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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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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: in the maternity clinics of two centres (the First Affiliated Hospital of Chongqing Medical University (FCQMU) and Chongqing Health Centre for Women and Children (CHC)).

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.

Interventions: Air pollution concentrations at their home addresses, including particulate matter (PM) with diameter $\leq 2.5\mu\text{m}$ (PM_{2.5}) and nitrogen dioxide (NO₂), during pre-conception and each trimester period (T1, T2, T3) were estimated using land-use regression (LUR) models.

Primary and secondary 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 during the whole pregnancy (Odd ratio (OR): 1.60, 99% confidence interval (CI): 1.03, 2.48) after co-adjusted for PM_{2.5}. Both PM_{2.5} and NO₂ exposure in the 90 days prior to conception (but not during) were associated with lower PDI score (β : -6.15, 99% CI: -9.69, -2.61; β : -2.83, 99% CI: -4.27, -0.93, respectively).

Conclusions: NO₂ levels during pregnancy were associated with increased risk of SGA, while both PM_{2.5} and NO₂ pre-conception were associated with adverse neurodevelopment outcomes at 12 months of age.

Keywords: Air pollution; birth outcomes; child cognition

Article summary

Strength and limitation

- 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.
- Our sample size was relatively small, limiting the statistical power to assess several outcomes.
- We defined exposure windows for clinically-defined trimesters.
- The performance of the NO₂ spatiotemporal model was moderate (COR-R²: 0.39), which may introduce exposure misclassification and therefore bias in the coefficients.

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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 PM_{2.5} 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).

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 pollutants exposure and neurodevelopmental outcomes (5, 16). Moreover, most of these studies were conducted in relatively developed countries where pollution is lower; little evidence has come from populations in developing countries such as China (17-20), that are more likely to experience more severe air pollution exposure.

The current study leveraged the Complex Lipids in Mothers and Babies (CLIMB) cohort, a prospective birth cohort recruited in Chongqing, China(21), with trimester-specific maternal PM_{2.5} and NO₂ air pollution exposure derived from a spatio-temporal LUR model (22). The aim of this analysis was to examine the association between PM_{2.5} and NO₂ air pollution 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 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.

Methods

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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2
3 128 From September 2015 to November 2016, a total of 1,500 women were recruited into the cohort.
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5 129 Participants attended six visits at the First Affiliated Hospital of Chongqing Medical University
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7 130 and Chongqing Health Centre for Women and Children: 11–14 weeks' gestation (visit 1), 22–
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9 131 28 week's gestation (visit 2), 32–34 week's gestation (visit 3), at birth (visit 4), 6 weeks
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11 132 postnatal (visit 5), and 12 months postnatal (visit 6).
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13 133 Women who withdrew from the study (n = 146), terminated their pregnancy (n = 29),
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15 134 miscarried (n = 12) or were lost to follow-up (n = 40) were excluded from the analysis, leaving
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17 135 a sample size of 1,273 women. Analyses were restricted to mothers whose detailed residential
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19 136 addresses during pregnancy were known (**Figure 1**). A total of 1,174 live births were thus
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21 137 included in the pregnancy and neonatal outcomes analysis. Subsequently, at 1 year follow-up,
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23 138 946 children were included in the analysis of neurodevelopment outcomes.

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24 139
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26 140 **Exposure assessment**

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28 141 The address of participants was collected at the first visit. Exposure assessment based on
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30 142 spatiotemporal land use regression (LUR) models for PM_{2.5} and NO₂ were developed for the
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32 143 study region. The study area focused on the urban center of the Chinese municipality of
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34 144 Chongqing (**Figure 2**). A description of the methodology of exposure modelling has been
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36 145 reported previously (22). Briefly, the models included both spatial and temporal components
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38 146 of exposure. PM_{2.5} and NO₂ concentration data were collected from 17 routine monitoring sites
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40 147 operated by the Chongqing Environmental Monitoring Center in 2015-2016. For the spatial
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42 148 component of models, we calculated annual average concentrations of each pollutant in 2015,
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44 149 and fit linear regression models using five groups of geographic data (road network, land use,
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46 150 topography, vegetation, and population density) as spatial predictor variables. For the temporal
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48 151 component of models, we calculated the residuals from the spatial component at each
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50 152 monitoring site on a daily basis by subtracting the predicted annual average concentration from
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52 153 the observed daily average concentrations measured in 2015 and 2016, and then fitted
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54 154 generalised additive models (GAM) using seven groups of meteorological data (temperature,
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56 155 amount of rainfall, rainfall events, relative humidity, horizontal visibility, wind direction and
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58 156 wind speed) as temporal predictor variables. The meteorological variables were used to account
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60 157 for the influence of weather on the change in air pollution concentration over time. To account
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159 158 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 (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.

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

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.

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).

Statistical analyses

Data were described in terms of mean ± 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.

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

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Results

Study Participants

Participant characteristics are presented in **Table 1**. Of those participating women, the mean age was 28 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 MDI score was 87.4 (SD: 14.9).

Exposure assessment

Median PM_{2.5} exposure levels were 57.31 µg/m³ (IQR: 5.76) and median NO₂ exposure levels were 50.46 µg/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 µg/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**).

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, 99% CI: -0.57, -0.07; per IQR increase). A risk between SGA and increases in NO₂ (per IQR) was found in T2 (OR: 1.46, 99% CI: 1.01, 2.11), T3 (OR: 1.58, 99% CI: 1.03, 2.42) and in the whole pregnancy period (OR: 1.44, 99% CI: 1.04, 2.00). 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 slightly reduced effect size for NO₂ and SGA in the whole pregnancy period (OR: 1.33, 99% CI: 0.92, 1.75) compared with the unadjusted model. We observed no evidence of associations with birth length in the adjusted models. After

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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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3 289 exposure to NO₂ in the whole pregnancy periods after adjusted for maternal age at enrolment,
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5 290 infant's sex, maternal BMI at 11–14 weeks' gestation, primiparity, monthly household income
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7 291 level, and season of births and PM_{2.5}. For childhood cognitive development, increased exposure
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9 292 to PM_{2.5} and NO₂ in the 90 days prior to conception were both associated with lower PDI scores,
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11 293 with the effect size per IQR being higher for PM_{2.5} than for NO₂. We also found a positive
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13 294 association between PM_{2.5} exposures in second trimester with PDI. While SGA was associated
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15 295 with NO₂ exposures, SGA was not found to mediate the effects of PM_{2.5} and NO₂ on BSID
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17 296 scores in this study.
18
19 297 Many studies from other geographic areas, including Europe (32-34), the United States (24,
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21 298 26), and Asia (17, 35-37) have found that prenatal air pollution exposure has a negative impact
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23 299 on a variety of neurodevelopmental outcomes. Our finding of a negative association between
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25 300 prenatal NO₂ air pollution exposure and infant neurocognitive development is consistent with
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27 301 these reports. A recent Chinese birth cohort study of 15,778 child-mother pairs in Foshan
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29 302 reported that maternal NO₂ exposure during pregnancy was associated with increased risk of
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31 303 suspected developmental delay (OR: 1.06, 95% CI: 0.94, 1.19) measured by a five-domain
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33 304 scale and developmental quotient (DQ) (17). A birth cohort study of 520 mother-child pairs in
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35 305 South Korea reported that maternal NO₂ exposure during pregnancy was associated with
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37 306 impairment of psychomotor development ($\beta = -1.30$, $p = 0.05$) but – as in the present study -
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39 307 not with cognitive function ($\beta = -0.84$, $p = 0.20$) (35). However, results from previous research
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41 308 varied by air pollutants. For example, a Chinese study of 1193 mother-newborn pairs in
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43 309 Changsha found significant associations between PM_{2.5} exposure in trimester 2 and lower
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45 310 neurobehavioral developmental scores, while other air pollutants such as PM₁₀, carbon
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47 311 monoxide (CO), and Sulfur dioxide (SO₂) had null or even reverse associations. In this study,
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49 312 we observed that the negative effect of NO₂ exposure during pregnancy on PDI is significant
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51 313 at 5% level, whereas no such effect was found for PM_{2.5}; in the co-exposure model, this
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53 314 negative effect of NO₂ was stronger and became significant at 1% level after adjustment for
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55 315 PM_{2.5}. This heterogeneity may relate to the time of exposure assessment, the type of
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57 316 instruments or evaluators, and the levels of air pollution. In addition, air pollution mixtures
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59 317 may have differed among the study regions, thus there are several potential explanations for
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61 318 the heterogeneity of the findings.
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63 319 To date, most studies on prenatal air pollution exposure and child neurodevelopment have been
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65 320 conducted in developed countries with relatively low levels of air pollution. In this study, the
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67 321 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 $\mu\text{g}/\text{m}^3$, IQR: 5.51) compared to studies in developed countries such as Europe and the United States. In a multi-centre European cohort, the mean $\text{PM}_{2.5}$ and NO_2 exposure levels during pregnancy were 13.4 $\mu\text{g}/\text{m}^3$ and 11.5 $\mu\text{g}/\text{m}^3$ (32). Researchers found that the psychomotor development score significantly decreased by 0.68 points (95% CI: -1.25, -0.11) for every 10 $\mu\text{g}/\text{m}^3$ increase in NO_2 , and there was also a non-significant decrease of 1.64 points (95% CI: -3.47, 0.18) for every 5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during pregnancy (32). Noticeably, we did not find associations of either NO_2 or $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$, PM_{10} , coarse particles, NO_2 and nitrogen oxides (NO_x) among 9482 children between 1 and 6 years; the authors found nonsignificant positive associations between prenatal $\text{PM}_{2.5}$ exposure and normal neurodevelopment (β : 1.64, 95% CI: -3.47, 0.18; per 5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$) (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 PM_{10} , $\text{PM}_{\text{coarse}}$, $\text{PM}_{2.5\text{absorbance}}$, NO_2 , NO_x , and Ozone (O_3) were linked to lower motor function in children, except for $\text{PM}_{2.5}$ (41). The inconsistent findings could be because of heterogeneity between studies in terms of exposure (e.g., exposure assessment methods used, $\text{PM}_{2.5}$ exposure levels, or composition of $\text{PM}_{2.5}$).

Aside from the conflicting findings regarding prenatal $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ could potentially induce maternal immune activation during pregnancy (42). Higher levels of cytokines or reactive oxygen species may

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3 355 potentially interfere fetal neurodevelopment through three mechanisms: crossing the placental
4 356 barrier into the fetal body, inducing fetal immune dysregulation, and contributing to inadequate
5 357 placental perfusion that affects nutritional processes and oxygenation of maternal blood(43).
6 358 More research is needed to investigate trimester effects of air pollution on neurodevelopment
7 359 and provide better understanding on the underlying biological mechanisms. Our study is the
8 360 first to consider an exposure window 90 days prior to conception for NO₂. A novel observation
9 361 is that effects of NO₂ or PM_{2.5} air pollution on child cognition can be seen at least 90 days prior
10 362 to conception, representing a potentially vulnerable periods in relation to air pollution on
11 363 neurodevelopment. Similar results were found in previous study recruited 1329 mother-child
12 364 pairs in Wuhan, China (12). This study reported a higher level of PM_{2.5} during preconception
13 365 (Median: 76.1 µg/m³) and in the first trimester (Median: 82.3 µg/m³). This study found for each
14 366 doubling of PM_{2.5} exposure during preconception, children's PDI scores was reduced by 8.23
15 367 (95% CI: -10.01, -6.44) points. A potential explanation is that preconception air pollution
16 368 exposures induce genetic and epigenetic alterations in sperm, that increase the risk of adverse
17 369 health outcomes in offspring(44, 45). To date, all studies examined the effect of maternal
18 370 preconception exposure while omitting paternal exposures (16). Future studies should consider
19 371 the effect of preconception paternal exposure in relation to childhood health outcomes.
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22 372 This study has several strengths. We developed an LUR model to capture spatial and temporal
23 373 variations of air pollution at individual level to reduce exposure misclassification if using
24 374 monitoring stations. This is one of the few studies to investigate both pre-conception and
25 375 prenatal PM_{2.5} and NO₂ exposure with neurodevelopment outcomes among young infants, in
26 376 the context of a relatively high air pollution urban environment.
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29 377 A major limitation of this study was that our sample size was relatively small, limiting the
30 378 statistical power to assess several outcomes, although the higher exposures in Chongqing than
31 379 in some other studies may increase probability of detecting effects. In terms of limitations, due
32 380 to a lack of information on participant time-activity patterns, exposure estimates in this study
33 381 refer only to ambient concentrations at home addresses, and no other activity spaces (e.g.,
34 382 indoor, workplace, commuting) were considered. We may have thus underestimated total air
35 383 pollution exposure. Second, we defined exposure windows for clinically-defined trimesters;
36 384 sensitive periods may be shorter or longer than 3 months, or they may exist in the overlap of
37 385 multiple trimesters. However, we were unable to investigate the sensitive time windows using
38 386 established methods such as distributed lag non-linear models due to the lack of highly time-
39 387 resolved air pollution estimates. Third, the performance of the NO₂ spatiotemporal model was

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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 been found particularly harmful to neurodevelopment in children (46).

Conclusion

This study provides evidence for an association between NO₂ exposure pre- and during pregnancy with birth and neurodevelopmental outcomes in a birth cohort in Chongqing, China. Exposure to NO₂ and PM_{2.5} exposure before pregnancy was associated with a lower psychomotor development score and further studies are warranted.

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

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Declarations

Ethics approval and consent to participate

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

Availability of data and materials

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

Conflicts of interests

The authors declare that they have no conflicts of interests.

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Author statement

Y. X., T.L.H., H.Z. and P.B. 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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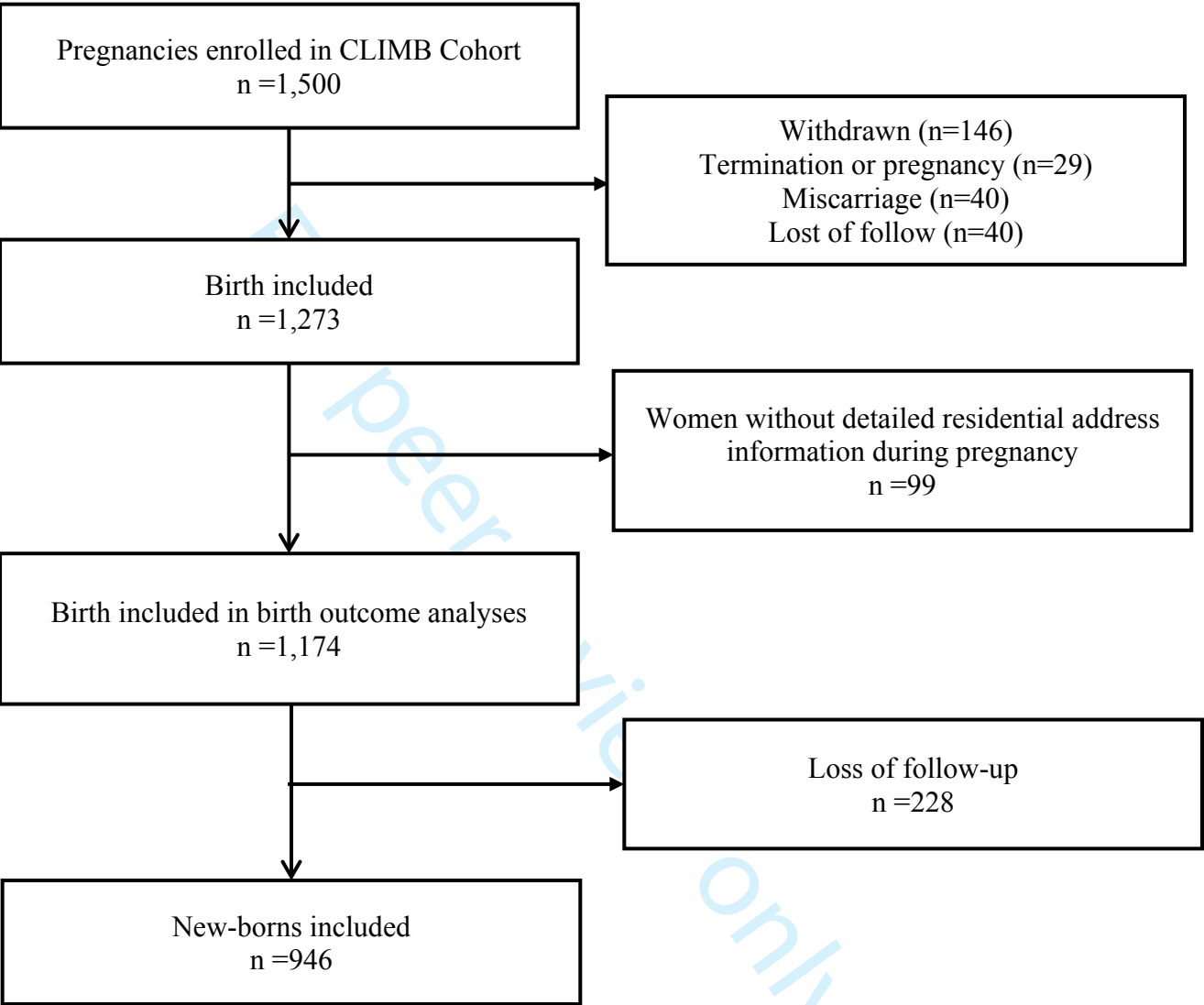
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Tables and figures

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/>).

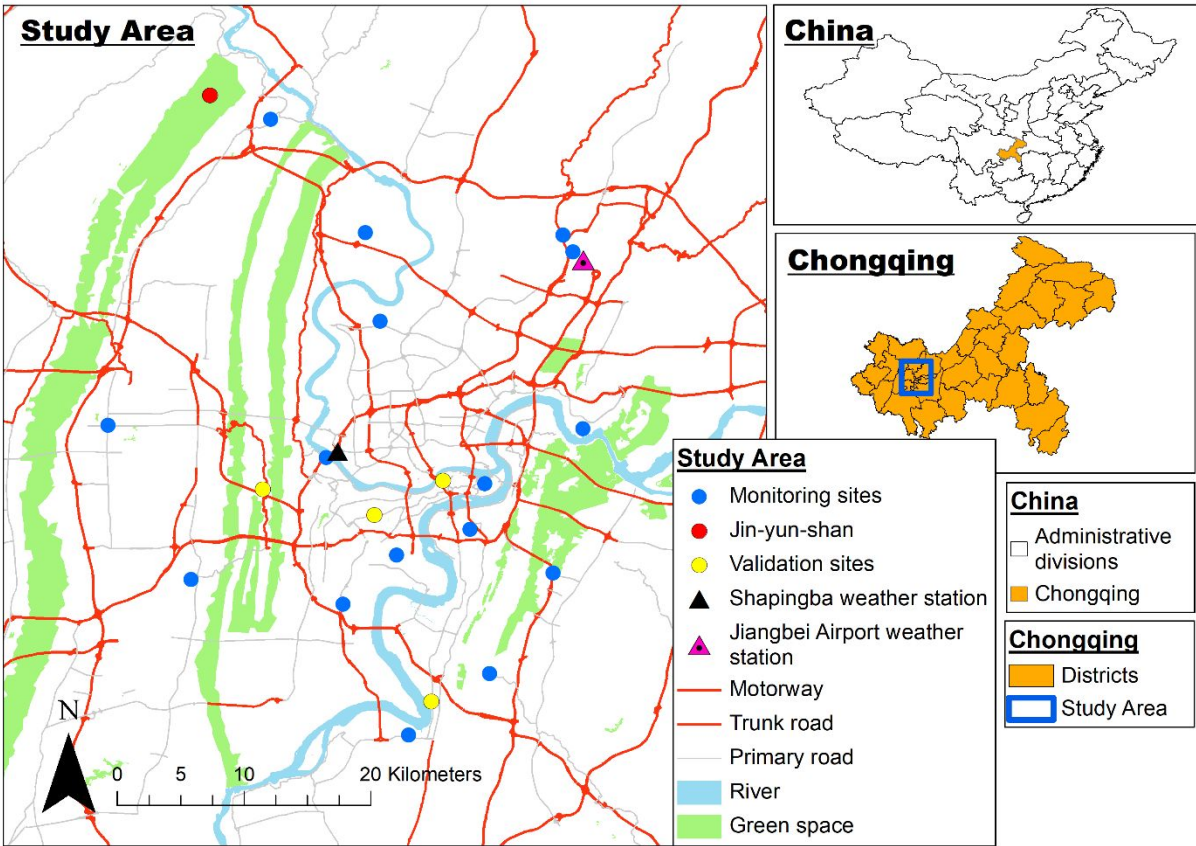


Table 1 Characteristics of study sample in the CLIMB cohort (N = 1,174)

Characteristic of mothers	N	n (%) or mean ± SD	Characteristic of child	N	n (%) or mean ± SD
Maternal age (Years)	1,174	28.7 ± 3.5	(week)	1,174	39.4 ± 1.5
BMI (kg/m²)	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%)	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		561 (47.9%)
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		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%)
Job	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%)
4000-7000 RMB		292 (30.9%)	Autumn (Sep-Nov)		198 (16.87%)
7000-10000 RMB		139 (14.7%)	Winter (Dec-Feb)		302 (25.72%)

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Table 2 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (adjusted models)

		Mean difference				Odd ratios	
		Birth weight, grams	Birth length, cm	PTB (case: 33)	LBW (case: 10)	LGA (case: 108)	SGA (case: 84)
		99% CI	99% CI	99% CI	99% CI	99% CI	99% CI
Per IQR increase in		(N=941)	(N=927)	(N=945)	(N=945)	(N=945)	(N=945)
Estimated exposure to PM _{2.5}	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 (0.16, 1.16)	1.4 (0.59, 3.33)	1.66 (0.58, 4.73)
	First trimester	6.21 (-99.01, 111.42)	0.04 (-0.42, 0.50)	0.88 (0.19, 4.02)	0.76 (0.16, 3.44)	0.86 (0.36, 2.05)	1.33 (0.45, 3.95)
	Second trimester	-37.64 (-129.82, 54.54)	0.02 (-0.38, 0.42)	1.62 (0.37, 7.05)	1.34 (0.22, 8.22)	1 (0.46, 2.20)	0.94 (0.41, 2.15)
	Third trimester	4.2 (-97.55, 105.95)	-0.17 (-0.62, 0.27)	0.92 (0.20, 4.17)	0.92 (0.21, 4.16)	1.29 (0.53, 3.13)	0.83 (0.33, 2.06)
	Total pregnancy	8.01 (-56.57, 72.59)	0.02 (-0.27, 0.30)	0.77 (0.31, 1.91)	0.62 (0.21, 1.66)	1.15 (0.65, 2.02)	0.84 (0.45, 1.57)
Estimated exposure to NO ₂	90 days prior to conception	-1.03 (-54.75, 52.68)	-0.04 (-0.27, 0.20)	0.84 (0.37, 1.91)	1.04 (0.41, 2.62)	1.31 (0.82, 2.10)	1.45 (0.88, 2.38)
	First trimester	-9.78 (-63.78, 44.22)	0.04 (-0.19, 0.28)	0.9 (0.41, 2.00)	1.03 (0.41, 2.62)	1.21 (0.76, 1.92)	1.57 (0.94, 2.62)
	Second trimester	-20.82 (-71.18, 29.54)	-0.06 (-0.28, 0.16)	1.31 (0.61, 2.81)	1.34 (0.61, 2.88)	1.21 (0.78, 1.89)	1.36 (0.85, 2.19)
	Third trimester	-9.5 (-70.66, 51.65)	-0.01 (-0.28, 0.26)	0.79 (0.32, 1.97)	0.95 (0.33, 2.73)	1.42 (0.83, 2.42)	1.51 (0.84, 2.71)
Total pregnancy		-8.45 (-46.96, 30.06)	0 (-0.17, 0.17)	0.97 (0.54, 1.74)	1.04 (0.57, 1.89)	1.2 (0.86, 1.69)	1.33 (0.92, 1.91)

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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Table 3 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and BSID scores (adjusted models)

		Mean difference	
		MDI 99% CI (N=946)	PDI 99% CI (N=946)
Per IQR increase in			
Estimated exposure to PM _{2.5}	90 days prior to conception	-1.98 (-6.21, 2.25)	-6.15 (-9.69, -2.61)
	First trimester	-1.66 (-6.08, 2.76)	-2.11 (-5.84, 1.62)
	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 exposure to NO ₂	90 days prior to conception	-0.72 (-2.98, 1.55)	-2.83 (-4.72, -0.93)
	First trimester	0.59 (-1.68, 2.86)	-1.91 (-3.83, 0.00)
	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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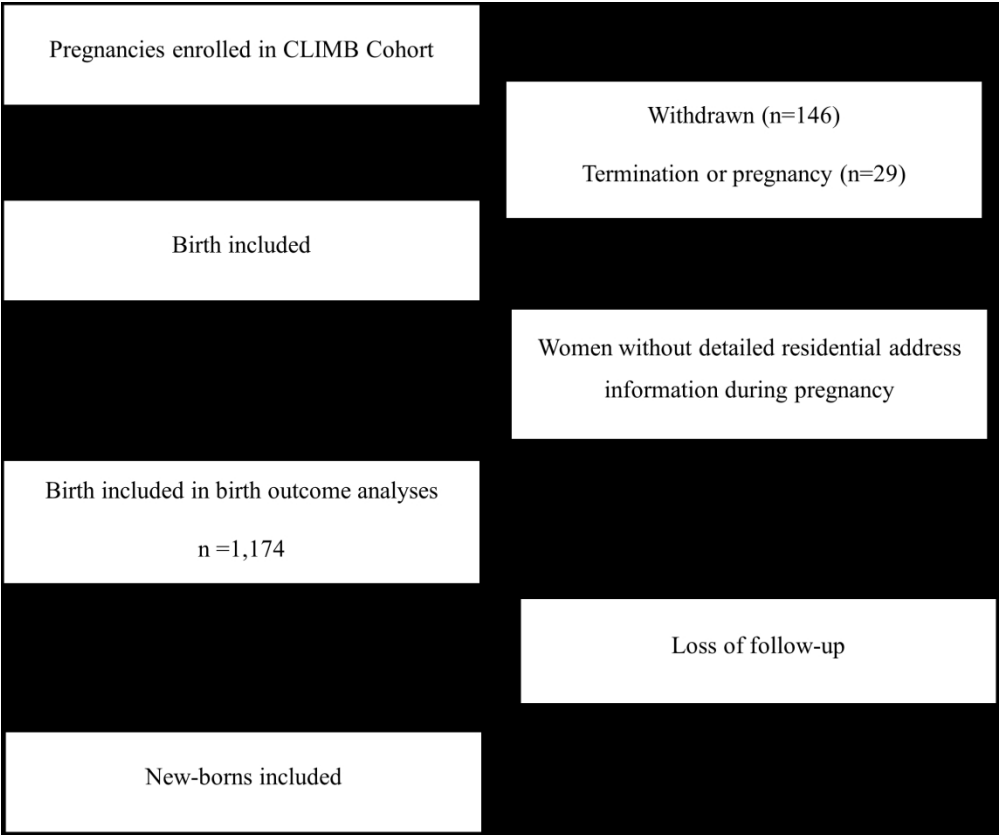


Figure 1 Flow chart of the study population in CLIMB

441x367mm (130 x 130 DPI)

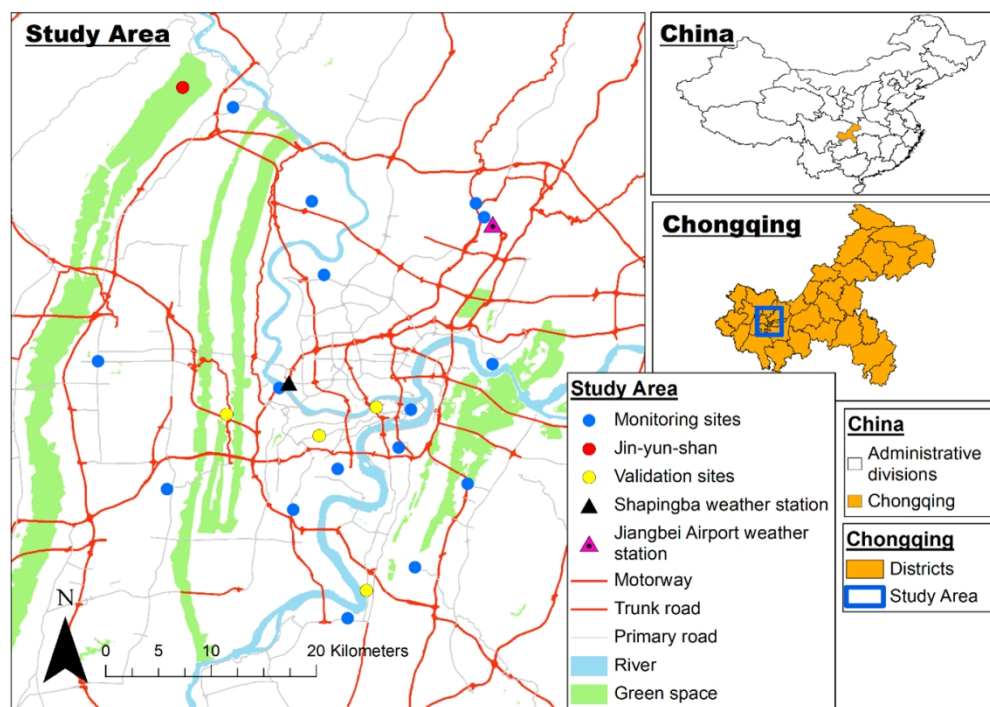


Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors, 2015; <https://data.nextgis.com/en/region/CN-50/>).

402x284mm (87 x 87 DPI)

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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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	
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	
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）	
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+	“一”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，Δ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	Δ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	
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	辅助下行走	
45	11.1	独站	
46	12	投球	
47	12.1	独走	
48	12.4	起立 I	
49	13.2	辅助下右足独站	
50	13.7	辅助下左足独站	
51	14.1	侧身走	
52	14.5	辅助上楼梯	
53	14.7	倒退走	
54	15.1	辅助下楼梯	
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：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	
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	

eTable 3 Distributions of PM_{2.5} and NO₂ exposure level in 90 days prior to conception, each trimester (T1, T2, and T3) and combined across whole pregnancy period (WP) (n = 1,174)

Estimated exposure (µg/m ³)							
	N	Minimum	25th percentile	Mean ± SD	Median (IQR)	75th percentile	Maximum
Estimated exposure to PM _{2.5}							
90 days prior to conception	1,174	38.17	44.00	52.91 ± 10.99	48.43 (40.07-57.07)	62.06	80.53
First trimester	1,174	37.26	43.77	52.07 ± 10.98	47.26 (39.31-56.31)	61.08	82.41
Second trimester	1,174	38.46	47.57	58.64 ± 12.21	57.97 (47.62-66.32)	67.19	90.02
Third trimester	1,174	37.03	47.25	61.83 ± 16.04	58.81 (42.7-74.9)	75.95	96.48
Total pregnancy	1,174	46.69	54.85	57.48 ± 3.97	57.31 (51.57-63.06)	60.61	66.98
Estimated exposure to NO ₂							
90 days prior to conception	1,174	25.86	45.49	49.59 ± 6.34	49.94 (41.87-58.01)	53.76	70.48
First trimester	1,174	20.81	44.60	48.8 ± 6.43	48.92 (41.85-55.99)	53.10	69.31
Second trimester	1,174	28.93	47.18	50.98 ± 6.23	51.20 (44.72-57.68)	54.90	70.42
Third trimester	1,174	20.57	47.20	51.79 ± 6.78	52.45 (45.97-58.93)	56.67	75.12
Total pregnancy	1,174	27.50	47.89	50.52 ± 5.08	50.41 (44.51-56.31)	53.40	67.53

eTable 4 Pearson’s correlations of PM_{2.5} and NO₂ between each of the five different pregnancy time periods (N = 1,174)

Estimated exposure to		PM _{2.5}					NO ₂				
		90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy	90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy
PM _{2.5}	90 days prior to conception	1									
	First trimester	-0.065	1								
	Second trimester	-0.779	-0.2012	1							
	Third trimester	0.288	-0.7613	-0.1688	1						
	Total pregnancy	-0.534	-0.2709	0.6838	0.3858	1					
NO ₂	90 days prior to conception	0.6383	0.0684	-0.4588	0.3714	0.0376	1				
	First trimester	0.1537	0.6352	-0.0159	-0.4927	-0.0633	0.5545	1			
	Second trimester	-0.431	0.0714	0.6269	-0.0133	0.7251	0.3345	0.5399	1		
	Third trimester	0.3027	-0.5213	0.0528	0.6817	0.4432	0.7149	0.2159	0.5145	1	
	Total pregnancy	0.0057	0.0781	0.2862	0.0737	0.4779	0.6786	0.7435	0.8755	0.7331	1

eTable 5 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (unadjusted models)

		Mean difference		Odd ratios			
		Birth weight, grams	Birth length, cm	PTB (case: 33)	LBW (case: 100)	LGA (case: 108)	SGA (case: 84)
		99% CI	99% CI	99% CI	99% CI	99% CI	99% CI
Per IQR increase in		(N=1,165)	(N=1,149)	(N=1,174)	(N=1,174)	(N=1,174)	(N=1,174)
Estimated exposure to PM _{2.5}	90 days prior to conception	9.28 (-44.04, 62.60)	-0.09 (-0.32, 0.14)	0.98 (0.46, 2.09)	1.35 (0.65, 2.82)	1.2 (0.79, 1.81)	0.98 (0.60, 1.58)
	First trimester	21.95 (-29.14, 73.04)	0.14 (-0.09, 0.36)	0.98 (0.48, 2.02)	1 (0.47, 2.14)	0.97 (0.64, 1.47)	0.78 (0.48, 1.27)
	Second trimester	-18.21 (-70.25, 33.84)	0.04 (-0.19, 0.27)	0.85 (0.40, 1.79)	0.61 (0.36, 1.04)	0.92 (0.60, 1.40)	1.33 (0.84, 2.10)
	Third trimester	-37.38 (-95.31, 20.56)	-0.32 (-0.57, -0.07)	1.35 (0.61, 2.99)	1.51 (0.65, 3.47)	1.08 (0.68, 1.72)	1.12 (0.67, 1.88)
	Total pregnancy	-20.02 (-66.93, 26.89)	-0.1 (-0.30, 0.10)	0.81 (0.42, 1.55)	0.69 (0.35, 1.37)	1.00 (0.69, 1.46)	1.2 (0.78, 1.84)
		-13.23 (-55.66, 29.19)	-0.12 (-0.31, 0.06)	1.2 (0.65, 2.19)	1.62 (0.85, 3.10)	1.21 (0.85, 1.70)	1.24 (0.84, 1.83)
Estimated exposure to NO ₂	90 days prior to conception	0.3 (-42.65, 43.25)	0.08 (-0.11, 0.27)	1.01 (0.55, 1.85)	1.15 (0.61, 2.17)	1.17 (0.83, 1.66)	1.27 (0.86, 1.87)
	First trimester	-22.85 (-63.02, 17.32)	-0.04 (-0.22, 0.13)	1.11 (0.63, 1.95)	1.08 (0.60, 1.95)	1.06 (0.77, 1.47)	1.46 (1.01, 2.11)
	Second trimester	-32.72 (-78.00, 12.57)	-0.16 (-0.36, 0.03)	1.13 (0.60, 2.16)	1.35 (0.68, 2.69)	1.24 (0.86, 1.80)	1.58 (1.03, 2.42)
	Third trimester	-16.58 (-51.79, 18.63)	-0.03 (-0.18, 0.12)	1.03 (0.63, 1.69)	1.13 (0.67, 1.91)	1.16 (0.87, 1.55)	1.44 (1.04, 2.00)
	Total pregnancy						

eTable 6 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (co-exposure models)

		Mean difference				Odd ratios	
		Birth weight, grams	Birth length, cm	PTB (case: 33)	LBW (case: 33)	LGA (case: 108)	SGA (case: 84)
		99% CI	99% CI	99% CI	99% CI	99% CI	99% CI
Per IQR increase in		(N=941)	(N=927)	(N=945)	(N=945)	(N=945)	(N=945)
Estimated exposure to PM _{2.5}	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, 1.11)	1.14 (0.43, 3.03)	1.18 (0.36, 3.87)
	First trimester	19.59 (-99.85, 139.04)	0 (-0.52, 0.52)	0.97 (0.17, 5.55)	0.66 (0.09, 4.54)	0.67 (0.25, 1.79)	0.73 (0.21, 2.61)
	Second trimester	-25.62 (-129.13, 77.90)	0.08 (-0.36, 0.53)	1.34 (0.25, 7.29)	0.94 (0.13, 6.83)	0.83 (0.34, 2.01)	0.69 (0.27, 1.75)
	Third trimester	13.77 (-99.47, 127.00)	-0.2 (-0.69, 0.29)	1.12 (0.20, 6.12)	0.94 (0.18, 4.99)	1 (0.38, 2.68)	0.57 (0.21, 1.56)
	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)
Estimated exposure to NO ₂	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, 3.22)	1.27 (0.74, 2.16)	1.39 (0.79, 2.46)
	First trimester	-14.53 (-75.84, 46.78)	0.05 (-0.22, 0.31)	0.91 (0.36, 2.28)	1.14 (0.44, 2.98)	1.33 (0.78, 2.27)	1.70 (0.93, 3.11)
	Second trimester	-14.46 (-71.01, 42.09)	-0.08 (-0.32, 0.17)	1.22 (0.51, 2.91)	1.36 (0.55, 3.35)	1.27 (0.77, 2.10)	1.50 (0.88, 2.55)
	Third trimester	-13.13 (-81.19, 54.93)	0.04 (-0.25, 0.34)	0.77 (0.28, 2.13)	0.97 (0.34, 2.83)	1.41 (0.78, 2.57)	1.77 (0.92, 3.40)
Total pregnancy		-15.02 (-60.15, 30.11)	0 (-0.20, 0.19)	1.08 (0.55, 2.12)	1.28 (0.64, 2.53)	1.21 (0.81, 1.80)	1.60 (1.03, 2.48)

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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eTable 7 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and BSID scores (unadjusted models)

		Mean difference	
		MDI 99% CI	PDI 99% CI
		(N=946)	(N=946)
Estimated exposure to PM _{2.5}	Per IQR increase in 90 days prior to conception	-3.54 (-5.94, -1.13)	-3.42 (-5.44, -1.40)
	First trimester	-1.07 (-3.51, 1.37)	0.04 (-2.01, 2.10)
	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)
Estimated exposure to NO ₂	90 days prior to conception	-1.90 (-3.82, 0.02)	-2.86 (-4.46, -1.26)
	First trimester	-0.08 (-2.05, 1.90)	-1.17 (-2.83, 0.48)
	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		0.67 (-0.95, 2.28)	-1.08 (-2.44, 0.28)

eTable 8 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and BSID scores (co-exposure models)

		Mean difference	
		MDI 99% CI	PDI 99% CI
		(N=946)	(N=946)
Estimated exposure to PM _{2.5}	Per IQR increase in 90 days prior to conception	-1.73 (-6.43, 2.98)	-4.74 (-8.67, -0.81)
	First trimester	-2.84 (-7.85, 2.18)	-0.45 (-4.68, 3.77)
	Second trimester	4.19 (-0.15, 8.53)	5.51 (1.86, 9.16)
	Third trimester	-3.84 (-8.60, 0.93)	0.04 (-3.99, 4.06)
	Total pregnancy	-0.85 (-4.04, 2.33)	1.69 (-0.99, 4.37)
Estimated exposure to NO ₂	Per IQR increase in 90 days prior to conception	-0.31 (-2.83, 2.20)	-1.72 (-3.82, 0.38)
	First trimester	1.28 (-1.30, 3.86)	-1.80 (-3.98, 0.37)
	Second trimester	-0.48 (-2.85, 1.90)	-2.11 (-4.11, -0.12)
	Third trimester	1.52 (-1.34, 4.38)	-1.92 (-4.34, 0.49)
	Total pregnancy	0.67 (-1.23, 2.57)	-1.68 (-3.28, -0.08)

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.

eTable 9 Mediation effect of SGA on the associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and MDI scores

		Total Effect	P value	Direct Effect	P value	Indirect Effect	P value
Estimated exposure to PM2.5	90 days prior to conception	-3.54	0.000	-3.543	0.000	0.007	0.745
	First trimester	-1.07	0.259	-1.083	0.000	0.013	0.715
	Second trimester	4.21	0.000	4.239	0.000	0.024	0.599
	Third trimester	-1.43	0.157	-1.422	0.000	-0.006	0.779
	Total pregnancy	1.64	0.042	1.65	0.000	-0.012	0.695
Estimated exposure to NO2	90 days prior to conception	-1.90	0.011	1.896	0.000	0.007	0.799
	First trimester	-0.08	0.921	0.067	0.330	0.009	0.744
	Second trimester	1.81	0.011	1.844	0.011	-0.03	0.596
	Third trimester	0.04	0.962	0.059	0.942	-0.021	0.728
	Total pregnancy	0.67	0.288	0.686	0.274	-0.021	0.672

eTable 10 Mediation effect of SGA on the associations between PM_{2.5} and NO₂ exposure in different premarital periods and PDI scores

		Total Effect	P value	Direct Effect	P value	Indirect Effect	P value
Estimated exposure to PM _{2.5}	90 days prior to conception	-3.422	0.000	-3.421	0.001	0.001	0.931
	First trimester	0.045	0.955	0.049	0.955	-0.005	0.872
	Second trimester	2.632	0.001	2.631	0.001	0.000	0.997
	Third trimester	-1.758	0.038	-1.762	0.038	0.003	0.849
	Total pregnancy	0.504	0.456	0.501	0.456	0.003	0.894
Estimated exposure to NO ₂	90 days prior to conception	-2.862	0.000	-2.869	0.000	0.007	0.762
	First trimester	-1.174	0.067	-1.179	0.067	0.005	0.826
	Second trimester	-0.003	0.996	-0.010	0.996	0.007	0.872
	Third trimester	-1.966	0.004	-1.985	0.004	0.018	0.711
	Total pregnancy	-1.079	0.041	-1.092	0.038	0.013	0.751

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eTable 11 Comparison of major confounders and outcomes for those with missing and non-missing outcome data and non-missing confounder data

	Excluded from analyses due to missing cognitive outcome data (n=256)	Included in analyses (n = 1,017)	p-value for difference
Maternal age, mean ± SD (week), mean ± SD	28.47 ± 0.22	28.78 ± 0.11	0.22
Maternal BMI (kg/m²), mean ± SD	39.34 ± 0.12	39.39 ± 0.04	0.69
Infant's sex			
Female, n (%)	21.13 ± 0.17	21.56 ± 0.09	0.03
Male, n (%)			0.676
Primiparity			0.583
Yes, n (%)	136 (53.33)	527 (51.87)	
No, n (%)	119 (46.67)	489 (48.13)	
Season			0.00
Spring (Mar-May), n (%)	226 (22.22)	791 (77.78)	
Summer (Jun-Aug), n (%)	61 (23.83)	195 (76.17)	
Autumn (Sep-Nov), n (%)	74 (32.46)	337 (35.62)	
Winter (Dec-Feb), n (%)	74 (32.46)	189 (19.98)	
	55 (24.12)	143 (15.12)	
	25 (10.96)	277 (29.28)	

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

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		Page
Reporting Item		Number
Title and abstract		
Title	#1a Indicate the study's design with a commonly used term in the title or the abstract	1

1	Abstract	#1b	Provide in the abstract an informative and balanced	2, 3
2			summary of what was done and what was found	
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6	Introduction			
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10	Background /	#2	Explain the scientific background and rationale for the	4, 5
11	rationale		investigation being reported	
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15	Objectives	#3	State specific objectives, including any prespecified	5
16			hypotheses	
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20	Methods			
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24	Study design	#4	Present key elements of study design early in the paper	5,6
25				
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27	Setting	#5	Describe the setting, locations, and relevant dates,	5,6
28			including periods of recruitment, exposure, follow-up, and	
29			data collection	
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34	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of	5,6
35			selection of participants. Describe methods of follow-up.	
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40	Eligibility criteria	#6b	For matched studies, give matching criteria and number of	6
41			exposed and unexposed	
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45	Variables	#7	Clearly define all outcomes, exposures, predictors,	6, 7, 8
46			potential confounders, and effect modifiers. Give diagnostic	
47			criteria, if applicable	
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53	Data sources /	#8	For each variable of interest give sources of data and	6, 7, 8
54	measurement		details of methods of assessment (measurement).	
55			Describe comparability of assessment methods if there is	
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more than one group. Give information separately for for
exposed and unexposed groups if applicable.

Bias	#9	Describe any efforts to address potential sources of bias	6, 7, 8
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8, 9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8, 9
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8, 9
Statistical methods	#12c	Explain how missing data were addressed	8, 9
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8, 9
Statistical methods	#12e	Describe any sensitivity analyses	8, 9
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	10

1			confirmed eligible, included in the study, completing follow-	
2			up, and analysed. Give information separately for for	
3			exposed and unexposed groups if applicable.	
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8	Participants	#13b	Give reasons for non-participation at each stage	10, 20
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11	Participants	#13c	Consider use of a flow diagram	10, 20
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17	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	10,22
18			clinical, social) and information on exposures and potential	
19			confounders. Give information separately for exposed and	
20			unexposed groups if applicable.	
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27	Descriptive data	#14b	Indicate number of participants with missing data for each	N/A
28			variable of interest	
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35	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	N/A
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41	Outcome data	#15	Report numbers of outcome events or summary measures	10,22
42			over time. Give information separately for exposed and	
43			unexposed groups if applicable.	
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52	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	10, 11
53			adjusted estimates and their precision (eg, 95% confidence	
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		interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	10, 11
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11, 12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12, 13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14
Other Information			

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Funding

#22

Give the source of funding and the role of the funders for

the present study and, if applicable, for the original study

on which the present article is based

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None

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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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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 $\leq 2.5\mu\text{m}$ (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 NO₂ during pregnancy were associated with increased risk of SGA and psychomotor development delay, while increased exposure to both PM_{2.5} and NO₂ pre-conception were associated with adverse psychomotor development outcomes at 12 months of age.

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 $\leq 2.5\mu\text{m}$ (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 PM_{2.5} 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.

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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 NO₂ 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 NO₂ 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 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 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.

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

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/m^2), 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

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

Statistical analyses

Data were described in terms of mean ± 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 PM_{2.5} 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 µg/m³ (IQR: 5.76) and median NO₂ exposure levels were 50.46 µg/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 µg/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 $r \sim 0.6$, **eTable 4 in the Supplement**).

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

Characteristic of mothers	N	n (%) / mean ± SD	Characteristic of child	N	n (%) /mean ± SD
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 abortion (%)	1,174		Yes		30 (2.6%)
Yes		553 (47.1%)	No		1,141 (97.2%)
No		621 (52.9%)	Large for gestational age (LGA)	1,174	
Smoking/drinking during pregnancy (%)	1,174		Yes		108 (9.2%)
Yes		5 (0.4%)	No		1,066 (90.8%)
No		1,169 (99.6%)	Small for gestational age (SGA)	1,174	
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	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 ≥ 85)		741 (72.9%)
2000 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	
			Spring (Mar-May)		411 (35.01%)
			Summer (Jun-Aug)		263 (22.40%)
			Autumn (Sep-Nov)		198 (16.87%)
			Winter (Dec-Feb)		302 (25.72%)

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

41 **Table 2 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (adjusted models)**

		Mean difference			Odd ratios		
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 (case: 30) (95% CI) (N=945)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
Estimated exposure to PM _{2.5}	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 (0.18, 1.29)	1.40 (0.72, 2.71)	1.66 (0.75, 3.68)
	First trimester	6.21 (-73.79, 86.20)	0.04 (-0.308, 0.388)	0.88 (0.28, 2.80)	0.76 (0.28, 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 (0.48, 4.68)	1.00 (0.55, 1.83)	0.94 (0.50, 1.76)
	Third trimester	4.20 (-73.17, 81.57)	-0.17 (-0.509, 0.162)	0.92 (0.29, 2.90)	0.92 (0.30, 2.85)	1.29 (0.65, 2.53)	0.83 (0.42, 1.66)
	Total pregnancy	8.01 (-41.10, 57.11)	0.02 (-0.198, 0.230)	0.77 (0.38, 1.54)	0.62 (0.30, 1.25)	1.15 (0.75, 1.77)	0.84 (0.52, 1.35)
Estimated exposure to NO ₂	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 (0.48, 1.98)	1.31 (0.91, 1.88)	1.45 (0.99, 2.12)
	First trimester	-9.78 (-50.84, 31.28)	0.04 (-0.133, 0.223)	0.90 (0.49, 1.65)	1.03 (0.51, 1.91)	1.21 (0.85, 1.72)	1.57 (1.06, 2.32)
	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 (0.47, 1.94)	1.42 (0.94, 2.13)	1.51 (0.97, 2.36)
	Total pregnancy	-8.45 (-37.73, 20.83)	0.00 (-0.125, 0.130)	0.97 (0.62, 1.51)	1.04 (0.66, 1.64)	1.20 (0.93, 1.56)	1.33 (1.01, 1.75)

24 All significant findings in the table are bold.
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.

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).

66 Table 3 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and continuous SID scores

		Crude models		Adjusted models*		Co-exposure models**	
Per IQR increase in		MDI (95% CI) (N=946)	PDI 95% CI (N=946)	MDI (95% CI) (N=945)	PDI 95% (N=945)	MDI (95% CI) (N=945)	PDI 95% CI (N=945)
Estimated exposure to PM _{2.5}	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, -3.46)	-1.73 (-5.30, 1.85)	-4.74 (-7.73, -1.75)
	First trimester	-1.07 (-2.93, 0.79)	0.04 (-1.52, 1.61)	-1.66 (-5.02, 1.70)	-2.11 (-4.95, 0.73)	-2.84 (-6.65, 0.97)	-0.45 (-3.67, 2.76)
	Second trimester	4.21 (2.43, 6.00)	2.63 (1.12, 4.14)	3.79 (0.85, 6.73)	3.76 (1.27, 6.25)	4.19 (0.89, 7.49)	5.51 (2.73, 8.28)
	Third trimester	-1.43 (-3.41, 0.55)	-1.76 (-3.42, -0.10)	-2.73 (-5.99, 0.53)	-1.37 (-4.12, 1.38)	-3.84 (-7.46, -0.22)	0.04 (-3.02, 3.09)
	Total pregnancy	1.64 (0.06, 3.21)	0.5 (-0.82, 1.83)	-0.27 (-2.34, 1.80)	0.23 (-1.52, 1.98)	-0.85 (-3.28, 1.57)	1.69 (-0.35, 3.73)
Estimated exposure to NO ₂	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, -1.39)	-0.31 (-2.22, 1.60)	-1.72 (-3.31, -0.12)
	First trimester	-0.08 (-1.57, 1.42)	-1.17 (-2.43, 0.08)	0.59 (-1.14, 2.32)	-1.91 (-3.37, -0.45)	1.28 (-0.68, 3.24)	-1.80 (-3.46, -0.15)
	Second trimester	1.81 (0.41, 3.22)	0.00 (-1.18, 1.18)	0.56 (-1.05, 2.17)	-0.75 (-2.11, 0.61)	-0.48 (-2.28, 1.33)	-2.11 (-3.63, -0.60)
	Third trimester	0.04 (-1.54, 1.62)	-1.97 (-3.29, -0.65)	0.51 (-1.45, 2.47)	-1.92 (-3.57, -0.27)	1.52 (-0.66, 3.69)	-1.92 (-3.76, -0.09)
	Total pregnancy	0.67 (-0.56, 1.89)	-1.08 (-2.11, -0.05)	0.41 (-0.83, 1.64)	-1.15 (-2.19, -0.11)	0.67 (-0.77, 2.12)	-1.68 (-2.89, -0.46)

23 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 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
26 adjusted for the other air pollutant.

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4 68 In the adjusted model, the risk of PDD was found to increase by 112% and 42% with each per-
5 69 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)
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7 70 in the 90 days prior to conception (**Table 4**). There was also a significant association between
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9 71 increased NO₂ exposure and the risk of PDD in T1 (OR: 1.29, 95% CI: 1.05, 1.58), T3 (OR:
10 72 1.27, 95% CI: 1.01, 1.60), and the whole pregnancy period (OR: 1.17, 95% CI: 1.02, 1.36). We
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12 73 did not observe any association with MDD in any pregnancy periods.
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74 **Table 4 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and mental and psychomotor developmental delay**

		Crude models		Adjusted models*		Co-exposure models**	
Per IQR increase in		MDD (95% CI) (N=946)	PDD (95% CI) (N=946)	MDD (95% CI) (N=945)	PDD (95% CI) (N=945)	MDD (95% CI) (N=945)	PDD (95% CI) (N=945)
Estimated exposure to PM _{2.5}	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, 2.70)	0.97 (0.63, 1.51)	1.78 (1.17, 2.71)
	First trimester	1.05 (0.83, 1.33)	1.04 (0.84, 1.28)	1.14 (0.73, 1.79)	1.42 (0.96, 1.88)	1.35 (0.80, 2.25)	1.16 (0.74, 1.82)
	Second trimester	0.63 (0.49, 0.80)	0.77 (0.63, 0.95)	0.81 (0.54, 1.22)	0.72 (0.51, 1.03)	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, 1.74)	1.39 (0.87, 2.23)	0.98 (0.64, 1.49)
	Total pregnancy	0.84 (0.69, 1.03)	0.98 (0.82, 1.18)	1.07 (0.82, 1.39)	1.07 (0.84, 1.30)	1.17 (0.86, 1.59)	0.90 (0.68, 1.20)
Estimated exposure to NO ₂	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, 1.68)	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, 1.53)	0.84 (0.65, 1.09)	1.24 (0.99, 1.57)
	Second trimester	0.79 (0.66, 0.95)	1.04 (0.88, 1.22)	0.94 (0.76, 1.15)	1.14 (0.95, 1.33)	0.98 (0.77, 1.24)	1.31 (1.06, 1.63)
	Third trimester	1.04 (0.85, 1.28)	1.25 (1.04, 1.50)	0.94 (0.73, 1.21)	1.27 (1.01, 1.60)	0.86 (0.65, 1.14)	1.28 (0.99, 1.65)
	Total pregnancy	0.92 (0.79, 1.07)	1.16 (1.01, 1.33)	0.94 (0.80, 1.11)	1.17 (1.02, 1.36)	0.9 (0.75, 1.08)	1.21 (1.02, 1.43)

23 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 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

26 adjusted for the other air pollutant.

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 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

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3 109 come from industrial and traffic emissions, construction activities, and dust, and negative
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5 110 correlations may occur if different sources contribute disproportionately to each pollutant.
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7 111 Their correlations may also be affected by seasonal changes and variations in weather patterns.
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9 112 Future research should also explore the impact of source-specific air pollution on children's
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11 113 cognitive health.

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13 114 To date, most studies on prenatal air pollution exposure and child neurodevelopment have been
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15 115 conducted in developed countries with relatively low levels of air pollution. In this study, the
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17 116 level of air pollution was higher (median $PM_{2.5}$: $57.31 \mu g/m^3$, IQR: 5.76; median NO_2 :
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19 117 $50.46 \mu g/m^3$, IQR: 5.51) compared to studies in developed countries such as Europe and the
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21 118 United States. In a multi-centre European cohort, the mean $PM_{2.5}$ and NO_2 exposure
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23 119 concentration during pregnancy were $13.4 \mu g/m^3$ and $11.5 \mu g/m^3$ (33). Researchers found that
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25 120 the psychomotor development score significantly decreased by 0.68 points (95% CI: -1.25, -
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27 121 0.11) for every $10 \mu g/m^3$ increase in NO_2 , and there was also a non-significant decrease of 1.64
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29 122 points (95% CI: -3.47, 0.18) for every $5 \mu g/m^3$ increase in $PM_{2.5}$ during pregnancy (33). Factors
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31 123 such as the types of pollutants and concentrations may differ between China and other regions
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33 124 with a lower air pollution level, leading to variations in the observed effects.

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35 125 Contrary to expectations, we found significant positive associations between prenatal exposure
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37 126 to $PM_{2.5}$ air pollution in the second trimester and PDI. However, no association was observed
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39 127 between $PM_{2.5}$ exposures in the second trimester and the risk of PDD. Given the existing
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41 128 literature and the conflicted observation here, we believe that this is likely to be
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43 129 spurious/sample specific. Some plausible explanations include the uneven distribution of PDI
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45 130 scores, the potentially inappropriate selection of the cut-off value of 85 (which may not
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47 131 effectively discriminate between groups), or the possibility that the observed outcome occurred
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49 132 by chance. Several epidemiological studies have reported associations between prenatal
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51 133 exposure to high levels of $PM_{2.5}$ and lower neurodevelopment in children ranging in age from
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53 134 6 months to 6 years (12, 34, 39-41). In agreement with our findings, a multi-centre cohort study
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55 135 from six European countries investigated the effects of prenatal exposure to multiple air
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57 136 pollutants including $PM_{2.5}$, PM_{10} , coarse particles, NO_2 and nitrogen oxides (NO_x) among 9482
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59 137 children between 1 and 6 years; the authors found nonsignificant positive associations between
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138 prenatal $PM_{2.5}$ exposure and normal neurodevelopment (β : 1.64, 95% CI: -3.47, 0.18; per $5 \mu g/m^3$
139 increase in $PM_{2.5}$) (33). Similarly, another study examining the effects of multiple
140 pollutant exposures on early childhood cognition at 40 days of age in a highly exposed area of
141 Spain also found PM_{10} , PM_{coarse} , $PM_{2.5\text{absorbance}}$, NO_2 , NO_x , and Ozone (O_3) were linked to lower

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motor function in children, except for PM_{2.5} (42). 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}).

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 (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 µg/m³) and in the first trimester (Median: 82.3 µg/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 µg/m³ (Mean PM_{2.5} in our study: 50.52 µg/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 µg/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 µg/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 been found particularly 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

206 This study provides evidence for an association between NO₂ exposure prior to- and during
207 pregnancy with birth and neurodevelopmental outcomes in a birth cohort in Chongqing, China.
208 Exposure to NO₂ and PM_{2.5} exposure before pregnancy was associated with a lower
209 psychomotor development score. Increased NO₂ exposure was linked to a risk of psychomotor
210 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
CO	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 $\leq 2.5\mu\text{m}$
PTB	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

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Declarations

Ethics approval and consent to participate

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

Data availability statement

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

Competing interests

The authors declare that they have no conflicts of interests.

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Contributors

Y. X., T.L.H., H.Z. and P.B. 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

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

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408 **Figures**

409 **Figure 1 Flow chart of the study population in CLIMB**

410 **Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors,**
411 **2015; <https://data.nextgis.com/en/region/CN-50/>).**

For peer review only

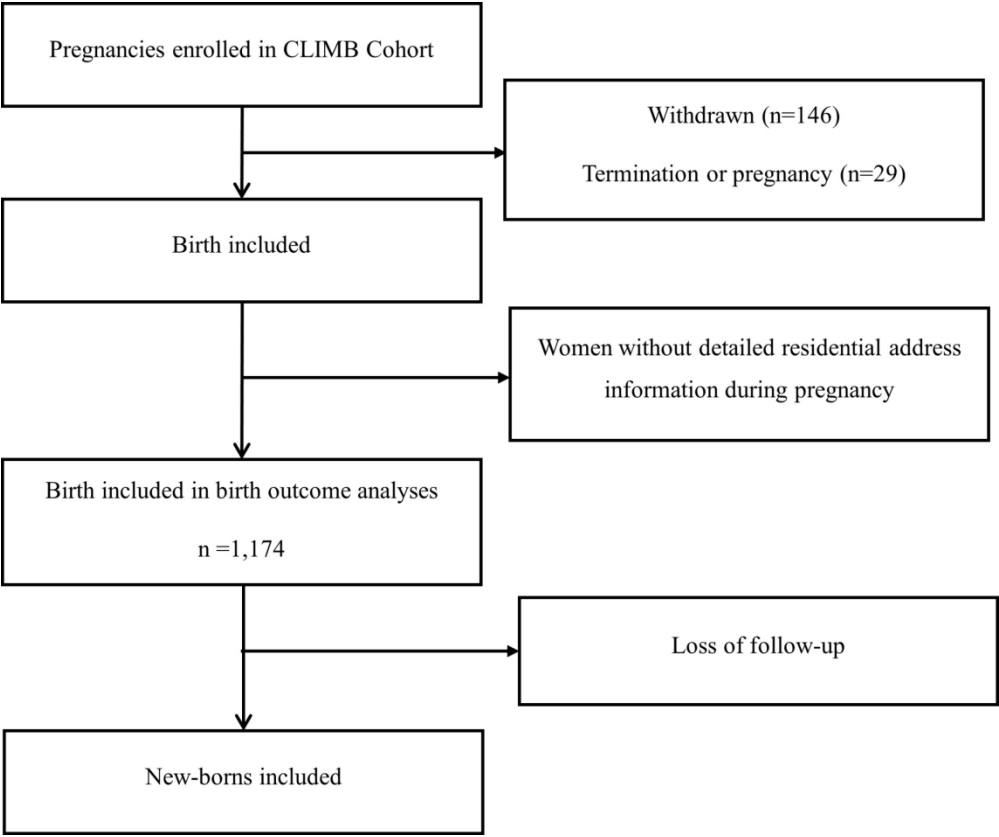


Figure 1 Flow chart of the study population in CLIMB

173x144mm (300 x 300 DPI)

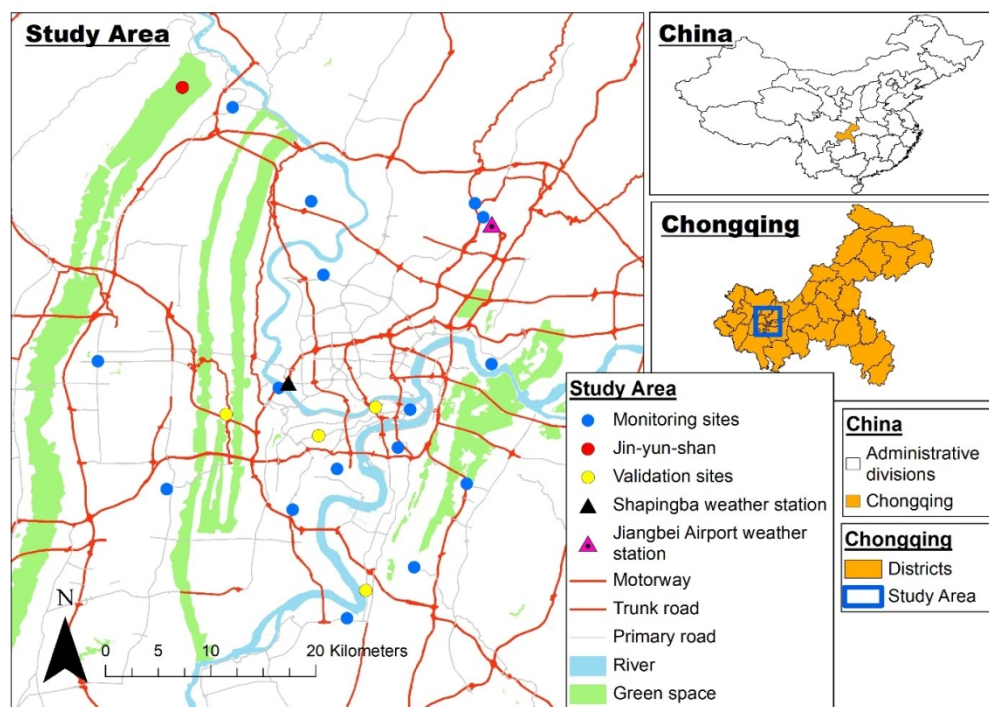


Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors, 2015; <https://data.nextgis.com/en/region/CN-50/>).

159x112mm (220 x 220 DPI)

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	

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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	

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	
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	

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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+	“一”的概念	
163	30+	理解三个方位词	

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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	
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	辅助下行走	
45	11.1	独站	
46	12	投球	
47	12.1	独走	
48	12.4	起立 I	
49	13.2	辅助下右足独站	
50	13.7	辅助下左足独站	
51	14.1	侧身走	
52	14.5	辅助上楼梯	
53	14.7	倒退走	
54	15.1	辅助下楼梯	
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：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	
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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eTable 3 Distributions of PM2.5 and NO2 exposure level in 90 days prior to conception, each trimester (T1, T2, and T3) and combined across whole pregnancy period (WP) (n = 1,174)

	Estimated exposure (µg/m ³)							
	N	Minimum	25 th percentile	Mean ± SD	Median	IQR	75 th percentile	Maximum
Estimated exposure to PM _{2.5}								
90 days prior to conception	1,174	38.17	44.00	52.91 ± 10.99	48.40	40.07	62.06	80.53
First trimester	1,174	37.26	43.77	52.07 ± 10.98	47.20	37.31	61.08	82.41
Second trimester	1,174	38.46	47.57	58.64 ± 12.21	57.90	49.62	67.19	90.02
Third trimester	1,174	37.03	47.25	61.83 ± 16.04	58.80	48.7	75.95	96.48
Total pregnancy	1,174	46.69	54.85	57.48 ± 3.97	57.30	47.76	60.61	66.98
Estimated exposure to NO ₂								
90 days prior to conception	1,174	25.86	45.49	49.59 ± 6.34	49.90	27	53.76	70.48
First trimester	1,174	20.81	44.60	48.8 ± 6.43	48.90	25.1	53.10	69.31
Second trimester	1,174	28.93	47.18	50.98 ± 6.23	51.20	27.2	54.90	70.42
Third trimester	1,174	20.57	47.20	51.79 ± 6.78	52.40	27.47	56.67	75.12
Total pregnancy	1,174	27.50	47.89	50.52 ± 5.08	50.40	25.1	53.40	67.53

eTable 4 Pearson's correlations of PM_{2.5} and NO₂ between each of the five different pregnancy time periods (N = 1,174)

Estimated exposure to		PM _{2.5}					NO ₂				
		90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy	90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy
PM _{2.5}	90 days prior to conception	1									
	First trimester	-0.065	1								
	Second trimester	-0.779	-0.2012	1							
	Third trimester	0.288	-0.7613	-0.1688	1						
	Total pregnancy	-0.534	-0.2709	0.6838	0.3858	1					
NO ₂	90 days prior to conception	0.6383	0.0684	-0.4588	0.3714	0.0376	1				
	First trimester	0.1537	0.6352	-0.0159	-0.4927	-0.0633	0.554	1			
	Second trimester	-0.431	0.0714	0.6269	-0.0133	0.7251	0.334	0.5399	1		
	Third trimester	0.3027	-0.5213	0.0528	0.6817	0.4432	0.714	0.2159	0.5145	1	
	Total pregnancy	0.0057	0.0781	0.2862	0.0737	0.4779	0.678	0.7435	0.8755	0.7331	1

eTable 5 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (unadjusted models)

Per IQR increase in		Mean difference		Odd ratios			
		Birth weight, grams (95% CI)	Birth length, cm (95% CI)	PTB (case: 33) (95% CI)	LBW (case: 30) (95% CI)	LGA (case: 108) (95% CI)	SGA (case: 84) (95% CI)
		(N=941)	(N=927)	(N=945)	(N=945)	(N=945)	(N=945)
Estimated exposure to PM _{2.5}	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 (0.77, 2.36)	1.2 (0.87, 1.64)	0.98 (0.68, 1.41)
	First trimester	21.95 (-16.90, 60.80)	0.14 (-0.03, 0.31)	0.98 (0.57, 1.70)	1 (0.59, 1.77)	0.97 (0.71, 1.33)	0.78 (0.54, 1.13)
	Second trimester	-18.21 (-57.78, 21.37)	0.04 (-0.13, 0.21)	0.85 (0.48, 1.50)	0.61 (0.33, 1.15)	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 (0.89, 2.85)	1.08 (0.76, 1.54)	1.12 (0.76, 1.66)
	Total pregnancy	-20.02 (-55.69, 15.65)	-0.1 (-0.26, 0.05)	0.81 (0.49, 1.33)	0.69 (0.41, 1.16)	1 (0.75, 1.34)	1.2 (0.87, 1.66)
Estimated exposure to NO ₂	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 (0.97, 2.65)	1.21 (0.93, 1.57)	1.24 (0.92, 1.66)
	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)
	Second trimester	-22.85 (-53.39, 7.70)	-0.04 (-0.17, 0.09)	1.11 (0.72, 1.70)	1.08 (0.69, 1.69)	1.06 (0.83, 1.36)	1.46 (1.10, 1.93)
	Third trimester	-32.72 (-67.16, 1.72)	-0.16 (-0.32, -0.01)	1.13 (0.69, 1.85)	1.35 (0.89, 2.28)	1.24 (0.94, 1.65)	1.58 (1.14, 2.18)
	Total pregnancy	-16.58 (-43.35, 10.20)	-0.03 (-0.15, 0.09)	1.03 (0.71, 1.50)	1.13 (0.77, 1.69)	1.16 (0.93, 1.44)	1.44 (1.13, 1.85)

All significant findings in the table are bold.

eTable 6 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (co-exposure models)

		Mean difference		Odd ratios			
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 (case: 30) (95% CI) (N=945)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
Estimated exposure to PM _{2.5}	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 (0.14, 1.22)	1.14 (0.55, 2.40)	1.18 (0.48, 2.92)
	First trimester	19.59 (-71.23, 110.41)	0.00 (-0.40, 0.39)	0.97 (0.26, 3.65)	0.66 (0.24, 3.05)	0.67 (0.32, 1.42)	0.73 (0.28, 1.93)
	Second trimester	-25.62 (-104.32, 53.09)	0.08 (-0.26, 0.42)	1.34 (0.37, 4.86)	0.94 (0.34, 4.21)	0.83 (0.42, 1.62)	0.69 (0.34, 1.40)
	Third trimester	13.77 (-72.33, 99.86)	-0.2 (-0.58, 0.17)	1.12 (0.31, 4.07)	0.94 (0.33, 3.35)	1.00 (0.48, 2.12)	0.57 (0.26, 1.23)
	Total pregnancy	21.13 (-36.41, 78.67)	0.02 (-0.23, 0.27)	0.73 (0.33, 1.61)	0.52 (0.24, 1.15)	0.98 (0.60, 1.61)	0.55 (0.32, 0.96)
Estimated exposure to NO ₂	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 (0.61, 2.64)	1.27 (0.84, 1.90)	1.39 (0.90, 2.15)
	First trimester	-14.53 (-61.15, 32.09)	0.05 (-0.16, 0.25)	0.91 (0.45, 1.83)	1.14 (0.45, 2.37)	1.33 (0.89, 2.00)	1.70 (1.07, 2.69)
	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)
	Third trimester	-13.13 (-64.87, 38.62)	0.04 (-0.18, 0.27)	0.77 (0.35, 1.67)	0.97 (0.43, 2.16)	1.41 (0.90, 2.23)	1.77 (1.08, 2.91)
	Total pregnancy	-15.02 (-49.33, 19.30)	0.00 (-0.15, 0.15)	1.08 (0.64, 1.80)	1.28 (0.75, 2.18)	1.21 (0.90, 1.63)	1.60 (1.15, 2.23)

24 All significant findings in the table are bold.

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 adjusted for the other air pollutant

eTable 7 Comparison of major confounders and outcomes for those with missing and non-missing outcome data and non-missing confounder data

	Excluded from analyses* (n=256)	Included in analyses (n = 1,017)	p-value
Maternal age, mean ± SD	28.47 ± 0.22	28.78 ± 0.11	0.22
Gestational week, mean ± SD	39.34 ± 0.12	39.39 ± 0.04	0.69
Maternal BMI (kg/m²), mean ± SD	21.13 ± 0.17	21.56 ± 0.09	0.03
Infant's sex			
Female, n (%)	136 (53.33)	527 (51.87)	0.676
Male, n (%)	119 (46.67)	489 (48.13)	
Primiparity			0.583
Yes, n (%)	226 (22.22)	791 (77.78)	
No, n (%)	61 (23.83)	195 (76.17)	
Season			0.00
Spring (Mar-May), n (%)	74 (32.46)	337 (35.62)	
Summer (Jun-Aug), n (%)	74 (32.46)	189 (19.98)	
Autumn (Sep-Nov), n (%)	55 (24.12)	143 (15.12)	
Winter (Dec-Feb), n (%)	25 (10.96)	277 (29.28)	
*Excluded from analyses due to missing cognitive outcome data			

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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 **Objectives:** To investigate the associations of traffic-related air pollution exposures in early

29 pregnancy with birth outcomes and infant neurocognitive development.

30 **Design:** Cohort study.

31 **Setting:** Eligible women attended six visits in the maternity clinics of two centres, the First

32 Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for

33 Women and Children.

34 **Participants:** Women who were between 20 and 40 years of age and were at 11–14 weeks

35 gestation with a singleton pregnancy were eligible for participation. Women were excluded if

36 they had a history of premature delivery before 32 weeks of gestation, maternal milk allergy

37 or aversion, or severe lactose intolerance. 1,273 pregnant women enrolled in 2015-2016 and

38 1,174 live births were included in this analysis.

39 **Exposures:** Air pollution concentrations at their home addresses, including particulate matter

40 (PM) with diameter $\leq 2.5\mu\text{m}$ (PM_{2.5}) and nitrogen dioxide (NO₂), during pre-conception and

41 each trimester period were estimated using land-use regression models.

42 **Outcome measures:** Birth outcomes (i.e., birthweight, birth length, preterm birth (PTB), low

43 birth weight (LBW), large for gestational age (LGA) and small for gestational age (SGA)

44 status) and neurodevelopment outcomes measured by the Chinese version of Bayley Scales of

45 Infant Development (CBSID).

46 **Results:** An association between SGA and per-interquartile range (IQR) increases in NO₂ was

47 found in the first trimester (odds ratio (OR): 1.57, 95% confidence interval (CI): 1.06, 2.32)

48 and during the whole pregnancy (OR: 1.33, 99% CI: 1.01, 1.75). Both PM_{2.5} and NO₂ exposure

49 in the 90 days prior to conception were associated with lower Psychomotor Development Index

50 (PDI) scores (β : -6.15, 95% CI: -8.84, -3.46; β : -2.83, 95% CI: -4.27, -1.39, respectively).

51 Increased NO₂ exposure was associated with an increased risk of psychomotor development

52 delay (PDD) during different trimesters of pregnancy.

53 **Conclusions:** Increased exposures to NO₂ during pregnancy were associated with increased

54 risks of SGA and psychomotor development delay, while increased exposures to both PM_{2.5}

55 and NO₂ pre-conception were associated with adverse psychomotor development outcomes at

56 12 months of age.

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58 **Keywords:** Air pollution; birth outcomes; child cognition

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59 **Article summary**

60 **Strengths and limitations of this study**

61 • This study uniquely explored the impacts of both pre-conception and prenatal exposure
62 to PM_{2.5} and NO₂ on neurodevelopmental outcomes in young infants, within an urban
63 environment characterized by relatively high air pollution levels.
64 • We developed an LUR model to capture spatial and temporal variations of air pollution
65 at individual level to reduce exposure misclassification.
66 • Our sample size was relatively small, limiting the statistical power to assess several
67 outcomes.
68 • We defined exposure windows for clinically-defined trimesters; sensitive periods may
69 be shorter or longer than 3 months, or may exist in the overlap of multiple trimesters.
70

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 $\leq 2.5\mu\text{m}$ (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 PM_{2.5} 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.

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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 NO₂ 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 NO₂
110 exposures during pre- and during pregnancy, with birth and infant neurocognitive development
111 outcomes at 12 months of age.

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

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

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 NO_2 and $\text{PM}_{2.5}$ 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 Chongqing. 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

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3 160 rate of urban population with access to gas in Chongqing was 95.34% (29), suggesting a low
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5 161 reliance on biomass cookstoves in urban areas.

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7 162 **Exposure assessment**

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10 163 The address of participants was collected at the first visit. Exposure assessment based on
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12 164 spatiotemporal land use regression (LUR) models for PM_{2.5} and NO₂ were developed for the
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14 165 study region. A description of the methodology of exposure modelling has been reported
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16 166 previously (19). Briefly, the models included both spatial and temporal components of
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18 167 exposure. PM_{2.5} and NO₂ concentration data were collected from 17 routine monitoring sites
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20 168 operated by the Chongqing Environmental Monitoring Center in 2015-2016. For the spatial
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22 169 component of models, we calculated annual average concentrations of each pollutant in 2015,
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24 170 and fit linear regression models using five groups of geographic data (road network, land use,
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26 171 topography, vegetation, and population density) as spatial predictor variables. For the temporal
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28 172 component of models, we calculated the residuals from the spatial component at each
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30 173 monitoring site on a daily basis by subtracting the predicted annual average concentration from
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32 174 the observed daily average concentrations measured in 2015 and 2016, and then fitted
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34 175 generalised additive models (GAM) using seven groups of meteorological data (temperature,
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36 176 amount of rainfall, rainfall events, relative humidity, horizontal visibility, wind direction and
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38 177 wind speed) as temporal predictor variables. The meteorological variables were used to account
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40 178 for the influence of weather on the change in air pollution concentration over time. To account
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42 179 for the remaining spatial autocorrelation, the smoothed terms of longitude and latitude were fit
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44 180 to spatiotemporal residuals which were calculated by subtracting the sum of the spatial
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46 181 temporal predictions from the measured daily average concentrations in 2015 and 2016. The
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48 182 performance of the PM_{2.5} spatiotemporal models was good (Correlation (COR)-R²: 0.72) and
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50 183 the NO₂ spatiotemporal model was low (COR-R²: 0.39) when providing concentration
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52 184 estimates in absolute terms.

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54 185 Combining the family address coordinates of each pregnant woman and the gestation period of
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56 186 the pregnancy (calculated from the date of last menstrual period to the date of delivery), we
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58 187 used this spatiotemporal model to estimate the average exposure of each pregnant woman in
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60 188 90 days prior to pregnancy (90D), first trimester (T1), second trimester (T2), third trimester
189 (T3) and whole pregnancy period (WP), respectively.

190 **Outcomes**

191 *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 (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.

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).

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/m^2), 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.

Statistical analyses

Data were described in terms of mean ± 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 PM_{2.5} 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

256 None.

For peer review only

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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 µg/m³ (IQR: 5.76) and median NO₂ exposure levels were 50.46 µg/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 µg/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**).

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

Characteristic of mother	N	n (%) / mean \pm SD	Characteristic of child	N	n (%) / mean \pm SD
Maternal age (Years)	1,174	28.7 \pm 3.5	Gestational week (week)	1,174	39.4 \pm 1.5
BMI (kg/m ²)	1,174	21.5 \pm 2.9	Birth weight (g)	1,165	3314.4 \pm 428.8
Han ethnicity (%)	1,174		Birth length (cm)	1,149	49.7 \pm 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 abortion (%)	1,174		Yes		30 (2.6%)
Yes		553 (47.1%)	No		1,141 (97.2%)
No		621 (52.9%)	Large for gestational age (LGA)	1,174	
Smoking/drinking during pregnancy (%)	1,174		Yes		108 (9.2%)
Yes		5 (0.4%)	No		1,066 (90.8%)
No		1,169 (99.6%)	Small for gestational age (SGA)	1,174	
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	946		MDI score		94.7 \pm 17.7
Full-time		762 (80.5%)	PDI score		87.4 \pm 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%)
2000 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%)
7000-10000 RMB		139 (14.7%)	Season of birth	1,174	
			Spring (Mar-May)		411 (35.01%)
			Summer (Jun-Aug)		263 (22.40%)
			Autumn (Sep-Nov)		198 (16.87%)
			Winter (Dec-Feb)		302 (25.72%)

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281 **Association with birth outcomes**

282 In the unadjusted models (**eTable 5 in the Supplement**), higher exposure concentrations of
 283 PM_{2.5} in T3 were significantly associated with lower birth length (β : -0.32, 95% CI: -0.51, -
 284 0.13; per IQR increase). We also observed increased NO₂ in T3 were significantly associated
 285 with lower birth length (β : -0.16, 95% CI: -0.32, -0.01; per IQR). A risk between SGA and
 286 increases in NO₂ (per IQR) was found in T2 (OR: 1.46, 95% CI: 1.10, 1.93), T3 (OR: 1.58,

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

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297 **Table 2. Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (adjusted models)**

		Mean difference			Odds ratios		
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 (case: 30) (95% CI) (N=945)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
Estimated exposure to PM _{2.5}	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 (0.18, 1.29)	1.40 (0.72, 2.71)	1.66 (0.75, 3.68)
	First trimester	6.21 (-73.79, 86.20)	0.04 (-0.308, 0.388)	0.88 (0.28, 2.80)	0.76 (0.28, 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 (0.46, 4.68)	1.00 (0.55, 1.83)	0.94 (0.50, 1.76)
	Third trimester	4.20 (-73.17, 81.57)	-0.17 (-0.509, 0.162)	0.92 (0.29, 2.90)	0.92 (0.30, 2.85)	1.29 (0.65, 2.53)	0.83 (0.42, 1.66)
	Total pregnancy	8.01 (-41.10, 57.11)	0.02 (-0.198, 0.230)	0.77 (0.38, 1.54)	0.62 (0.28, 1.25)	1.15 (0.75, 1.77)	0.84 (0.52, 1.35)
Estimated exposure to NO ₂	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 (0.49, 1.98)	1.31 (0.91, 1.88)	1.45 (0.99, 2.12)
	First trimester	-9.78 (-50.84, 31.28)	0.04 (-0.133, 0.223)	0.90 (0.49, 1.65)	1.03 (0.49, 1.91)	1.21 (0.85, 1.72)	1.57 (1.06, 2.32)
	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 (0.47, 1.94)	1.42 (0.94, 2.13)	1.51 (0.97, 2.36)
	Total pregnancy	-8.45 (-37.73, 20.83)	0.00 (-0.125, 0.130)	0.97 (0.62, 1.51)	1.04 (0.66, 1.64)	1.20 (0.93, 1.56)	1.33 (1.01, 1.75)

24 All significant findings in the table are bold.

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.

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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_{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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322 **Table 3. Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and continuous SID scores**

Per IQR increase in		Crude models		Adjusted models*		Co-exposure models**	
		MDI (95% CI) (N=946)	PDI 95% CI (N=946)	MDI (95% CI) (N=945)	PDI 95% (N=945)	MDI (95% CI) (N=945)	PDI 95% CI (N=945)
Estimated exposure to PM _{2.5}	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, -3.46)	-1.73 (-5.30, 1.85)	-4.74 (-7.73, -1.75)
	First trimester	-1.07 (-2.93, 0.79)	0.04 (-1.52, 1.61)	-1.66 (-5.02, 1.70)	-2.11 (-4.95, 0.73)	-2.84 (-6.65, 0.97)	-0.45 (-3.67, 2.76)
	Second trimester	4.21 (2.43, 6.00)	2.63 (1.12, 4.14)	3.79 (0.85, 6.73)	3.76 (1.27, 6.25)	4.19 (0.89, 7.49)	5.51 (2.73, 8.28)
	Third trimester	-1.43 (-3.41, 0.55)	-1.76 (-3.42, -0.10)	-2.73 (-5.99, 0.53)	-1.37 (-4.12, 1.38)	-3.84 (-7.46, -0.22)	0.04 (-3.02, 3.09)
	Total pregnancy	1.64 (0.06, 3.21)	0.5 (-0.82, 1.83)	-0.27 (-2.34, 1.80)	0.23 (-1.52, 1.98)	-0.85 (-3.28, 1.57)	1.69 (-0.35, 3.73)
Estimated exposure to NO ₂	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, -1.39)	-0.31 (-2.22, 1.60)	-1.72 (-3.31, -0.12)
	First trimester	-0.08 (-1.57, 1.42)	-1.17 (-2.43, 0.08)	0.59 (-1.14, 2.32)	-1.91 (-3.37, -0.45)	1.28 (-0.68, 3.24)	-1.80 (-3.46, -0.15)
	Second trimester	1.81 (0.41, 3.22)	0.00 (-1.18, 1.18)	0.56 (-1.05, 2.17)	-0.75 (-2.11, 0.61)	-0.48 (-2.28, 1.33)	-2.11 (-3.63, -0.60)
	Third trimester	0.04 (-1.54, 1.62)	-1.97 (-3.29, -0.65)	0.51 (-1.45, 2.47)	-1.92 (-3.57, -0.27)	1.52 (-0.66, 3.69)	-1.92 (-3.76, -0.09)
	Total pregnancy	0.67 (-0.56, 1.89)	-1.08 (-2.11, -0.05)	0.41 (-0.83, 1.64)	-1.15 (-2.19, -0.11)	0.67 (-0.77, 2.12)	-1.68 (-2.89, -0.46)

323 All significant findings in the table are bold.

324 *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.

325 **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
326 adjusted for the other air pollutant.

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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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Table 4. Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and mental and psychomotor developmental delay

Per IQR increase in		Crude models		Adjusted models*		Co-exposure models**	
		MDD (95% CI) (N=946)	PDD (95% CI) (N=946)	MDD (95% CI) (N=945)	PDD (95% CI) (N=945)	MDD (95% CI) (N=945)	PDD (95% CI) (N=945)
Estimated exposure to PM _{2.5}	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, 2.71)	0.97 (0.63, 1.51)	1.78 (1.17, 2.71)
	First trimester	1.05 (0.83, 1.33)	1.04 (0.84, 1.28)	1.14 (0.73, 1.79)	1.42 (0.96, 1.88)	1.35 (0.80, 2.25)	1.16 (0.74, 1.82)
	Second trimester	0.63 (0.49, 0.80)	0.77 (0.63, 0.95)	0.81 (0.54, 1.22)	0.72 (0.51, 1.03)	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, 1.74)	1.39 (0.87, 2.23)	0.98 (0.64, 1.49)
	Total pregnancy	0.84 (0.69, 1.03)	0.98 (0.82, 1.18)	1.07 (0.82, 1.39)	1.07 (0.84, 1.36)	1.17 (0.86, 1.59)	0.90 (0.68, 1.20)
Estimated exposure to NO ₂	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, 1.68)	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, 1.53)	0.84 (0.65, 1.09)	1.24 (0.99, 1.57)
	Second trimester	0.79 (0.66, 0.95)	1.04 (0.88, 1.22)	0.94 (0.76, 1.15)	1.14 (0.95, 1.33)	0.98 (0.77, 1.24)	1.31 (1.06, 1.63)
	Third trimester	1.04 (0.85, 1.28)	1.25 (1.04, 1.50)	0.94 (0.73, 1.21)	1.27 (1.01, 1.61)	0.86 (0.65, 1.14)	1.28 (0.99, 1.65)
	Total pregnancy	0.92 (0.79, 1.07)	1.16 (1.01, 1.33)	0.94 (0.80, 1.11)	1.17 (1.02, 1.36)	0.9 (0.75, 1.08)	1.21 (1.02, 1.43)

All significant findings in the table are bold.

*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.

**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 adjusted for the other air pollutant.

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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 (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

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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 $PM_{2.5}$: $57.31 \mu g/m^3$, IQR: 5.76; median NO_2 : $50.46 \mu g/m^3$, 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 NO_2 exposure concentration during pregnancy were $13.4 \mu g/m^3$ and $11.5 \mu g/m^3$ (36). Researchers found that the psychomotor development score significantly decreased by 0.68 points (95% CI: -1.25, -0.11) for every $10 \mu g/m^3$ increase in NO_2 , and there was also a non-significant decrease of 1.64 points (95% CI: -3.47, 0.18) for every $5 \mu g/m^3$ 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 $PM_{2.5}$, PM_{10} , coarse particles, NO_2 and nitrogen oxides (NO_x) 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 PM_{10} , PM_{coarse} , $PM_{2.5}$ absorbance, NO_2 , NO_x , and Ozone (O_3) 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 µg/m³) and in the first trimester (Median: 82.3 µg/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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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 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 µg/m³) (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 µg/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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3 464 pollutants such as polycyclic aromatic hydrocarbons (PAH), black carbon (BC) and Ozone,
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5 465 which have been found particularly harmful to neurodevelopment in children (58). Although we
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7 466 have accounted for most of the important confounders in this study, unfortunately, we did not
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9 467 collect information on the feeding patterns of infants. This may undermine the validity and
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11 468 reliability of our findings.

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15 470 **CONCLUSION**

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17 471 This study provides evidence for an association between NO₂ exposure prior to- and during
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19 472 pregnancy with birth and neurodevelopmental outcomes in a birth cohort in Chongqing, China.
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21 473 Exposure to NO₂ and PM_{2.5} exposure before pregnancy was associated with a lower
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23 474 psychomotor development score. Increased NO₂ exposure was linked to a risk of psychomotor
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25 475 development delay during various pregnancy trimesters.

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29 477 **Declarations**

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31 478 **Ethics approval and consent to participate**

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34 479 Ethical approval for this study was granted by the Ethics Committee of Chongqing Medical
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36 480 University (#2014034). The participants provided their written informed consent to
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38 481 participate in this study. Written informed consent was obtained from the individual(s) for the
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40 482 publication of any potentially identifiable images or data included in this article.

41 483 **Data availability statement**

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44 484 The data that support the findings of this study are available from Chongqing Medical
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46 485 University but restrictions apply to the availability of these data, which were used under
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48 486 license for the current study, and so are not publicly available. Data are however available
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50 487 from the authors upon reasonable request and with permission of Chongqing Medical
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52 488 University.

53 489 **Competing interests**

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55 490 The authors declare that they have no conflicts of interests.

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58 491 **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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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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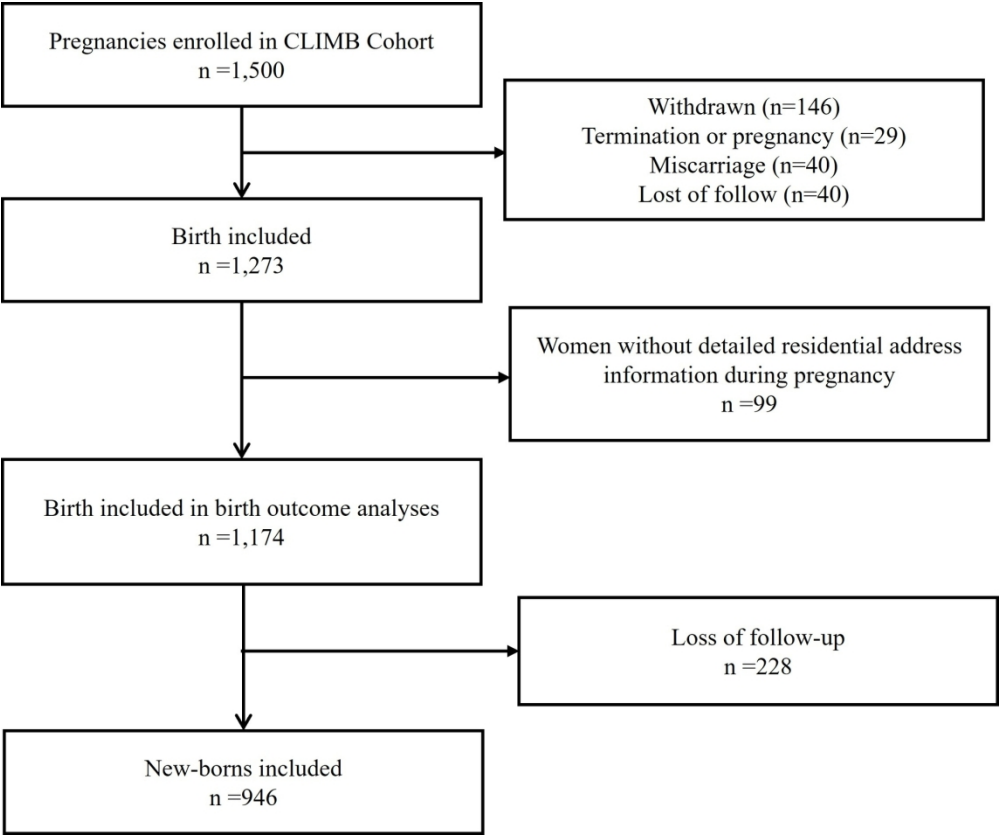


Figure 1 Flow chart of the study population in CLIMB

173x144mm (300 x 300 DPI)

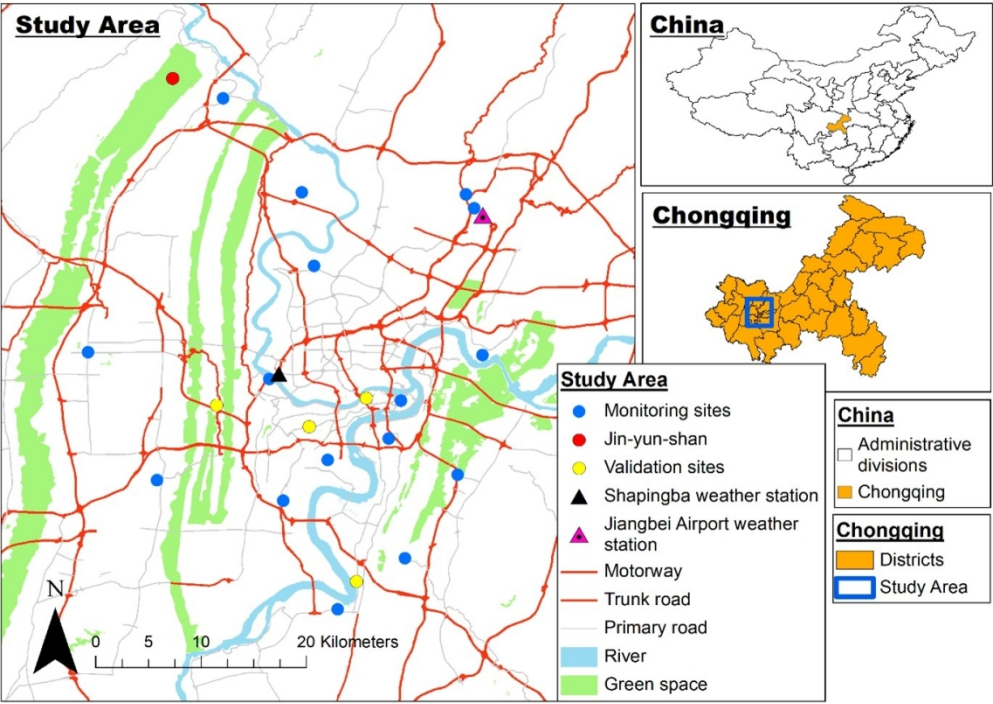


Figure 2 Study area and location of monitoring sites (OpenStreetMap contributors, 2015; <https://data.nextgis.com/en/region/CN-50/>).

159x112mm (220 x 220 DPI)

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	

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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	

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	
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）	
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+	“一”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	辅助下行走	
45	11.1	独站	
46	12	投球	
47	12.1	独走	
48	12.4	起立 I	
49	13.2	辅助下右足独站	
50	13.7	辅助下左足独站	
51	14.1	侧身走	
52	14.5	辅助上楼梯	
53	14.7	倒退走	
54	15.1	辅助下楼梯	
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：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	
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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eTable 3 Distributions of PM_{2.5} and NO₂ exposure level in 90 days prior to conception, each trimester (T1, T2, and T3) and combined across whole pregnancy period (WP) (n = 1,174)

	Estimated exposure (µg/m ³)							
	N	Minimum	25 th percentile	Mean ± SD	Median	IQR	75 th percentile	Maximum
Estimated exposure to PM _{2.5}								
90 days prior to conception	1,174	38.17	44.00	52.91 ± 10.99	48.40	40.07	62.06	80.53
First trimester	1,174	37.26	43.77	52.07 ± 10.98	47.20	37.31	61.08	82.41
Second trimester	1,174	38.46	47.57	58.64 ± 12.21	57.90	49.62	67.19	90.02
Third trimester	1,174	37.03	47.25	61.83 ± 16.04	58.80	48.7	75.95	96.48
Total pregnancy	1,174	46.69	54.85	57.48 ± 3.97	57.30	47.76	60.61	66.98
Estimated exposure to NO ₂								
90 days prior to conception	1,174	25.86	45.49	49.59 ± 6.34	49.90	27	53.76	70.48
First trimester	1,174	20.81	44.60	48.8 ± 6.43	48.90	25.1	53.10	69.31
Second trimester	1,174	28.93	47.18	50.98 ± 6.23	51.20	27.2	54.90	70.42
Third trimester	1,174	20.57	47.20	51.79 ± 6.78	52.40	27.47	56.67	75.12
Total pregnancy	1,174	27.50	47.89	50.52 ± 5.08	50.40	25.1	53.40	67.53

eTable 4 Pearson's correlations of PM_{2.5} and NO₂ between each of the five different pregnancy time periods (N = 1,174)

Estimated exposure to		PM _{2.5}					NO ₂				
		90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy	90 days prior to conception	First trimester	Second trimester	Third trimester	Total pregnancy
PM _{2.5}	90 days prior to conception	1									
	First trimester	-0.065	1								
	Second trimester	-0.779	-0.2012	1							
	Third trimester	0.288	-0.7613	-0.1688	1						
	Total pregnancy	-0.534	-0.2709	0.6838	0.3858	1					
NO ₂	90 days prior to conception	0.6383	0.0684	-0.4588	0.3714	0.0376	1				
	First trimester	0.1537	0.6352	-0.0159	-0.4927	-0.0633	0.554	1			
	Second trimester	-0.431	0.0714	0.6269	-0.0133	0.7251	0.334	0.5399	1		
	Third trimester	0.3027	-0.5213	0.0528	0.6817	0.4432	0.714	0.2159	0.5145	1	
	Total pregnancy	0.0057	0.0781	0.2862	0.0737	0.4779	0.678	0.7435	0.8755	0.7331	1

eTable 5 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (unadjusted models)

Per IQR increase in		Mean difference		Odd ratios			
		Birth weight, grams (95% CI)	Birth length, cm (95% CI)	PTB (case: 33) (95% CI)	LBW (case: 30) (95% CI)	LGA (case: 108) (95% CI)	SGA (case: 84) (95% CI)
		(N=941)	(N=927)	(N=945)	(N=945)	(N=945)	(N=945)
Estimated exposure to PM _{2.5}	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 (0.77, 2.36)	1.2 (0.87, 1.64)	0.98 (0.68, 1.41)
	First trimester	21.95 (-16.90, 60.80)	0.14 (-0.03, 0.31)	0.98 (0.57, 1.70)	1 (0.59, 1.77)	0.97 (0.71, 1.33)	0.78 (0.54, 1.13)
	Second trimester	-18.21 (-57.78, 21.37)	0.04 (-0.13, 0.21)	0.85 (0.48, 1.50)	0.61 (0.33, 1.15)	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 (0.89, 2.85)	1.08 (0.76, 1.54)	1.12 (0.76, 1.66)
	Total pregnancy	-20.02 (-55.69, 15.65)	-0.1 (-0.26, 0.05)	0.81 (0.49, 1.33)	0.69 (0.41, 1.16)	1 (0.75, 1.34)	1.2 (0.87, 1.66)
Estimated exposure to NO ₂	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 (0.93, 2.65)	1.21 (0.93, 1.57)	1.24 (0.92, 1.66)
	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)
	Second trimester	-22.85 (-53.39, 7.70)	-0.04 (-0.17, 0.09)	1.11 (0.72, 1.70)	1.08 (0.69, 1.69)	1.06 (0.83, 1.36)	1.46 (1.10, 1.93)
	Third trimester	-32.72 (-67.16, 1.72)	-0.16 (-0.32, -0.01)	1.13 (0.69, 1.85)	1.35 (0.89, 2.28)	1.24 (0.94, 1.65)	1.58 (1.14, 2.18)
	Total pregnancy	-16.58 (-43.35, 10.20)	-0.03 (-0.15, 0.09)	1.03 (0.71, 1.50)	1.13 (0.77, 1.69)	1.16 (0.93, 1.44)	1.44 (1.13, 1.85)

All significant findings in the table are bold.

eTable 6 Associations between PM_{2.5} and NO₂ exposure in different pregnancy periods and adverse birth outcomes (co-exposure models)

		Mean difference		Odd ratios			
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 (case: 30) (95% CI) (N=945)	LGA (case: 108) (95% CI) (N=945)	SGA (case: 84) (95% CI) (N=945)
Estimated exposure to PM _{2.5}	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 (0.04, 1.22)	1.14 (0.55, 2.40)	1.18 (0.48, 2.92)
	First trimester	19.59 (-71.23, 110.41)	0.00 (-0.40, 0.39)	0.97 (0.26, 3.65)	0.66 (0.25, 3.05)	0.67 (0.32, 1.42)	0.73 (0.28, 1.93)
	Second trimester	-25.62 (-104.32, 53.09)	0.08 (-0.26, 0.42)	1.34 (0.37, 4.86)	0.94 (0.42, 4.21)	0.83 (0.42, 1.62)	0.69 (0.34, 1.40)
	Third trimester	13.77 (-72.33, 99.86)	-0.2 (-0.58, 0.17)	1.12 (0.31, 4.07)	0.94 (0.33, 3.35)	1.00 (0.48, 2.12)	0.57 (0.26, 1.23)
	Total pregnancy	21.13 (-36.41, 78.67)	0.02 (-0.23, 0.27)	0.73 (0.33, 1.61)	0.52 (0.24, 1.15)	0.98 (0.60, 1.61)	0.55 (0.32, 0.96)
Estimated exposure to NO ₂	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 (0.61, 2.64)	1.27 (0.84, 1.90)	1.39 (0.90, 2.15)
	First trimester	-14.53 (-61.15, 32.09)	0.05 (-0.16, 0.25)	0.91 (0.45, 1.83)	1.14 (0.58, 2.37)	1.33 (0.89, 2.00)	1.70 (1.07, 2.69)
	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)
	Third trimester	-13.13 (-64.87, 38.62)	0.04 (-0.18, 0.27)	0.77 (0.35, 1.67)	0.97 (0.43, 2.16)	1.41 (0.90, 2.23)	1.77 (1.08, 2.91)
	Total pregnancy	-15.02 (-49.33, 19.30)	0.00 (-0.15, 0.15)	1.08 (0.64, 1.80)	1.28 (0.75, 2.18)	1.21 (0.90, 1.63)	1.60 (1.15, 2.23)

24 All significant findings in the table are bold.

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 adjusted for the other air pollutant