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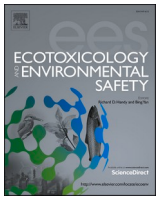

Associations between maternal exposure to air pollution during pregnancy and trajectories of infant growth: A birth cohort study

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ABSTRACT

Objective: We examined the relationships between infants' growth trajectories and prenatal exposure to air pollution, which is still under-investigated.
Methods: A birth cohort study was constructed using medical records of pregnant women and infants born between 2015 and 2019 in Foshan, China. Using satellite-based spatial-temporal models, prenatal exposure to air pollutants including particulate matter with an aerodynamic dimension of < 2.5 μm ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3) was assessed at each woman's residence. Latent class growth modeling was used to identify trajectories of physical (body length and weight) growth and neurodevelopment, which were repeatedly measured within 1 year after birth. Logistic regression models were used to investigate the associations between prenatal exposure to air pollution and the risks of growth disorders, adjusting for an array of potential confounders.
Results: We identified two growth trajectories for body length [normal: 3829 (93%); retardation: 288 (7%)], three for weight [normal: 2475 (59.6%); retardation: 390 (9.4%); overgrowth: 1287 (31%)], and two for neurodevelopment [normal: 956 (66.1%); retardation: 491 (33.9%)]. For exposure over whole pregnancy, SO_2 was associated with an increased risk of body length retardation (OR for per 1 μg/m^3 increment: 1.09, 95%CI: 1.01–1.17); $PM_{2.5}$ (OR: 1.05, 95%CI: 1.03–1.07), SO_2 (OR: 1.15, 95%CI: 1.08–1.22), and NO_2 (OR: 1.05, 95%CI: 1.03–1.07) were positively associated with neurodevelopmental retardation. Such associations appeared stronger for exposures over the first and second trimesters. No significant associations were detected for weight growth.
Conclusions: Maternal exposure to air pollution during pregnancy was associated with higher risks of impairments in both physical growth, particularly body length, and neurodevelopment.

1. Introduction

Child growth is a complex and dynamic process. The early-life stage (from conception to 2 years old) is particularly critical because human bodies grow up rapidly and are highly susceptible to hazardous factors during this period (Isaevska et al., 2021). Exposure to various environmental hazards can result in adverse effects, interfering with the growth and development of children (Kim et al., 2016). Moreover, extensive evidence has also shown that growth disorders (either overgrowth or delay) in early life can raise the chances of developing various chronic health conditions later in life (Guo et al., 2020).

Air pollution is a global environmental hazard. It has been suggested that air pollution can induce systemic inflammation and oxidative stress, and consequently affect fetal growth through various mechanisms such as altering placental volume and blood flow, inducing epigenetic changes in placental and fetal tissues, and altering mitochondrial

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content (Nobles et al., 2019). In recent years, increasing studies have shown that prenatal exposure to air pollution is associated with various adverse birth outcomes, such as preterm birth (PTB, gestation <37 weeks), fetal growth restriction (FGR), and low birth weight (LBW, birth weight < 2500 g) (Kim et al., 2016; van den Hooven et al., 2012), supporting the negative impact of air pollution on fetal development. By comparison, epidemiological studies on the associations between prenatal air pollution exposure and postnatal growth and development of children remain limited, and the findings are still conflicting (Tan et al., 2021; Yang et al., 2018).

To be noted, most previous studies were cross-sectional in design, which only measured infant growth outcomes at a certain time point and therefore were unable to assess the dynamic changes over time (Cao et al., 2019; Westergaard et al., 2017). Although a limited number of longitudinal studies have also been conducted, these studies mainly used statistical methods such as multi-level models, growth measurement models, or repeated measurement analysis to deal with the longitudinal data of infant growth and neurodevelopment (de Bont et al., 2020; Kim et al., 2018). For these models, a prerequisite assumption is that the study samples should come from the same population and follow the same developmental trend or trajectory. However, such homogeneity hypothesis is often difficult to meet, given the great individual variations in growth. In other words, findings from studies using these conventional statistical models are subject to the bias caused by the great heterogeneity in infant growth. In this case, trajectory modeling approaches such as latent class growth modeling (LCGM) are more appropriate to be used to identify the growth trend of children because they can identify different growth trajectories without the requirement of the homogeneity assumption (Boamah-Kaali et al., 2021).

A better understanding of the health effects of air pollution on infant growth is imperative to the development of effective strategies to improve the health of children as well as adults later. Therefore, we used LCGM to characterize the dynamic trends of physical growth and neurodevelopment in infants using a birth cohort in China, and to further examine the associations between prenatal exposure to air pollution and infant growth. We hypothesized that prenatal exposure to air pollution would be associated with increased risks of growth disorders in infants.

2. Methods

2.1. Study design and participants

Using medical information from expectant mothers and children admitted to Foshan Women and Children Hospital (the biggest maternity hospital in Foshan, China, which offers maternal and child healthcare services for local women and children), a birth cohort was created. Our earlier works have documented the birth cohort's specifics (Yang et al., 2020b; Yang et al., 2020c). In short, it is a common practice in China that pregnant women who receive their first antenatal examination are registered and documented at a medical institution accredited by the government, which then follows the registered women until they give birth. After birth, children are also taken to the hospital by their caregivers for a series of health assessments, including measurements of physical growth and neurodevelopment. We built the cohort by linking the medical records of women and their offspring using unique identities. The Sun Yat-sen University School of Public Health's Ethics Committee provided ethical approval on the present study.

In this study, we included infants who were born between November, 2015 and January, 2019. First, we excluded individuals 1) who did not provide information on the residential address that was used in address-specific exposure assessment; 2) who lacked physical examination and neurodevelopment information in the first year after birth; or 3) who had missing values for important covariates used in statistical analysis. For the LCGM analysis, at least three measurements at different time points are required (Nguena Nguefack et al., 2020a). Thus, we only included subjects with four measurements within the first year after birth for the analyses on body length and weight (4117 and 4152, respectively). For the analysis of neurodevelopment, 1447 subjects with three measurements were included, as the assessment was usually not performed until infants reached 3 months of age. According to Nagin et al., a dataset of at least 300–500 cases is sufficient for running LCGM. Therefore, all three cohorts included in the data analyses would have sufficient statistical power (Nagin, 2005). The process of participant selection is shown in the flowchart (Fig. S1).

2.2. Measurements

2.2.1. Physical growth and neurodevelopment

Measurements of body length and weight were performed by trained medical workers when infants were born and reached ages 3, 6, and 9 months. Neurodevelopment assessment was carried out utilizing the Neuropsychological Examination Scale for Chinese Children (NESCC), as previously described in our study (Su et al., 2022). In brief, the NESCC was developed by the Capital Institute of Pediatrics and the Institute of Psychology of the Chinese Academy of Sciences to assess the neurodevelopment status of 0- to 6-year-old Chinese children with reference to the widely used Gesell Development Diagnosis Scale (GDDS). Five developmental areas are covered by age-specific questions in the NESCC, including gross motor, fine motor, language, adaptability, and social responsiveness. A child was grouped into different groups based on his or her age (months), and then a group of items (1−3) were used to evaluate each domain. An individual score was given for each domain, and the average of the five domains was used to calculate the full-scale score. The developmental quotient (DQ) was then computed (DQ = (full-scale score/age) 100). We used the DQ as a measure of overall neurodevelopment for each infant.

2.2.2. Air pollution exposure

Air pollution exposure data were derived from China's High Air Pollution platform (https://weijing-rs.github.io/product.html) and the Tracking Air Pollution in China (http://tapdata.org.cn/?page_id=129). These two platforms used satellite remote sensing data, land use information, and other spatial-temporal predictors to build high-resolution (10 km × 10 km) spatial-temporal models to estimate the near-surface concentrations of several major air pollutants, including particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3). The models performed well in predicting the long-term concentrations of air pollution over Mainland China. In particular, the cross-validation coefficient of determination (CV-R^2) and root-mean-square error (RMSE) were 0.91 and 12.67 μg/m^3 for $PM_{2.5}$ (2013–2020), 0.84 and 10.1 μg/m^3 for SO_2 (2013–2020), 0.84 and 8.0 μg/m^3 for NO_2 (2013–2020), and 0.68 and 28.4 μg/m^3 for O_3 (2013–2020), respectively (Wei et al., 2021; Wei et al., 2023; Wei et al., 2022; Xue et al., 2020).

In this study, the residential addresses of pregnant women were geocoded into longitude and latitude data. Afterward, daily air pollution concentrations at each woman's home were calculated using bilinear interpolation. By averaging daily concentrations from the date of conception (the last menstrual period) to delivery, we calculated the mean levels of exposure to the four air pollutants mentioned above over the whole course of pregnancy. Additionally, average concentrations for each trimester—including trimester 1 (from 1 to 13 weeks), trimester 2 (from 14 to 26 weeks), and trimester 3 (from 27 weeks to delivery)—were also calculated.

2.2.3. Covariates

Potential confounding variables were selected mainly based on literature review. We included maternal age at delivery (years), employment status (employed or unemployed), education (middle school or below, high school, or college or above), delivery mode (natural or cesarean), gestational diabetes mellitus (yes or no), hypertension during pregnancy (yes or no), feeding pattern for the first 6

months (breast-feeding, artificial-feeding, or mix-feeding), infant's sex (male or female), and preterm birth (yes or no), all of which were extracted from the medical records.

2.3. Statistical analysis

2.3.1. Trajectory modeling

We used the LCGM approach to identify the potential trajectories of physical growth and neurodevelopment in infants. LCGM assumes that in each class or subgroup, individuals have the same evolution of growth and development. Then, it calculates the percentage of the population falls into each of these groupings. Additionally, the model calculates each person's posterior group probability, which is the likelihood that they belong to a particular subgroup (Nguena Nguefack et al., 2020b). Several goodness-of-fit and model adequacy indices are used to compare different models and to select the best one. The criteria include:1) the smallest group should include at least 5% of the sample; 2) Akaike information criterion (AIC): smaller values suggest better fit; 3) Bayesian Information criterion (BIC): smaller values suggest better fit; 4) Entropy index: it is used to evaluate the accuracy of classification. The Entropy index ranges from 0 to 1, and when the entropy index is equal to 0.6, it indicates that about 20% of individuals have classification errors, and an Entropy index of $\geq$ 0.8 indicates that the accuracy of classification is more than 90%; 5) Lo-Mendell-Rubin (LMR) index: the likelihood ratio test index LMR is used to compare the fitting performance of models with different categories. If the *P*-value reaches a significant level ($<$ 0.05), it indicates that the model with M categories is better than the model with M-1 categories (Rosato and Baer, 2012).

In the present analysis, the growth trajectories of length and weight were constructed using data collected at ages 0, 3, 6, and 9 months, while the neurodevelopment trajectories were constructed using neurodevelopmental assessments at ages 3, 6, and 9 months. Growth disorders (either overgrowth or delay) identified by LCGM were used as categorical outcome variables in the subsequent regression analyses on their associations with air pollution exposure.

2.3.2. Associations between air pollution during pregnancy and infants' growth and development trajectory

Logistic regression was used to investigate the associations between prenatal exposure to $PM_{2.5}$, SO_2, NO_2, and O_3 and infants' physical growth and neurodevelopment. Air pollutants were included in the models as continuous variables. Odds ratio (OR) with 95% confidence intervals (CI) for per 1 $\mu g/m^3$ increment in the concentrations of air pollutants in relation to growth disorders were calculated with adjustment for maternal age at delivery, delivery mode, employment status, feeding pattern for the first 6 months, education, gestational diabetes mellitus, hypertension during pregnancy, infant's sex, and PTB. Each air pollutant was examined in a separate model, as strong correlations were observed among the pollutants (Table S3).

2.4. Sensitivity analysis

In sensitivity analysis, 1) we included two pollutants into the same model (i.e., two-pollutant models) for mutual adjustment; 2) we excluded children with PTB or LBW; and 3) we made additional adjustment for parity.

All statistical analyses were conducted using R 4.1.2 (R Core Team, Vienna, Austria). A two-tailed *P* value of $<$ 0.05 was considered statistically significant.

3. Results

3.1. General characteristics of study participants

We included 4117 infants for analysis of body length growth, 4152 for weight growth, and 1447 for neurodevelopment. In general, the distribution of demographic characteristics was similar among the three cohorts. More infants were males ($>$ 55%). The mean maternal age of delivery was about 29.59 years, and most pregnant women were employed. In each group, approximately 16% of women were diagnosed with gestational diabetes and 1% with gestational hypertension (Table 1). Table S3 displays the distribution of the air pollutants. Generally, the levels of $PM_{2.5}$, SO_2, NO_2, and O_3 were slightly higher in the first trimester than in the other two trimesters.

3.2. Infants' growth and neurodevelopment trajectory

The goodness-of-fit and model adequacy indices were used to choose the best group-based trajectory model (Zhao et al., 2022) (Table S1). The parameter estimation results of the LCGM model fitting for infants' physical growth and neurodevelopment are shown in Table 2.

For growth trajectories of body length, three groups were identified (Fig. 1). The first category (accounting for 47.6%) was characterized by a high initial value and a slow growth rate, especially at the early stage. The second category (accounting for 45.4%) had a similar trend but with

Table 1
General Characteristics of Children in Different Analytical Cohorts.

Variables	Length Cohort[a]	Weight Cohort[b]	Neurodevelopment Cohort[c]
	(N = 4117)	(N = 4152)	(N = 1447)
Infants' sex, n (%)			
Female	1841 (44.7)	1857 (44.7)	640 (44.2)
Male	2276 (55.3)	2295 (55.3)	807 (55.8)
Maternal age at delivery (Mean±SD)	29.59 (4.65)	29.59 (4.66)	29.22 (4.60)
Occupation, n (%)			
Employed	2178 (52.9)	2196 (52.9)	773 (53.4)
Unemployed	1939 (47.1)	1956 (47.1)	674 (46.6)
Gestational diabetes mellitus, n (%)			
Yes	669 (16.2)	678 (16.3)	223 (15.4)
No	3448 (73.8)	3474 (83.7)	1224 (84.6)
Hypertension, n (%)			
Yes	41 (1.0)	41 (1.0)	15 (1.0)
No	4076 (99.0)	4111 (99.0)	1432 (99.0)
Breastfeeding, n (%)			
Breast-feeding	175 (4.3)	177 (4.3)	36 (2.5)
Artificial-feeding	3942 (92.5)	3842 (92.5)	1361 (94.1)
Mix- feeding	0 (0.0)	130 (3.2)	50 (3.5)
Mode of delivery, n (%)			
Natural	2023 (49.1)	2055 (49.5)	717 (49.6)
Cesarean	2098 (50.9)	2097 (50.5)	730 (50.4)
Low Birth Weight, n (%)			
Yes	624 (15.2)	83 (2.0)	7 (0.5)
No	3528 (74.8)	4069 (98.0)	1440 (99.5)
Premature Birth, n (%)			
Yes	648 (15.7)	624 (15.0)	176 (12.2)
No	3469 (84.3)	3528 (85.0)	1271 (87.8)

Abbreviations: SD, standard deviation;
[a] The population included in the analysis of infant body length and developmental trajectory;
[b] The population included in the analysis of infant body weight and developmental trajectory;
[c] The population included in the analysis of infant neurodevelopmental trajectory.

Table 2
Results of parameter estimation for the LCGM model.

	Length			Weight			Neural development		
Class	Estimate of the mean	Standard error	*P* value	Estimate of the mean	Standard error	*P* value	Estimate of the mean	Standard error	*P* value
Class 1[a]	(N = 1960, p = 47.6%)			(N = 392, p = 9.4%)			(N = 491, p = 33.9%)		
α_1	48.18	0.12	**< 0.001**	1.89	0.10	**< 0.001**	86.10	0.78	**< 0.001**
β_1	12.52	0.06	**< 0.001**	-0.26	1.14	0.817	2.72	0.67	**< 0.001**
β_1^2	-1.93	0.03	**< 0.001**	2.53	1.12	**0.024**			
Class 2[a]	(N = 1868, p = 45.4%)			(N = 1287, p = 31.0%)			(N = 956, p = 66.1%)		
α_2	49.99	0.06	**< 0.001**	3.37	0.02	**< 0.001**	92.94	0.78	**< 0.001**
β_2	13.95	0.07	**< 0.001**	9.18	0.03	**< 0.001**	3.31	0.35	**< 0.001**
β_2^2	-1.83	0.00	**< 0.001**	-5.60	0.00	**< 0.001**			
Class 3[a]	(N = 289, p = 7.0%)			(N = 2473, p = 59.6%)					
α_3	40.28	0.44	**< 0.001**	3.02	0.02	**< 0.001**			
β_3	14.81	0.27	**< 0.001**	6.27	0.03	**< 0.001**			
β_3^2	-3.15	0.00	**< 0.001**	-3.49	0.00	**< 0.001**			

[a] α_k represents the intercept; β_k and β_k^2 represent slopes and quadratic term coefficients, respectively; N represents the number of individuals; p represents the proportion of individuals in this category. *P* values in bold indicate statistical significance (< 0.05).

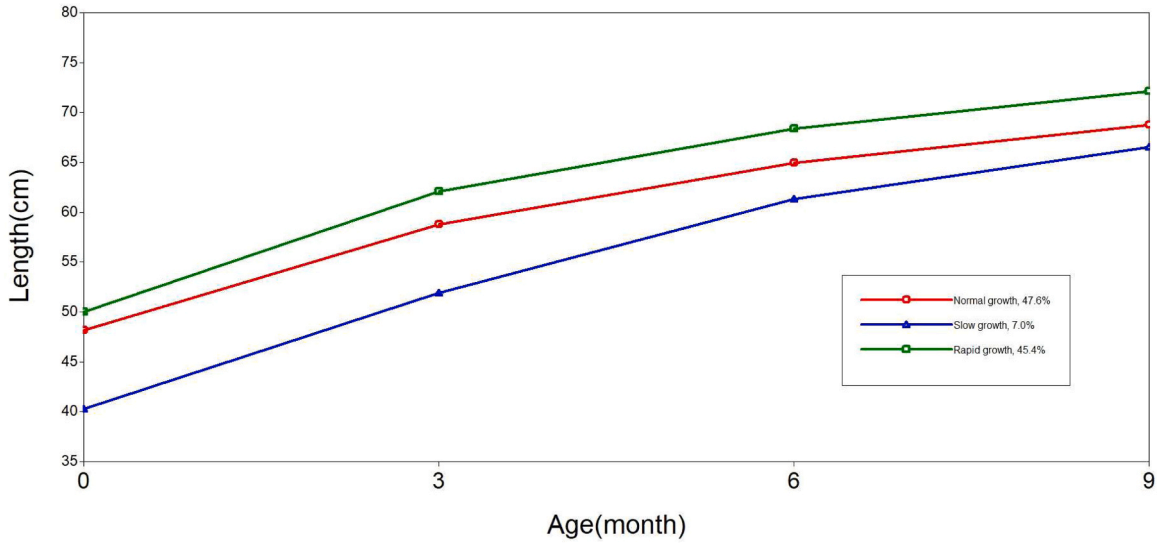

Fig. 1. Growth trajectories of body length identified by Latent Class Growth Model.

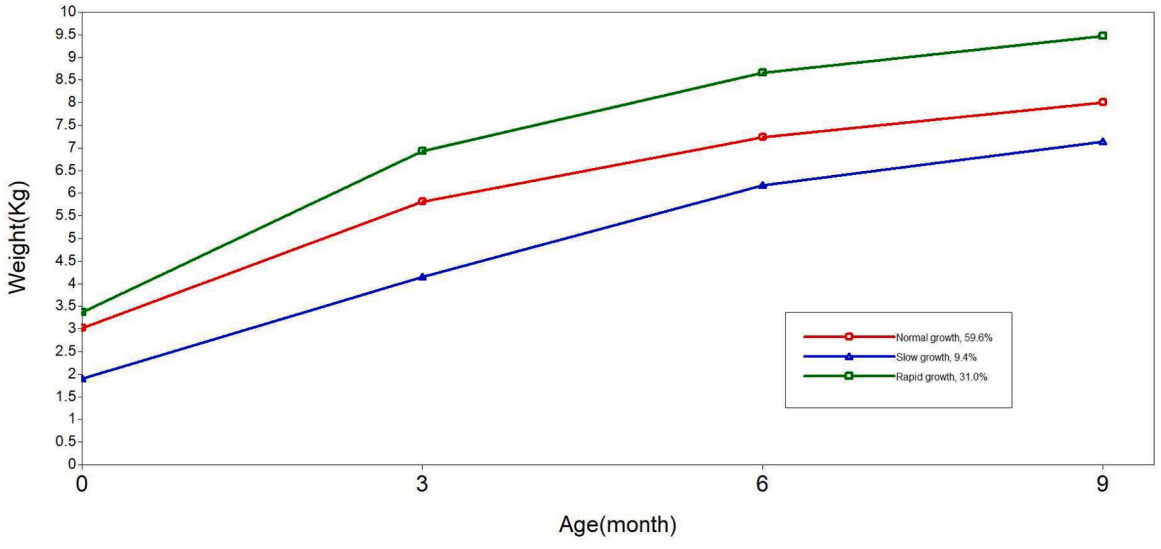

Fig. 2. Growth trajectories of body weight identified by Latent Class Growth Model.

a higher initial value and a greater growth rate. The third category (accounting for 7.0%) had the lowest initial value of body length. In this group, body length also increased with age, but the growth rate slowed down more rapidly than in the other two groups. We combined categories 1 and 2 into one group and treated it as the group with normal length growth, while category 3 was treated as the group with delayed length growth.

For weight growth, three different classifications were identified (Fig. 2). The first category (accounting for 9.4%) was defined as the retardation group; the second category (accounting for 31.0%) was defined as the overgrowth group; and the third category (accounting for 59.6%) was defined as the normal growth group.

Two growth classifications were identified for neurodevelopment (Fig. 3). The first category was defined as the "normal neurodevelopmental group", which accounted for 66.1% of the study population. The second category accounted for 33.9% and was defined as the neurodevelopmental delay group.

3.3. The association between air pollution and Infants' Growth and Development Trajectory

The logistic regression results are shown in Table 3. For exposure over the whole pregnancy, SO_2 exposure was associated with raised possibilities of body length retardation (OR: 1.09, 95%CI: 1.01–1.17) and neurodevelopment delay (OR: 1.15, 95%CI: 1.08–1.22); $PM_{2.5}$ (OR: 1.05, 95%CI: 1.03–1.07) and NO_2 (OR: 1.05, 95%CI: 1.03–1.07) exposure were also associated with neurodevelopmental delay. There was no evidence of significant associations between any air pollutant and weight growth.

We also found some trimester-specific relationships between air pollution and infant growth. For body length growth, we found stronger associations for the second and third trimesters. For example, SO_2 exposure during trimester 2 (OR: 1.08, 95%CI: 1.01–1.14) and trimester 3 (OR: 1.06, 95%CI: 1.01–1.12) was related to higher risks of body length retardation, whereas $PM_{2.5}$ exposure during the third trimester was associated with the highest risk of body length retardation (OR: 1.02, 95%CI: 1.00–1.03). For neurodevelopment, we found stronger relationships for the first and second trimesters. In particular, stronger correlations were found for $PM_{2.5}$, SO_2, and NO_2 exposure during the first and second trimesters than for the third trimester.

3.4. Sensitivity analysis

In two-pollutant models, after adjusting for $PM_{2.5}$ or NO_2, the association between SO_2 and length retardation was generally consistent, especially for the exposures over the entire pregnancy and the second trimester (Table S4). For neurodevelopmental delay, its associations with $PM_{2.5}$ and SO_2 exposure during the entire trimester were also unchanged after adjustment for other pollutants (Table S5).

After excluding infants with PTB or LBW, the relationships between $PM_{2.5}$ and SO_2 and length growth were somewhat attenuated (Table S5a). Compared with the findings in the original analyses, the relationships between air pollution and neurodevelopmental delay did not change significantly (Table S5c). After adjusting for parity, the associations observed in the original analyse s did not change remarkably, either (Table S7).

4. Discussion

In this study, we identified different trajectories for both physical growth and neurodevelopment using repeatedly measured data among infants with LCGM modeling. We further found that the risks of body length retardation and neurodevelopmental delay were higher for infants whose mothers were exposed to higher levels of air pollution.

Our findings indicate that prenatal exposure to $PM_{2.5}$, NO_2, and SO_2 was significantly related to higher risks of length growth retardation. Some previous studies have shown that childhood exposure to SO_2 was inversely related to height in adolescents or adults (Huang et al., 2017; Klis and Wronka, 2020), but fewer studies tracked growth trajectories in infants. Particularly, a study carried out in Hong Kong explored the correlation between average exposure to air pollution during three growing periods from conception to age 8 and height by age (~9, ~11, ~13, and ~15 years), and reported that shorter height was associated with higher SO_2 exposure. The authors argued that air pollution may impair the growth and developmental trajectory instead of age-specific height (Huang et al., 2018). By comparison, more studies reported negative correlations between maternal exposure to $PM_{2.5}$, NO_2, and SO_2, and infant length at birth (Bergstra et al., 2021; He et al., 2018; Soesanti et al., 2023; Yang et al., 2023). To be noted, fetal growth is a dynamic process, and theoretically, air pollution's impact on fetal growth and development probably begins in pregnancy. Indeed, some studies concentrated on the effects of air pollution on fetal growth in utero and found that prenatal exposure to $PM_{2.5}$ and SO_2 was significantly associated with reduced femur length and humerus length in the

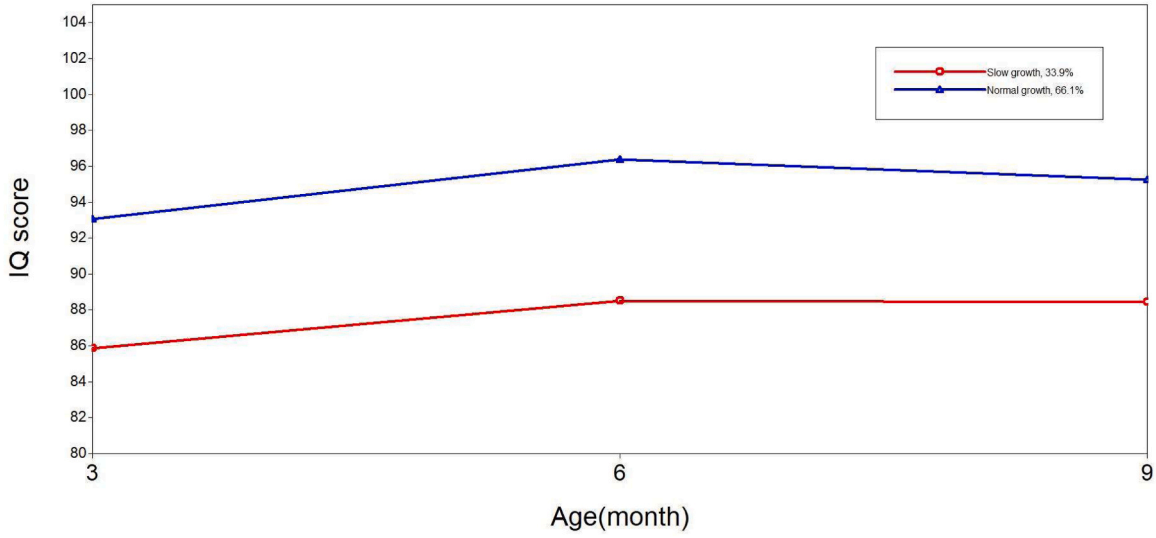

Fig. 3. Neurodevelopmental trajectories identified by Latent Class Growth Model.

Table 3
Associations between air pollution and length, weight, and neurodevelopment trajectories.

Period	Pollutants	Odds ratio for length growth delay (95%CI)[a]	Odds ratio for weight growth delay (95%CI)[a]	Odds ratio for weight overgrowth (95%CI)[a]	Odds ratio for neurodevelopmental delay (95%CI)[a]
First trimester	$PM_{2.5}$	0.99 (0.98, 1.00)	1.01 (0.99, 1.01)	0.99 (0.98, 1.00)	**1.01 (1.00, 1.02)**
	SO_2	1.00 (0.95, 1.06)	1.01 (0.98, 1.03)	0.99 (0.95, 1.04)	**1.09 (1.04, 1.13)**
	NO_2	0.98 (0.97, 0.99)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	**1.01 (1.00, 1.02)**
	O_3	**1.00 (1.00, 1.01)**	1.00 (0.99, 1.00)	**1.00 (1.00, 1.01)**	**1.01 (1.00, 1.01)**
Second trimester	$PM_{2.5}$	1.01 (0.99, 1.02)	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	**1.03 (1.02, 1.04)**
	SO_2	**1.08 (1.01, 1.14)**	1.01 (0.99, 1.04)	1.04 (0.99, 1.09)	**1.10 (1.06, 1.15)**
	NO_2	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	**1.03 (1.02, 1.04)**
	O_3	1.00 (0.99, 1.01)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)
Third trimester	$PM_{2.5}$	**1.02 (1.00, 1.03)**	0.99 (0.99, 1.00)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)
	SO_2	**1.06 (1.01, 1.12)**	1.00 (0.98, 1.03)	1.02 (0.98, 1.07)	1.03 (0.98, 1.08)
	NO_2	**1.01 (1.00, 1.02)**	0.99 (0.99, 1.00)	1.01 (0.99, 1.02)	1.00 (0.99, 1.01)
	O_3	0.99 (0.99, 1.00)	**1.00 (1.00, 1.01)**	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Pregnancy	$PM_{2.5}$	1.01 (0.99, 1.04)	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)	**1.05 (1.03, 1.07)**
	SO_2	**1.09 (1.01, 1.17)**	1.01 (0.98, 1.05)	1.03 (0.97, 1.10)	**1.15 (1.08, 1.22)**
	NO_2	0.99 (0.97, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)	**1.05 (1.03, 1.07)**
	O_3	0.99 (0.98, 1.01)	1.00 (0.99, 1.00)	0.99 (0.98, 1.01)	0.99 (0.98, 1.00)

[a] Odds ratio (OR) of height, weight growth delay, and neurodevelopment delay associated with per 1 unit increase in air pollutant concentrations adjusted for maternal age at delivery, employment status, education, delivery mode, feeding pattern for the first 6 months, gestational diabetes mellitus, hypertension during pregnancy, child's sex, premature birth. ORs in bold indicate statistical significance (P value < 0.05).

second trimester and third trimester (Shao et al., 2020; Wang et al., 2017).

We also observed that higher prenatal exposure to $PM_{2.5}$, NO_2, and SO_2 was associated with increased risks of neurodevelopmental delay in infants. A number of previous epidemiological studies have also shown that prenatal exposure to $PM_{2.5}$ could increase the risk of delayed neurodevelopment (Ahmed et al., 2022; Binter et al., 2022; Chen et al., 2020; Guxens et al., 2014; Hurtado-Díaz et al., 2021; Iglesias-Vázquez et al., 2022; Lertxundi et al., 2019; Morgan et al., 2023; Ni et al., 2022; Shih et al., 2023; Su et al., 2022; Wang et al., 2022; Wang et al., 2021; Xu et al., 2022). Different from our results, most of these studies reported that the sensitive window of $PM_{2.5}$ exposure was the second and third trimesters (Chen et al., 2020; Hurtado-Díaz et al., 2021; Morgan et al., 2023; Shih et al., 2023). Some other studies have also found significant associations between NO_2 and neurodevelopment, which was in line with our findings, despite the instruments (i.e., scales) employed to measure neurodevelopment varied among these studies (Ahmed et al., 2022; Guxens et al., 2012; Iglesias-Vázquez et al., 2022; Kim et al., 2014; Lertxundi et al., 2019; Ni et al., 2022; Shang et al., 2020; Yu et al., 2022). Although the overall associations reported in previous studies are similar to our findings, the reported sensitive time windows are also different. According to Ni et al., children had a greater risk of developing behavioral functioning problems resulting from abnormal development of the nervous system, if their mothers experienced higher NO_2 exposure in the first and second trimesters (Ni et al., 2022). As for SO_2, few studies to date have explored its association with neurodevelopment in children. One study from Taiwan showed that exposure to even modest levels of SO_2 during pregnancy was associated with poor neurodevelopment in early childhood (Lin et al., 2014). Another study reported that prenatal SO_2 exposure was inversely related to gross motor, adaptive behavior, and language development, but not fine motor or social behavior (Yu et al., 2021).

No significant associations between prenatal air pollution exposure and weight growth trajectories were found. Many epidemiological studies have explored the associations between prenatal air pollution exposure and birth weight, but the results are mixed (Bartha et al., 2023; Boamah-Kaali et al., 2021; Bravo et al., 2023; Fleisch et al., 2015; Fossati et al., 2020; Liao et al., 2023; Patterson et al., 2021; Shao et al., 2020; Starling et al., 2020; Zhou et al., 2023). More studies, preferably with larger sample size, are needed to further investigate the association between prenatal air pollution exposure and the trajectory of postnatal weight growth.

There are several hypotheses, albeit not fully clear yet, about the biological mechanisms underlying how pollution affects infant growth. Studies have reported that prenatal exposure to air pollution may have a lasting effect by changing developmental programming (Madaniyazi et al., 2022). Air pollution can cause oxidative stress, endothelial and cardiovascular alterations, systemic, pulmonary, and placental inflammation, and reduced trans-placental nutrition and oxygen exchange, which can limit the placenta's function and the intrauterine growth of fetus (Westergaard et al., 2017). Increased oxidative stress can also cause neuroinflammation, which can interfere with the signals of satiety, causing stunted growth in children (Tan et al., 2021). Besides, by altering the developing gut microbiome, air pollution exposure may have an impact on a baby's early development through the gut-brain axis (Patterson et al., 2021). In addition to the above-mentioned mechanisms, some air pollutants can also directly pass the fetal blood-brain barrier, triggering permanent fetal neurological impairments such as neuroinflammation, microglia activation, and neuronal cell death or damage through oxidative stress and inflammatory mechanisms (Ha, 2021). The crucial occasions in brain development include the formation of the neural tube (GW3–4), the process of neural tube differentiating into what will become various components of the nervous system (GW4–12), and the proliferation and organization of synapses (GW20), all of which happen during early pregnancy and mid-gestation (Berghuis and Roze, 2019). The brain is especially sensitive to environmental exposures during these periods, which may explain the stronger associations between air pollution exposure during the first and second trimesters and the neurodevelopmental delay observed in our study. More studies are warranted to better elucidate the biological mechanisms underlying the adverse effects of air pollution on infant growth.

A major advantage of our study is that we employed a growth trajectory modeling approach to deal with the heterogeneity in infant growth, which allowed us to better characterize how the length, weight, and neurodevelopment status change over time. In addition, we calculated air pollution exposure based on each individual's residential address using bilinear interpolation method, which has relatively higher precision and accuracy compared with the monitoring data-based methods that were commonly used in previous studies.

Our study also has certain shortcomings. Firstly, the limited sample size has compromised the statistical power and validity, thereby restricting our capability to detect the impact of air pollution on growth trajectories. Secondly, our results were subject to residual confounding as data on some confounders were lacking, such as maternal smoking during pregnancy. However, given the low smoking rate among Chinese women (Yang et al., 2020a), it may have a limited impact. Thirdly, we estimated air pollution exposure at fixed addresses and did not consider

the possible relocations during pregnancy. However, the study period of our study was relatively short, and this was less likely to result in substantial bias. Fourthly, we only followed the infants for less than a year, and the identified growth disorders in the early-life stage could be temporary as catch-up growth in later stages was possible. Therefore, our findings should be interpreted with cautions. Fifthly, maternal body mass index (BMI), especially before-pregnancy BMI, is another factor that is associated with infant growth, but we did not have such data to control its potential influence. Lastly, as our study was based on a single hospital, the generalizability of our findings was inevitably reduced.

5. Conclusion

Based on a birth cohort study in Foshan, China, we identified different growth trajectories of length, weight, and neurodevelopment in infants. We further found that prenatal exposure to air pollution, specifically $PM_{2.5}$, NO_2, and SO_2, was linked with elevated risks of body length retardation and neurodevelopmental delay. Our results suggest that prenatal air pollution exposure could negatively affect the growth of infants. Therefore, air pollution mitigation, which requires continuing efforts and support from governments and industry, could be an effective measure for the prevention of early-life growth impairments. From an individual perspective, some personal measures, such as employing an air purification device during pregnancy, may also help.

CRediT authorship contribution statement

Jiaying Fu: Methodology, Software, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Qingmei Lin:** Data curation, Writing – review & editing. **Jing Wei:** Formal analysis. **Baozhuo Ai:** Software, Writing – review & editing. **Meijun Li:** Software, Writing – review & editing. **Weidong Luo:** Data curation, Writing – review & editing. **Saijun Huang:** Data curation, Writing – review & editing. **Hong Yu:** Data curation, Writing – review & editing. **Yin Yang:** Writing – review & editing. **Hualiang Lin:** Writing – review & editing. **Xi Su:** Supervision, Writing – review & editing. **Zilong Zhang:** Conceptualization, Methodology, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Due to privacy issues, the authors do not have permission to share data. Requests could be made to the Foshan Women and Children Hospital (https://www.fsfy.com/).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.115792.

References

Ahmed, S.M., et al., 2022. Maternal and childhood ambient air pollution exposure and mental health symptoms and psychomotor development in children: an australian population-based longitudinal study. Environ. Int 158, 107003.
Bartha, I., et al., 2023. The influence of air pollution on gestational age at delivery and birthweight in patients with or without respiratory allergy: a nested case-control study. Acta Obstet. Gynecol. Scand. 102, 1593–1601.
Berghuis, S.A., Roze, E., 2019. Prenatal exposure to PCBs and neurological and sexual/pubertal development from birth to adolescence. Curr. Probl. Pedia Adolesc. Health Care 49, 133–159.
Bergstra, A.D., et al., 2021. The influence of industry-related air pollution on birth outcomes in an industrialized area. Environ. Pollut. 269, 115741.
Binter, A.C., et al., 2022. Urban environment and cognitive and motor function in children from four European birth cohorts. Environ. Int. 158, 106933.
Boamah-Kaali, E., et al., 2021. Prenatal and postnatal household air pollution exposure and infant growth trajectories: evidence from a rural ghanaian pregnancy cohort. Environ. Health Perspect. 129, 117009.
de Bont, J., et al., 2020. Early life exposure to air pollution, green spaces and built environment, and body mass index growth trajectories during the first 5 years of life: a large longitudinal study. Environ. Pollut. 266, 115266.
Bravo, M.A., et al., 2023. Weekly prenatal PM(2.5) and NO(2) exposures in preterm, early term, and full term infants: Decrements in birth weight and critical windows of susceptibility. Environ. Res., 117509
Cao, Z., et al., 2019. Maternal exposure to ambient fine particulate matter and fetal growth in Shanghai, China. Environ. Health 18, 49.
Chen, B., et al., 2020. Sex-specific influence of prenatal air pollutant exposure on neonatal neurobehavioral development and the sensitive window. Chemosphere 254, 126824.
Fleisch, A.F., et al., 2015. Prenatal exposure to traffic pollution: associations with reduced fetal growth and rapid infant weight gain. Epidemiology 26, 43–50.
Fossati, S., et al., 2020. Prenatal air pollution exposure and growth and cardio-metabolic risk in preschoolers. Environ. Int 138, 105619.
Guo, P., et al., 2020. Ambient air pollution and markers of fetal growth: a retrospective population-based cohort study of 2.57 million term singleton births in China. Environ. Int 135, 105410.
Guxens, M., et al., 2012. Prenatal exposure to residential air pollution and infant mental development: modulation by antioxidants and detoxification factors. Environ. Health Perspect. 120, 144–149.
Guxens, M., et al., 2014. Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts. Epidemiology 25, 636–647.
Ha, S., 2021. Air pollution and neurological development in children. Dev. Med Child Neurol. 63, 374–381.
He, T., et al., 2018. Ambient air pollution, H19/DMR methylation in cord blood and newborn size: a pilot study in Zhengzhou City, China. Chemosphere 212, 863–871.
van den Hooven, E.H., et al., 2012. Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: a prospective cohort study. Environ. Health Perspect. 120, 150–156.
Huang, J.V., et al., 2017. The association of air pollution with pubertal development: evidence From Hong Kong's "Children of 1997" Birth Cohort. Am. J. Epidemiol. 185, 914–923.
Huang, J.V., et al., 2018. The association of air pollution with height: evidence from Hong Kong's "Children of 1997" birth cohort. Am. J. Hum. Biol. 30.
Hurtado-Díaz, M., et al., 2021. Prenatal PM(2.5) exposure and neurodevelopment at 2 years of age in a birth cohort from Mexico city. Int. J. Hyg. Environ. Health 233, 113695.
Iglesias-Vázquez, L., et al., 2022. Maternal exposure to air pollution during pregnancy and child's cognitive, language, and motor function: ECLIPSES study. Environ. Res. 212, 113501.
Isaevska, E., et al., 2021. Exposure to ambient air pollution in the first 1000 days of life and alterations in the DNA methylome and telomere length in children: a systematic review. Environ. Res. 193, 110504.
Kim, E., et al., 2014. Prenatal exposure to PM_{10} and NO_2 and children's neurodevelopment from birth to 24 months of age: mothers and Children's Environmental Health (MOCEH) study. Sci. Total Environ. 481, 439–445.
Kim, E., et al., 2016. Particulate matter and early childhood body weight. Environ. Int. 94, 591–599.
Kim, J.S., et al., 2018. Longitudinal associations of in utero and early life near-roadway air pollution with trajectories of childhood body mass index. Environ. Health 17, 64.
Klis, K., Wronka, I., 2020. Associations between childhood and adolescence exposure to air pollution and adult height in polish women. Environ. Res. 189, 109965.
Lertxundi, A., et al., 2019. Prenatal exposure to PM(2.5) and NO(2) and sex-dependent infant cognitive and motor development. Environ. Res. 174, 114–121.
Liao, J., et al., 2023. Identifying critical windows of air pollution exposure during preconception and gestational period on birthweight: a prospective cohort study. Environ. Health 22, 71.
Lin, C.C., et al., 2014. Multilevel analysis of air pollution and early childhood neurobehavioral development. Int. J. Environ. Res Public Health 11, 6827–6841.
Madaniyazi, L., et al., 2022. Early life exposure to indoor air pollutants and the risk of neurodevelopmental delays: the Japan Environment and Children's Study. Environ. Int. 158, 107004.
Morgan, Z.E.M., et al., 2023. Prenatal exposure to ambient air pollution is associated with neurodevelopmental outcomes at 2 years of age. Environ. Health 22, 11.
Nagin, D.S., Group-based modeling of development. 2005.

Nguena Nguefack, H.L., et al., 2020a. Trajectory modelling techniques useful to epidemiological research: a comparative narrative review of approaches. Clin. Epidemiol. 12, 1205–1222.
Nguena Nguefack, H.L., et al., 2020b. Trajectory modelling techniques useful to epidemiological research: a comparative narrative review of approaches. Clin. Epidemiol. 12, 1205–1222.
Ni, Y., et al., 2022. Associations of Pre- and postnatal air pollution exposures with child behavioral problems and cognitive performance: a U.S. multi-cohort study. Environ. Health Perspect. 130, 67008.
Nobles, C.J., et al., 2019. Ambient air pollution and fetal growth restriction: physician diagnosis of fetal growth restriction versus population-based small-for-gestational age. Sci. Total Environ. 650, 2641–2647.
Patterson, W.B., et al., 2021. Prenatal exposure to ambient air pollutants and early infant growth and adiposity in the Southern California Mother's Milk Study. Environ. Health 20, 67.
Rosato, N.S., Baer, J.C., 2012. Latent class analysis: a method for capturing heterogeneity. Soc. Work Res. 36, 61–69.
Shang, L., et al., 2020. Effects of prenatal exposure to NO(2) on children's neurodevelopment: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 27, 24786–24798.
Shao, X., et al., 2020. Prenatal exposure to ambient air multi-pollutants significantly impairs intrauterine fetal development trajectory. Ecotoxicol. Environ. Saf. 201, 110726.
Shih, P., et al., 2023. Air pollution during the perinatal period and neurodevelopment in children: a national population study in Taiwan. Dev. Med Child Neurol. 65, 783–791.
Soesanti, F., et al., 2023. The effect of exposure to traffic related air pollutants in pregnancy on birth anthropometry: a cohort study in a heavily polluted low-middle income country. Environ. Health 22, 22.
Starling, A.P., et al., 2020. Prenatal exposure to traffic and ambient air pollution and infant weight and adiposity: the Healthy Start study. Environ. Res 182, 109130.
Su, X., et al., 2022. Prenatal exposure to air pollution and neurodevelopmental delay in children: a birth cohort study in Foshan, China. Sci. Total Environ. 816, 151658.
Tan, Y., et al., 2021. Prenatal exposure to air pollutants and early childhood growth trajectories: a population-based prospective birth cohort study. Environ. Res 194, 110627.
Wang, H., et al., 2022. Prenatal and early postnatal exposure to ambient particulate matter and early childhood neurodevelopment: a birth cohort study. Environ. Res. 210, 112946.
Wang, P., et al., 2021. Prenatal exposure to ambient fine particulate matter and early childhood neurodevelopment: a population-based birth cohort study. Sci. Total Environ. 785, 147334.
Wang, W., et al., 2017. Prenatal NO(2) exposure and ultrasound measures of foetal growth: a prospective cohort study in Wuhan, China. Occup. Environ. Med. 74, 204–210.
Wei, J., et al., 2021. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens. Environ. 252.
Wei, J., et al., 2022. Ground-Level NO(2) surveillance from space across china for high resolution using interpretable spatiotemporally weighted artificial intelligence. Environ. Sci. Technol. 56, 9988–9998.
Wei, J., et al., 2023. Ground-level gaseous pollutants (NO2, SO2, and CO) in China: daily seamless mapping and spatiotemporal variations. Atmos. Chem. Phys. 23, 1511–1532.
Westergaard, N., et al., 2017. Ambient air pollution and low birth weight - are some women more vulnerable than others? Environ. Int 104, 146–154.
Xu, X., et al., 2022. Maternal PM(2.5) exposure during gestation and offspring neurodevelopment: findings from a prospective birth cohort study. Sci. Total Environ. 842, 156778.
Xue, T., et al., 2020. Estimating spatiotemporal variation in ambient ozone exposure during 2013-2017 using a data-fusion model. Environ. Sci. Technol. 54, 14877–14888.
Yang, D., et al., 2020a. Epidemiology of lung cancer and lung cancer screening programs in China and the United States. Cancer Lett. 468, 82–87.
Yang, J., et al., 2023. The final 28 Days:prenatal exposure to air pollution and child anthropometric outcomes. J. Environ. Manag. 342, 118289.
Yang, S., et al., 2018. Ambient air pollution the risk of stillbirth: a prospective birth cohort study in Wuhan, China. Int J. Hyg. Environ. Health 221, 502–509.
Yang, Y., et al., 2020b. Maternal air pollution exposure associated with risk of congenital heart defect in pre-pregnancy overweighted women. Sci. Total Environ. 712, 136470.
Yang, Y., et al., 2020c. The mediation effect of maternal glucose on the association between ambient air pollution and birth weight in Foshan, China. Environ. Pollut. 266, 115128.
Yu, T., et al., 2021. Effects of prenatal exposures to air sulfur dioxide/nitrogen dioxide on toddler neurodevelopment and effect modification by ambient temperature. Ecotoxicol. Environ. Saf. 230, 113118.
Yu, T., et al., 2022. Effects of prenatal exposures to air sulfur dioxide/nitrogen dioxide on toddler neurodevelopment and effect modification by ambient temperature. Ecotoxicol. Environ. Saf. 230, 113118.
Zhao, J., et al., 2022. Association between screen time trajectory and early childhood development in children in China. JAMA Pedia 176, 768–775.
Zhou, W., et al., 2023. Associations between maternal exposure to ambient air pollution and very low birth weight: a birth cohort study in Chongqing, China. Front Public Health 11, 1123594.