.00	52.91 ± 10.99	wnloaded t nt Superied 48.4 and 48.4	62.06	80.53		
First trimester	1,174	37.26	43.77	52.07 ± 10.98	4/.2 6 5 .31	61.08	82.41		
Second trimester	1,174	38.46	47.57	58.64 ± 12.21	57.9 [°] B.∰ <mark>₽</mark> .62	67.19	90.02		
Third trimester	1,174	37.03	47.25	61.83 ± 16.04	58.8 ± 58.7	75.95	96.48		
Total pregnancy	1,174	46.69	54.85	57.48 ± 3.97	57.3 ± ± .76	60.61	66.98		
Estimated exposure to NO ₂				Via	ainin br				
90 days prior to conception	1,174	25.86	45.49	49.59 ± 6.34	49.94 ± 8.27	53.76	70.48		
First trimester	1,174	20.81	44.60	48.8 ± 6.43	48.9 2 ± 8 .51	53.10	69.31		
Second trimester	1,174	28.93	47.18	50.98 ± 6.23	51.2 ₽ ± ξ .72	54.90	70.42		
Third trimester	1,174	20.57	47.20	51.79 ± 6.78	52.45 ± \$ 47	56.67	75.12		
Total pregnancy	1,174	27.50	47.89	50.52 ± 5.08	50.48 ± \$51	53.40	67.53		
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		BMJ Open son's correlations of PM2.5 and NO2 between each of the five different pregnancy time									Page 44 of 45
	eTable 4 Pearson's correla	tions of PM2.5 a	nd NO2 betw	ween each o	f the five di	fferent preg	yright, inceperation nancy timeperation	ods (N = 1,	,174)		
	Estimated exposure to			PM _{2.5}			ng for		NO ₂		
		90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy	90 days p	First trimester	Second trimester	Third trimester	Total pregnancy
PM _{2.5}	90 days prior to conception	1					to conceptible from http://bmjopen.bmj.com/ on Spelated to text and data mining, Altraining, and sim 0.554 training, 0.714 on 0.678 to 0.678 to				
	First trimester	-0.065	1				ent S Put S Souther to the second sec				
	Second trimester	-0.779	-0.2012	1			uperi vt an				
	Third trimester	0.288	-0.7613	-0.1688	1		d dat				
	Total pregnancy	-0.534	-0.2709	0.6838	0.3858	1	a mir				
NO ₂	90 days prior to conception	0.6383	0.0684	-0.4588	0.3714	0.0376	1 g,				
	First trimester	0.1537	0.6352	-0.0159	-0.4927	-0.0633	0.554 ع ير الم	1			
	Second trimester	-0.431	0.0714	0.6269	-0.0133	0.7251		0.5399	1		
	Third trimester	0.3027	-0.5213	0.0528	0.6817	0.4432	0.714 9g G	0.2159	0.5145	1	
	Total pregnancy	0.0057	0.0781	0.2862	0.0737	0.4779	0.6786mil	0.7435	0.8755	0.7331	1
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1 2 3 4 5	eTable 5 Associations b	between PM2.5 and NO2 expo	sure in different preg	gnancy periods and ac	/bmjopen-2023-080175 o 1 by copyright, including dverstiding	mes (unadjusted n	10dels)
6 7		Mean dif	fference		for c	Odd ratios	
7 8 F 9 10	Per IQR increase in	Birth weight, grams (95% CI) (N=941)	Birth length, cm (95% CI) (N=927)	PTB (case: 33) (95% CI) (N=945)	LB W Statese: 30) (201)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
Estimated	90 days prior to conception	9.28 (-31.26, 49.83)	-0.09 (-0.27, 0.09)	0.98 (0.56, 1.74)	1.35 4 (9.7 2), 2.36)	1.2 (0.87, 1.64)	0.98 (0.68, 1.41)
12 13exposure	First trimester	21.95 (-16.90, 60.80)	0.14 (-0.03, 0.31)	0.98 (0.57, 1.70)	1 (6.57 0 1.77)	0.97 (0.71, 1.33)	0.78 (0.54, 1.13)
14 15 ^{to} PM _{2.5}	Second trimester	-18.21 (-57.78, 21.37)	0.04 (-0.13, 0.21)	0.85 (0.48, 1.50)	0.61 م (م 2 م م م م الم م م م م م م م م م م م م م م	0.92 (0.67, 1.27)	1.33 (0.94, 1.89)
	Third trimester	-37.38 (-81.43, 6.68)	-0.32 (-0.51, -0.13)	1.35 (0.74, 2.47)	1.51	1.08 (0.76, 1.54)	1.12 (0.76, 1.66)
16 17	Total pregnancy	-20.02 (-55.69, 15.65)	-0.1 (-0.26, 0.05)	0.81 (0.49, 1.33)	0.69a (64), 1.16)	1 (0.75, 1.34)	1.2 (0.87, 1.66)
1 Estimated	90 days prior to conception	-13.23 (-45.50, 19.03)	-0.12 (-0.26, 0.02)	1.2 (0.76, 1.89)	1.62	1.21 (0.93, 1.57)	1.24 (0.92, 1.66)
19 20 ^{exposure}	First trimester	0.3 (-32.36, 32.96)	0.08 (-0.06, 0.22)	1.01 (0.64, 1.60)	1.15 (0.7), 1.86)	1.17 (0.90, 1.52)	1.27 (0.94, 1.71)
20^{Mposure} 21 to NO ₂	Second trimester	-22.85 (-53.39, 7.70)	-0.04 (-0.17, 0.09)	1.11 (0.72, 1.70)	1.08 4 0.00, 1.69)	1.06 (0.83, 1.36)	1.46 (1.10, 1.93)
21 to NO ₂ 22	Third trimester	-32.72 (-67.16, 1.72)	-0.16 (-0.32, -0.01)	1.13 (0.69, 1.85)	1.35	1.24 (0.94, 1.65)	1.58 (1.14, 2.18)
23	Total pregnancy	-16.58 (-43.35, 10.20)	-0.03 (-0.15, 0.09)	1.03 (0.71, 1.50)	1.13 (0. 5, 1.69)	1.16 (0.93, 1.44)	1.44 (1.13, 1.85)
All signific	cant findings in the table are be	old.			, an		
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42				0	n/ on June 12, 2025 at Agence Bibliographique de d similar technologies.		
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1					right			
2 3	aTable 6 Associations be	atwaan PM25 and NO2 ave	acture in different prog	nancy pariods and a	i o	omas (co-avnosura	models)	
eTable 6 Associations between PM _{2.5} and NO ₂ exposure in different pregnancy periods and adverse birgh outcomes (co-exposure models)								
6		Mean difference		· ·	Odd ratios			
7	Per IQR increase in	Birth weight, grams	Birth length, cm	PTB (case: 33)	LBW (CA E: 30)	LGA (case: 108)	SGA (case: 84)	
9		(95% CI)	(95% CI)	(95% CI)	(99 % KI)	(95% CI)	(95% CI)	
9 10		(N=941)	(N=927)	(N=945)	(Kaja to jeta)	(N=945)	(N=945)	
1 Estimated	90 days prior to conception	75.00 (-9.86, 159.86)	0.23 (-0.14, 0.60)	0.98 (0.56, 1.89)	0.41 (8.34) 1.22)	1.14 (0.55, 2.40)	1.18 (0.48, 2.92)	
12 exposure	First trimester	19.59 (-71.23, 110.41)	0.00 (-0.40, 0.39)	0.97 (0.26, 3.65)	0.66 (0 .745 3.05)	0.67 (0.32, 1.42)	0.73 (0.28, 1.93)	
13 ¹ 14to PM _{2.5}	Second trimester	-25.62 (-104.32, 53.09)	0.08 (-0.26, 0.42)	1.34 (0.37, 4.86)	0.94 (🖉 🖉 4.21)	0.83 (0.42, 1.62)	0.69 (0.34, 1.40)	
1410 F 1012.5	Third trimester	13.77 (-72.33, 99.86)	-0.2 (-0.58, 0.17)	1.12 (0.31, 4.07)	0.94 (2.35)	1.00 (0.48, 2.12)	0.57 (0.26, 1.23)	
16	Total pregnancy	21.13 (-36.41, 78.67)	0.02 (-0.23, 0.27)	0.73 (0.33, 1.61)	0.52 (👰 🧏 🛱 1.15)	0.98 (0.60, 1.61)	0.55 (0.32, 0.96)	
¹ Estimated	90 days prior to conception	-18.63 (-64.02, 26.76)	-0.09 (-0.29, 0.10)	1.24 (0.61, 2.49)	1.3 (G. 64 2.64)	1.27 (0.84, 1.90)	1.39 (0.90, 2.15)	
18 19exposure	First trimester	-14.53 (-61.15, 32.09)	0.05 (-0.16, 0.25)	0.91 (0.45, 1.83)	1.14 🔁 🧏 2.37)	1.33 (0.89, 2.00)	1.70 (1.07, 2.69)	
20	Second trimester	-14.46 (-57.45, 28.54)	-0.08 (-0.26, 0.11)	1.22 (0.63, 2.36)	1.36 (0.68 2.71)	1.27 (0.87, 1.87)	1.50 (1.00, 2.24)	
$20 \text{ to } \text{NO}_2$	Third trimester	-13.13 (-64.87, 38.62)	0.04 (-0.18, 0.27)	0.77 (0.35, 1.67)	0.97 (9.43 2.16)	1.41 (0.90, 2.23)	1.77 (1.08, 2.91)	
22 23	Total pregnancy	-15.02 (-49.33, 19.30)	0.00 (-0.15, 0.15)	1.08 (0.64, 1.80)	1.28 (2.18)	1.21 (0.90, 1.63)	1.60 (1.15, 2.23)	
2All significant findings in the table are bold.								
² Models adjusted for maternal age at enrolment, infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly house hour income level, and season of births, and adjusted								
²⁶ for the other air pollutant								
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