

Effect of early-life exposure to PM_{2.5} on childhood asthma/wheezing: a birth cohort study

Guimin Chen^{1,2} | He Zhou^{2,3} | Guanhao He⁴ | Sui Zhu⁴ | Xiaoli Sun⁵ | Yufeng Ye⁶ | Hanwei Chen⁶ | Jianpeng Xiao² | Jianxiong Hu² | Fangfang Zeng⁴ | Pan Yang⁴ | Yanhui Gao⁴ | Zhongrong He^{2,7} | Jiong Wang^{1,2} | Ganxiang Cao^{2,3} | Yumeng Chen^{2,3} | Hao Feng⁴ | Wenjun Ma^{4,8} | Chaoqun Liu^{4,8} | Tao Liu^{4,8} 

¹School of Public Health, Southern Medical University, Guangzhou, China

²Guangdong Provincial Center for Disease Control and Prevention, Guangdong Provincial Institute of Public Health, Guangzhou, China

³School of Public Health, Guangdong Pharmaceutical University, Guangzhou, China

⁴Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou, China

⁵Gynecology Department, Guangdong Women and Children Hospital, Guangzhou, China

⁶Guangzhou Panyu Central Hospital, Guangzhou, China

⁷School of Public Health, Sun Yat-sen University, Guangzhou, China

⁸Disease Control and Prevention Institute of Jinan University, Jinan University, Guangzhou, China

Correspondence

Tao Liu and Chaoqun Liu, Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, No.601 West, Huangpu Road, Tianhe District, Guangzhou 510632, China. Email: gzt_2002@163.com; chaoqunliu@jnu.edu.cn

Funding information

This study was funded by the National Natural Science Foundation of China (42175181, 81874276, and 81773497); the Natural Science Foundation of Guangdong Province (2019A1515011264); and the Science and Technology Program of Guangzhou (202102080565). The funding has no role in the scientific conduct of the study.

Editor: Ömer Kalayci

Abstract

Background: Although studies have investigated the association between early-life exposure to fine particulate matter (PM_{2.5}) and childhood asthma/wheezing, results are inconsistent and the susceptible exposure window remains largely unknown.

Methods: A prospective birth cohort study was conducted to recruit pregnant women during their early pregnancy, and to follow up them and their children up to 3–4 years old. Diagnosis of asthma/wheezing was extracted from children's medical records. A spatiotemporal land-use regression (ST-LUR) model was used to assess maternal exposure to PM_{2.5} during pregnancy and their children's exposure after birth. The Cox proportional hazards model and accelerated failure time model (for violation of proportional hazards assumption) were applied to estimate the effects of prenatal and postnatal exposures to PM_{2.5} on the risk of childhood asthma/wheezing.

Results: A total of 3725 children were included, and 392 children (10.52%) were diagnosed with asthma/wheezing. Both prenatal and postnatal exposures to PM_{2.5} were positively associated with the risk of asthma/wheezing. Each interquartile range (IQR) increment in PM_{2.5} exposure during the entire pregnancy (4.8 µg/m³) and the period from birth to the end of follow-up (1.5 µg/m³) was associated with adjusted hazard ratios (HRs) of 1.44 [95% confidence interval (CI): 1.13, 1.85] and 2.74 (95% CI: 2.59, 2.91), respectively. Subgroup analyses showed greater HRs for PM_{2.5} exposures during the pseudoglandular stage (6–16 gestational weeks [GWs]: IQR = 4.8 µg/m³,

Guimin Chen and He Zhou contributed equally to this work.

© 2022 EAACI and John Wiley and Sons A/S. Published by John Wiley and Sons Ltd.

HR = 1.10, 95% CI: 1.02, 1.18) and canalicular stage (16–24 GWs: IQR = 4.8 $\mu\text{g}/\text{m}^3$, HR = 1.13, 95% CI: 1.03, 1.23) than other stages, and also showed significant effects in the first three-year period after birth (IQR = 1.5 $\mu\text{g}/\text{m}^3$, HR = 2.37, 95% CI: 2.24, 2.51).

Conclusion: Higher prenatal and postnatal $\text{PM}_{2.5}$ exposures may increase the risk of childhood asthma/wheezing. The pseudoglandular stage, canalicular stage, and the first three years after birth may be key susceptible to exposure windows.

KEYWORDS

air pollution, asthma, birth cohort, children, pregnancy, wheezing

1 | INTRODUCTION

Asthma is a common chronic disease that affects people of all ages particularly for children. The Global Asthma Report showed that 14% of the world's children experienced asthma symptoms.^{1,2} The prevalence of asthma is still increasing globally.^{2–4} China is the largest middle-income country with a pronounced increase in childhood asthma. An investigation in ten Chinese cities showed that the normalized prevalence (based on the 1990 data) of children's asthma increased from 1% in 1990 to 6.8% during 2010–2012.⁵ Although the prevalence of asthma in China is lower than the global average level, the population size of 1.4 billion means huge disease burden. Hence, it is necessary to formulate asthma prevention strategies by identifying possible modifiable factors and the most vulnerable exposure window for asthma.

Increasing evidence has indicated the associations between air pollution and childhood asthma/wheezing.^{6–9} Several studies further found positive associations of prenatal exposure to fine particulate matter ($\text{PM}_{2.5}$) with childhood asthma.^{8–10} A newer meta-analysis that included a total of 1,030,823 mother–child pairs from 9 eligible epidemiologic studies reported that prenatal exposure to $\text{PM}_{2.5}$ was positively associated with the risk of childhood asthma and wheezing (OR = 1.06, 95% CI: 1.02–1.11; per 5 $\mu\text{g}/\text{m}^3$), but exposure to $\text{PM}_{2.5}$ during each trimester alone did not significantly increase the risk of asthma and wheezing in children.¹¹ This inconsistent result may be largely due to variable methods for exposure assignment. Most studies have applied relatively arbitrary assignment of exposure windows (e.g., clinically defined trimesters) rather than based on the developmental processes of the respiratory system.¹² The process of programming respiratory outcomes does not necessarily occur within clinically defined trimesters. In humans, lung development occurs through five sequential stages: embryonic (0–6 GWs), pseudoglandular (6–16 GWs), canalicular (16–24 GWs), sacular (24–36 GWs), and alveolar (36 GWs to ~7–10 years).¹³ To date, little is known about the impact of $\text{PM}_{2.5}$ exposure in different lung developmental stages on the risk of childhood asthma/wheezing, especially in highly polluted developing countries such as China. Such information could help precisely identify the susceptible exposure windows of air pollution and facilitate improvement of prenatal care

Key Message

This birth cohort study found that higher prenatal and postnatal $\text{PM}_{2.5}$ exposures may increase the risk of childhood asthma/wheezing, and the susceptible exposure windows included pseudoglandular stage, canalicular stage, and the first three years after birth.

and effective implementation of intervention by clinicians to prevent the occurrence of asthma/wheezing.

In this study, we conducted a Prospective Birth Cohort Study on Prenatal Environments and Offspring Health (PEOH cohort) in Guangzhou, China. We aimed to estimate the associations of $\text{PM}_{2.5}$ exposures during both prenatal and postnatal periods with childhood asthma/wheezing, and to identify the potential susceptible exposure windows.

2 | METHODS

2.1 | Study setting and participants

Information of all participants was obtained from the PEOH cohort study conducted in the Guangzhou Panyu Central Hospital, Guangzhou, China, which has been described elsewhere.^{14–16} Pregnant women were recruited from antenatal care clinics and were investigated in a face-to-face interview by a trained public health professional using a structured questionnaire (baseline investigation), which was initiated in January 2016, and was completed before December 2017. A total of 4928 pregnant women were initially recruited.

2.2 | Follow-up investigation

Pregnant women were first followed up and investigated during their hospitalization for childbirth. Maternal information was collected using a questionnaire, and neonatal birth records were collected

from maternal medical records. Then, we followed up on all singleton live-born children when they visited the child health care clinics, pediatric outpatient department, or emergency department. Their parents or anyone who accompanied with the children were given an investigation to collect the children's information. Children's health information including clinical symptoms, diagnosed diseases, and anthropometric measurements were collected from their medical records. The follow-up investigation for children was completed before July 31, 2020. After excluding those children with missing key variables, a total of 3725 children were finally included (Figure S1).

The PEOH was approved by the Ethics Committee of Guangdong Provincial Center for Disease Control and Prevention (W96-027E-2,015,001), and registered in the Chinese Clinical Trial Registry (ChiCTR-ROC-17013496). Every recruited participant was provided a detailed introduction and explanation of this study and signed the informed consent.

2.3 | Ascertainment of asthma and wheezing

Asthma is defined as recurrent and variable clinical features including wheezing, chest tightness, persistent cough, shortness of breath, and expiratory airflow limitation.¹⁷ Wheezing is a common symptom in patients with bronchospasm and airway obstruction; it is often regarded as a precursor to childhood asthma and has significant prognostic value for the early diagnosis of asthma.¹⁸ Diagnoses of asthma and wheezing in children were identified and extracted from children's medical records recorded by physicians. Asthma cases were recorded using the International Classification of Diseases, 10th Revision (ICD-10: J45), and wheezing cases were recorded using ICD-10 of R06.2. Diagnoses of wheeze include children with recurrent wheezing, for which we use the time of the first wheeze as the time of onset. Due to the inherent difficulties in early-life asthma diagnosis, the number of asthma children was small ($n = 17$). Therefore, we combined asthma and wheezing together ($n = 392$) as a comprehensive outcome to increase the statistical power. Once a child was recorded as having asthma and also wheezing, we recorded the child as an asthma patient.

2.4 | Exposure assessment of air pollution

A spatiotemporal land-use-regression model (ST-LUR) was used to assess each individual weekly exposure to $PM_{2.5}$ during the study period, which has been described in detail elsewhere.^{14,19} For maternal exposure assessment during pregnancy, we predicted the weekly $PM_{2.5}$ concentrations at each individual residence address and workplace address. Time-weighted individual daily $PM_{2.5}$ exposure was estimated by multiplying the outdoor and indoor $PM_{2.5}$ concentrations by the percentages of time spent outdoor and indoor, respectively.^{14,20} These daily time-weighted estimates were then aggregated into average exposures for the entire pregnancy and five stages [the embryonic stage (0–6 gestational weeks

[GWs]), pseudoglandular stage (6–16 GWs), canalicular stage (16–24 GWs), saccular stages (24–36 GWs), and alveolar stage (>36 GWs)] based on the developmental processes of the respiratory system (Figure S2).^{21,22}

For children's exposure assessment, we applied only the predicted daily $PM_{2.5}$ concentration at their residence address, because the children spend most time at home or near their residence. Moreover, children's activity patterns varied largely during different childhood stages, and it is hard to be precisely measured. The daily predicted $PM_{2.5}$ concentrations were aggregated into average exposures during each child's first one year, first two years, first three years, and one year before the end of follow-up (Figure S2). We also estimated each individual exposure to other air pollutants (SO_2 , NO_2 , CO, and O_3) using the above methods. The detailed information is shown in supplementary materials.

2.5 | Covariates

In accordance with previous publications and literature, the following variables were considered as covariates: maternal age, gravidity, parity, maternal occupation, yearly income per capita, passive smoking, feeding method, history of asthma, premature, gestational diabetes mellitus, and season of conception.^{9,23} Considering the influence of pregnancy nutrition on maternal and fetal health, we also considered the maternal diet as covariates.

2.6 | Statistical analysis

First, a Chi-square test was used to assess the differences in characteristics between the case group and control group. A Pearson's correlation was applied to estimate the correlations among air pollutants during the prenatal and postnatal periods, and the correlations of average exposures to $PM_{2.5}$ during different phases of early life.

Second, we used a Cox proportional hazards model to assess associations of asthma/wheezing incidence with early-life (prenatal and postnatal) $PM_{2.5}$ exposures. When the tests of proportional hazards assumptions showed violations ($P < 0.05$) (Table S1), the accelerated failure time (AFT) model was used alternatively. Associations were estimated through hazard ratios (HRs) and their 95% confidence intervals (CIs), associated with per interquartile range (IQR) increase in exposures to $PM_{2.5}$.

2.7 | Sensitivity analyses

Several sensitivity analyses were conducted. First, we conducted two-pollutant models by simultaneously including one of the gaseous pollutants (SO_2 , NO_2 , CO, and O_3) and $PM_{2.5}$ in our models. Second, we mutually adjusted for the prenatal and postnatal $PM_{2.5}$ exposures to test the potential confounding effects with each other.

R software (version 4.0.5, R Development Core Team 2019, <https://www.r-project.org>). All tests were conducted 2-sided, and effects with $p < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of study participants

Out of 3725 included children, 392 (10.52%) were diagnosed with asthma/wheezing from January 2016 to July 2020. The mean age of children was 3.2 ± 0.8 years. A total of 179,785 person-months (including pregnancy and childhood) were successfully followed up. Compared with children without asthma/wheezing, those children with asthma/wheezing tend to be males, born by a mother with large parity, artificial feeding, and had less vitamin consumption (Table 1).

The median $PM_{2.5}$ concentrations during pregnancy and childhood period were $31.9 \mu\text{g}/\text{m}^3$ and $31.1 \mu\text{g}/\text{m}^3$, respectively (Table 2). The average $PM_{2.5}$ concentration during the entire pregnancy was significantly correlated with O_3 ($r = .16$), SO_2 ($r = .40$), NO_2 ($r = .66$) and CO ($r = .54$) (Figure S3). The average $PM_{2.5}$ during the childhood was also correlated with O_3 ($r = -.42$), SO_2 ($r = .81$), NO_2 ($r = .77$) and CO ($r = .66$) (Figure S4).

3.2 | Effect of prenatal exposure to $PM_{2.5}$ on childhood asthma/wheezing

The adjusted HR of asthma/wheezing for each IQR ($4.8 \mu\text{g}/\text{m}^3$) increment in $PM_{2.5}$ concentration during the entire pregnancy was 1.44 (95% CI: 1.13, 1.85). Subgroup analyses showed similar effects of $PM_{2.5}$ exposures during the pseudoglandular stage (IQR = $4.8 \mu\text{g}/\text{m}^3$, HR = 1.10, 95% CI: 1.02, 1.18) and canalicular stage (IQR = $4.8 \mu\text{g}/\text{m}^3$, HR = 1.13, 95% CI: 1.03, 1.23) on the risk of asthma/wheezing (Table 3). However, the associations were insignificant for the other stages.

3.3 | Effect of postnatal exposure to $PM_{2.5}$ on childhood asthma/wheezing

The adjusted HRs of asthma/wheezing for each IQR increment in $PM_{2.5}$ concentrations during the studied childhood (IQR = $1.5 \mu\text{g}/\text{m}^3$), the first 1 year, first 2 years, first 3 years, and the 1 year before the end of follow-up were 2.74 (95% CI: 2.59, 2.91), 1.57 (95% CI: 1.43, 1.73), 2.37 (95% CI: 2.15, 2.61), 2.37 (95% CI: 2.24, 2.51), and 2.27 (95% CI: 2.18, 2.37), respectively (Table 4).

3.4 | Sensitivity analyses

The results of two-pollutant models showed robust effects of prenatal and postnatal exposures to $PM_{2.5}$ on asthma/wheezing. The

association was not statistically significant after adjustment for ambient CO ($p > .05$) (Figure 1), which may be due to the close correlation between the $PM_{2.5}$ and CO (Figure S3). In addition, the mutual adjustment for prenatal and postnatal $PM_{2.5}$ exposures did not substantially change the effects of $PM_{2.5}$.

4 | DISCUSSION

This study applied a prospective birth cohort study to investigate the effects of $PM_{2.5}$ exposures in early life on the risk of childhood asthma/wheezing. We found significantly positive effects of both prenatal and postnatal exposures to $PM_{2.5}$ on childhood asthma/wheezing. Moreover, subgroup analyses suggested that the effects of $PM_{2.5}$ were greater during the pseudoglandular stage (6–16 GWs) and canalicular stage (16–24 GWs) than other stages, and that the effects of $PM_{2.5}$ were statistically significant in the first three years after birth, indicating the potential key exposure windows. Therefore, it is crucial to reduce air pollution in early life particularly during the key exposure windows to prevent asthma/wheezing in childhood.

Our findings of the significant effect of prenatal exposure to $PM_{2.5}$ on the development of childhood asthma/wheezing and the potential key exposure windows are consistent with previous studies.^{9,10,24} A large cross-sectional survey among 5788 preschool children aged 3–5 years in central China observed strong evidence that early-life $PM_{2.5}$ exposures increased the risk of childhood asthma among preschool children.²⁴ Jung et al.⁹ using a birth cohort study including 184,604 children born during 2004–2011 in Taiwan observed a positive association between $PM_{2.5}$ exposures during 6–22 GWs and 9–46 weeks after birth and incidence of childhood asthma. Hsu et al. based on a pregnancy cohort in America and included 736 full-term (>37 week) children recruited at birth from 2002–2009 and followed prospectively up to 6 years, reporting that prenatal exposure to $PM_{2.5}$ during 16–25 GWs was significantly associated with the development of asthma at 6 years of age, and the significant sensitive exposure window extended to 12th–26th weeks gestation among boys.¹⁰

The underlying biological mechanisms of $PM_{2.5}$ exposure during early life causing asthma/wheezing may be closely related to the interference with lung development. During the pseudoglandular period, the tracheobronchus continues to elongate, and cartilage, smooth muscle, and connective tissue differentiate from the stroma. After 16 weeks, the development of the airway is mainly the increase of volume and the perfection of structure.¹³ The canalicular period mainly develops respiratory bronchioles. There are 2–3 thin-walled cystic primitive alveoli at the end of each respiratory bronchiole.¹³ The developing lung during these two stages may be more susceptible to inhaled $PM_{2.5}$.^{25,26}

We also found that postnatal exposure to higher $PM_{2.5}$ concentrations may increase the risk of childhood asthma/wheezing, and that the first three years may be another key exposure window, which is consistent with many previous studies.^{8,9,23,24,27} For

TABLE 1 General characteristics of study subjects

Variables	Total (n = 3725)	Asthma/wheezing		χ^2	p Value
		Yes (n = 392)	No (n = 3333)		
Children sex, n (%)					
Boys	1984 (53.3)	261 (66.6)	1723 (51.7)	30.62	<.001
Girls	1741 (46.7)	131 (33.4)	1610 (48.3)		
Maternal age (y), n (%)					
18–25	193 (5.2)	22 (5.6)	171 (5.1)	7.19	.066
26–30	1253 (33.6)	124 (31.6)	1129 (33.9)		
31–35	1304 (35.0)	159 (40.6)	1145 (34.4)		
>35	975 (26.2)	87 (22.2)	888 (26.6)		
Maternal occupation, n (%)					
Manual worker	183 (4.9)	22 (5.6)	161 (4.8)	12.94	.044
Government official and clerk	78 (2.1)	12 (3.1)	66 (2.0)		
Housewife	372 (10.0)	43 (11.0)	329 (9.9)		
Unemployment	278 (7.5)	43 (11.0)	235 (7.1)		
Technician	689 (18.5)	65 (16.6)	624 (18.7)		
Business	2008 (53.9)	193 (49.2)	1815 (54.5)		
Others	117 (3.1)	14 (3.6)	103 (3.1)		
Parity, n (%)					
1	1132 (30.4)	96 (24.5)	1036 (31.1)	7.86	.020
2	2220 (59.6)	249 (63.5)	1971 (59.1)		
≥3	373 (10.0)	47 (12.0)	326 (9.8)		
Gravidity, n (%)					
1	1104 (29.6)	101 (25.8)	1003 (30.1)	3.84	.279
2	1432 (38.4)	163 (41.6)	1269 (38.1)		
3	792 (21.3)	82 (20.9)	710 (21.3)		
≥4	397 (10.7)	46 (11.7)	351 (10.5)		
Marital status, n (%)					
Married	3626 (97.3)	383 (97.7)	3243 (97.3)	0.09	.760
Others	99 (2.7)	9 (2.3)	90 (2.7)		
Yearly income per capita (×1000 Yuan), n (%)					
<30	193 (5.2)	22 (5.6)	171 (5.1)	-	.449 ^a
30~	2228 (59.8)	248 (63.3)	1980 (59.4)		
100~	1088 (29.2)	100 (25.5)	988 (29.6)		
≥200	178 (4.8)	17 (4.3)	161 (4.8)		
Refused to answer/missing	38 (1.0)	5 (1.3)	33 (1.0)		
Maternal education (y), n (%) ^a					
≤9	578 (15.5)	69 (17.6)	509 (15.3)	1.59	.452
13–15	2144 (57.6)	223 (56.9)	1921 (57.6)		
>15	1003 (26.9)	100 (25.5)	903 (27.1)		
BMI before pregnancy (kg/m ²), n (%)					
Under/normal weight (<24.0)	3184 (85.5)	336 (85.7)	2848 (85.4)	5.14	.077
Overweight (24.0–27.9)	438 (11.8)	39 (9.9)	399 (12.0)		
Obesity (≥28)	103 (2.8)	17 (4.3)	86 (2.6)		

(Continues)

TABLE 1 (Continued)

Variables	Total (n = 3725)	Asthma/wheezing		χ^2	p Value
		Yes (n = 392)	No (n = 3333)		
Feeding method, n (%)					
Artificial feeding	400 (10.7)	60 (15.3)	340 (10.2)	13.05	.005
Breast feeding	449 (12.1)	45 (11.5)	404 (12.1)		
Mixed feeding	431 (11.6)	32 (8.2)	399 (12.0)		
Refused to answer/missing answer/missing	2445 (65.6)	255 (65.1)	2190 (65.7)		
Passive smoking, n (%)					
Yes	2599 (69.8)	267 (68.1)	2332 (70.0)	0.49	.485
No	1126 (30.2)	125 (31.9)	1001 (30.0)		
Meat consumption (times/week), n (%)					
≤13	330 (8.9)	31 (7.9)	299 (9.0)	-	.650 ^a
14–21	3359 (90.2)	356 (90.8)	3003 (90.1)		
≥22	36 (1.0)	5 (1.3)	31 (0.9)		
Vegetable consumption (times/week), n (%)					
≤7	407 (10.9)	42 (10.7)	365 (11.0)	3.74	.291
8–14	1313 (35.2)	122 (31.1)	1191 (35.7)		
≥15	2005 (53.8)	228 (58.2)	1777 (53.3)		
Milk consumption (times/week), n (%)					
≤5	1466 (39.4)	164 (41.8)	1302 (39.1)	2.60	.457
6–7	2080 (55.8)	212 (54.1)	1868 (56.0)		
≥8	179 (4.8)	16 (4.1)	163 (4.9)		
Fruit consumption (times/week), n (%)					
≤5	341 (9.2)	32 (8.2)	309 (9.3)	4.70	.195
6–7	3041 (81.6)	334 (85.2)	2707 (81.2)		
≥8	343 (9.2)	26 (6.6)	317 (9.5)		
Vitamin consumption (times/week), n (%)					
≤5	1543 (41.4)	186 (47.4)	1357 (40.7)	9.53	.023
6–7	2059 (55.3)	199 (50.8)	1860 (55.8)		
≥8	123 (3.3)	7 (1.8)	116 (3.5)		
History of gestational diabetes mellitus, n (%)					
No	3516 (94.4)	368 (93.9)	3148 (94.4)	-	.590 ^a
Yes	197 (5.3)	22 (5.6)	175 (5.3)		
Refused to answer/missing	12 (0.3)	2 (0.5)	10 (0.3)		
Maternal history of asthma, n (%)					
No	3546 (95.2)	371 (94.6)	3175 (95.3)	0.17	.678
Yes	179 (4.8)	21 (5.4)	158 (4.7)		
Season of conception, n (%)					
Warm (May to October)	1775 (47.7)	1605 (48.2)	170 (43.4)	3.03	.078
Cold (November to April)	950 (52.3)	1728 (51.8)	222 (56.6)		
	Mean ± SD			t-test	p
Children's age at end of follow-up (y), Mean±SD	3.21 ±0.78	1.49 ±0.92	3.41 ±0.44	40.55	<.001
Children's gestation age at birth (GWs), Mean±SD	39.74 ±2.08	39.65 ±1.61	39.75 ±2.13	1.12	.262

Abbreviation: BMI, body mass index.

^aFisher's exact test.

TABLE 2 Exposures to ambient air pollutants during different stages in early life

Air pollution concentration	Median	P ₂₅	P ₇₅
During the pregnancy			
PM _{2.5} (μg/m ³)	31.9	29.7	34.5
The embryonic stage (0–6 GWs)	32.8	28.1	38.2
The pseudoglandular stage (6–16 GWs)	33.3	29.8	37.4
The canalicular stage (16–24 GWs)	32.4	26.3	36.7
The saccular stage (24–36 GWs)	30.5	24.5	35.7
The alveolar stage (>36 GWs)	30.7	24.3	36.6
SO ₂ (μg/m ³)	10.3	9.8	10.7
NO ₂ (μg/m ³)	36.4	33.9	40.0
O ₃ (μg/m ³)	45.1	42.3	46.9
CO (mg/m ³)	0.7	0.7	0.7
During the childhood			
PM _{2.5} (μg/m ³)	31.1	30.3	31.8
The first 1 year after birth	36.1	35.6	36.7
The first 2 years after birth	34.1	32.7	35.8
The first 3 years after birth	32.4	31.1	33.5
One year before the end of follow-up	26.8	26.7	27.8
SO ₂ (μg/m ³)	9.2	8.8	9.7
NO ₂ (μg/m ³)	41.3	40.6	42.3
O ₃ (μg/m ³)	52.5	51.9	53.4
CO (mg/m ³)	0.8	0.7	0.8

Note: P₂₅—the 25% centile; P₇₅—the 75% centile.

example, a study conducted in Georgian children found a positive association of PM_{2.5} exposure in the first year of life with the risk of asthma by age five.⁸ A birth cohort study in Taiwan found that postnatal exposure to PM_{2.5} was significantly associated with later asthma development.⁹ A large cross-sectional survey in Wuhan, China also observed increased risks of childhood (aged 3–5 years) asthma associated with PM_{2.5} exposures during the first year after birth.²⁴

This significant effect of postnatal exposure to PM_{2.5} on childhood asthma/wheezing may be related to the rapid development of the respiratory system after birth. More than 85% of alveolarization takes place after birth, and the lung develops fastest within 3–4 years old.²¹ The fast development of the respiratory system, immature immune system, higher ventilation rates, and increased lung surface area per kilogram of body weight makes infant particularly vulnerable to environmental harmful factors such as air pollution.^{13,28} Toxicants can make the respiratory epithelium in the developing lung more permeable.²⁸ Animal experiments have also indicated that exposure to higher PM_{2.5} in the early postnatal

periods of mouse can decrease the number of alveoli, enlarge the alveolar spaces, and increase the lung elastance.²⁹

Some studies observed inconsistent results with the present study. For example, Clark et al. used outpatient and hospitalization records of all children born in southwestern British Columbia in 1999 and 2000 ($n = 37,401$) to assess the incidence of asthma diagnosis up to 3–4 years of age, but they did not find significant associations between PM_{2.5} exposure occurring in utero and during first year and asthma, which may be because the lower PM_{2.5} concentration in their study area.²³ Additionally, air pollution exposures in Clark et al.'s study were assigned at the level of six-digit postal codes instead of full addresses, and the number of monitors for ambient PM_{2.5} was only seven, which may lead to misclassification bias of exposure. Similarly, Sbihi et al.³⁰ applied a birth cohort that consisted of 65,254 children born between 1999 and 2002 in the greater Vancouver metropolitan region with lower air pollution and followed until age 10 years, and also reported the null association between PM_{2.5} and asthma. Furthermore, a recent study by Norbäck et al.³¹ randomly recruited children (3–6 years) from daycare centers in six major cities in China and found prenatal exposure to PM_{2.5} did not associate significantly with onset and remission of wheeze. We noticed that Norbäck et al. defined asthma using the information of questionnaires, which may lead to bias of misclassification. By contrast, this study was conducted in the Pearl River Delta region with severer air pollution than in developed countries, and the air pollution exposure was assessed using an ST-LUR model. In addition, we defined wheezing/asthma cases were defined based on children's medical record and may have captured transient wheezing illnesses that are common in infants and often resolves in childhood. Therefore, our results may provide more reliable associations of exposure to PM_{2.5} in early life with the risk of childhood asthma/wheezing.

Our findings, combined with previous studies, have important implications for the prevention of childhood asthma/wheezing. These novel insights could help clinical workers and pregnant women to understand the adverse effects of PM_{2.5} exposure on the respiratory system and to take measures to reduce air pollution exposure particularly during the susceptible windows. Moreover, our findings provide important information for public health policy making and planning to prevent the occurrence of asthma in informing environmental and healthcare policymakers to make greater efforts to improve the air quality.

4.1 | Strengths and limitations

There are several strengths in this study. First, this is a prospective birth cohort study that provides a stronger causal argument on the effect of PM_{2.5} exposure on asthma/wheezing. Second, we simultaneously estimated the effects of prenatal and postnatal exposures to PM_{2.5} on the risks of asthma/wheezing in children. Hence, we can identify the potential susceptible exposure window spanning from pregnancy to childhood. Third, we applied an ST-LUR model to

TABLE 3 Effect (HR, 95%CI) of prenatal exposure to PM_{2.5} (per 4.8 µg/m³ increment^a) on

	Total participants (mean age = 39.7 GWs)	Asthma/wheezing cases (mean age = 39.8 GWs)	Model 1		Model 2 ^b	
			Crude HR (95% CI)	<i>p</i>	Adjust HR (95% CI)	<i>p</i>
The entire pregnancy	3725	392 (10.5%)	1.02 (0.87,1.20)	.821	1.44 (1.13,1.85)	.004
The embryonic stage (0–6 GWs)			1.03 (0.96,1.09)	.422	0.96 (0.82,1.12)	.621
The pseudoglandular stage (6–16 GWs)			1.09 (1.01,1.17)	.024	1.16 (1.03,1.30)	.017
The canalicular stage (16–24 GWs)			1.02 (0.96,1.09)	.510	1.29 (1.07,1.56)	.009
The saccular stage (24–36 GWs)			0.95 (0.89,1.01)	.126	1.01 (0.82,1.25)	.903
The alveolar stage (>36 GWs)			0.95 (0.90,1.01)	.117	0.87 (0.75,1.02)	.094

^aThe IQR of PM_{2.5} exposure during entire pregnancy was 4.8 µg/m³. We applied the same scale for each subgroup, which was to increase the comparisons of associations among subgroups.

^bAdjustment for maternal age, gravidity, parity, maternal occupation, yearly income per capita, passive smoking, feeding method, maternal diet, history of asthma, and gestational diabetes mellitus, premature, and season of conception.

TABLE 4 Effect (HR, 95% CI) of postnatal exposure to PM_{2.5} (per 1.5 µg/m³ increment^a) on childhood asthma/wheezing

	Total participants (mean age = 3.2 years)	Asthma/wheezing cases (mean age = 1.5 years)	Model 1		Model 2 ^b	
			Crude HR (95% CI)	<i>p</i>	Adjust HR (95% CI)	<i>p</i>
The studied childhood period ^c	3725	392 (10.5%)	2.55 (2.41,2.71)	<.001	2.74 (2.59,2.91)	<.001
The first one year after birth		154 (4.1%)	1.57 (1.43,1.73)		1.57 (1.43,1.73)	
The first two years after birth ^c		282 (7.6%)	2.28 (2.07,2.52)		2.37 (2.15,2.61)	
The first three years after birth		365 (9.8%)	2.25 (2.13,2.37)		2.37 (2.24,2.51)	
One year before the end of follow-up ^c		392 (10.5%)	2.18 (2.09,2.27)		2.27 (2.18,2.37)	

^aThe HRs were calculated by the accelerated failure time models because the proportional hazards assumption was not met in these models.

^bThe IQR of PM_{2.5} exposure during the studied childhood period was 1.5 µg/m³. We applied the same scale for each subgroup, which was to increase the comparison of associations among subgroups.

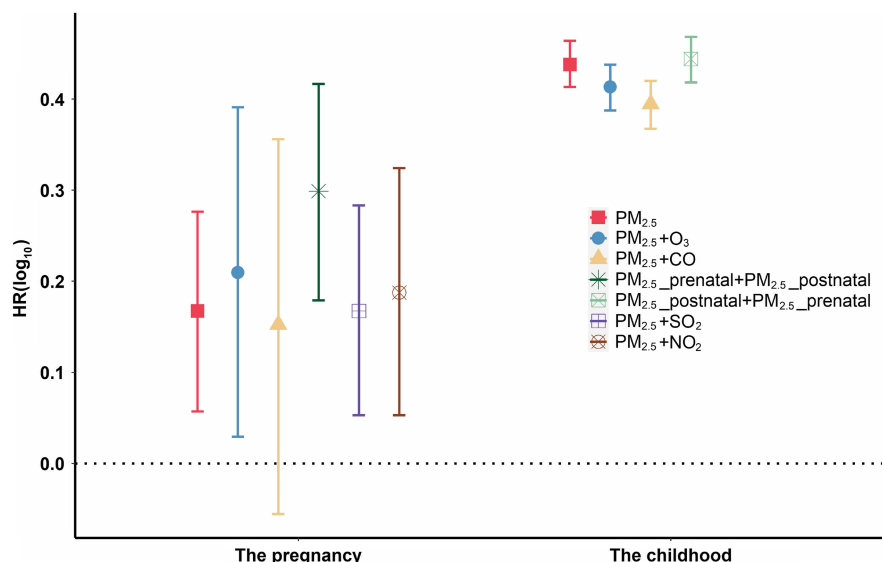
^cAdjustment for maternal age, gravidity, parity, maternal occupation, yearly income per capita, passive smoking, feeding method, maternal diet, history of asthma, and gestational diabetes mellitus, premature, and season of conception.

assess each individual level of air pollution exposure, and also considered maternal indoor and outdoor activity patterns in assessing prenatal exposures to air pollutants.

Several limitations should be considered. Firstly, study participants were recruited from only one hospital and the sample size was relatively small, which may have limited the generalization of our findings. Second, although the diagnoses of asthma and wheezing were extracted from medical records, we cannot rule out the potential misclassification of outcome measurement due to the inherent difficulties in early-life asthma diagnosis that some of the cases of wheezing were not asthma. Moreover, the number of diagnosed

asthma cases was small, and we pooled asthma and wheezing together as a comprehensive outcome, which prevented us from separately estimating the effects of PM_{2.5} exposure on the risks of asthma and wheezing. It was suggested that not all wheezing is asthma although they have similar characteristics.³² Third, we cannot rule out the bias, due to the occurrence of loss to follow-up in this dynamic cohort. We passively investigated children when they visited the child health care clinics, pediatric outpatient department, or emergency department. Those children who did not visit the hospital were lost, which may lead to the underestimation of the effects of PM_{2.5}. Fourth, more than two-thirds of the participants had

FIGURE 1 Sensitivity analyses of effects of $PM_{2.5}$ exposures on childhood asthma/wheezing by additionally adjusting for gaseous air pollutants and mutually adjusting for prenatal or postnatal exposure to $PM_{2.5}$



missing data on feeding methods, which may confound the effects of $PM_{2.5}$. However, our additional analyses of those participants with information on feeding methods showed that adjustment for feeding methods did not substantially change the association between $PM_{2.5}$ exposure and childhood asthma/wheezing (Table S2). Finally, some detailed information about children, such as nutritional status, diet, indoor air pollution exposure, and activity patterns, were not collected. The potential confounding effects of these variables were not adjusted for in this study.

5 | CONCLUSIONS

Higher $PM_{2.5}$ exposure in early life may increase the risk of childhood asthma/wheezing, and the key susceptible exposure windows may include pseudoglandular stage (6–16 GWs), canalicular stage (16–24 GWs), and the first three years after birth. Targeted measures are needed to reduce exposure to $PM_{2.5}$ in early life particularly in the key susceptible exposure windows.

AUTHOR CONTRIBUTIONS

Guimin Chen: Conceptualization (equal); writing – original draft (equal). **He Zhou:** Data curation (lead); formal analysis (equal). **Guanhao He:** Conceptualization (equal); writing – original draft (equal). **Sui Zhu:** Writing – review and editing (equal). **Xiaoli Sun:** Writing – review and editing (equal). **Yufeng Ye:** Data curation (equal). **Hanwei Chen:** Data curation (equal). **Jianpeng Xiao:** Formal analysis (equal). **Jianxiang Hu:** Formal analysis (equal). **Fangfang Zeng:** Formal analysis (equal). **Pan Yang:** Writing – review and editing (equal). **Yanhui Gao:** Formal analysis (equal). **Zhongrong He:** Data curation (equal). **Jiong Wang:** Data curation (equal). **Ganxiang Cao:** Data curation (equal). **Yumeng Chen:** Data curation (equal). **Hao Feng:** Data curation (equal). **Wenjun Ma:** Writing – review and editing (equal). **Chaoqun Liu:** Conceptualization (equal); writing – original draft (equal). **Tao Liu:** Conceptualization (lead).

CONFLICT OF INTEREST

None declared.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13822>.

ORCID

Tao Liu  <https://orcid.org/0000-0003-1451-5251>

REFERENCES

- Ahmetaj L. The Global Asthma Report. 2014:2014.
- Morales E. The Global Asthma Report. 2018:2018.
- WHO. Don't pollute my future! The impact of the environment on children's health. <https://www.who.int/publications/item/WHO-FWC-IHE-17.01>. Date last updated: March 21 2017. Date last accessed: December 9 2021.
- Eder W, Ege MJ, von Mutius E. The Asthma Epidemic. *N Engl J Med*. 2006;355(21):2226–2235.
- Yinping Z, Baizhan L, Chen H. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. *Chin Sci Bull*. 2013;58(31):4182–4189.
- Gasana J, Dillikar D, Mendy A, Forno E, Ramos Vieira E. Motor vehicle air pollution and asthma in children: a meta-analysis. *Environ Res*. 2012;117:36–45.
- Fan J, Li S, Fan C, Bai Z, Yang K. The impact of $PM_{2.5}$ on asthma emergency department visits: a systematic review and meta-analysis. *Environ Sci Pollut Res Int*. 2016;23(1):843–850.
- Pennington AF, Strickland MJ, Klein M, et al. Exposure to mobile source air pollution in early-life and childhood asthma incidence: the kaiser air pollution and pediatric asthma study. *Epidemiology*. 2018;29(1):22–30.
- Jung CR, Chen WT, Tang YH, Hwang BF. Fine particulate matter exposure during pregnancy and infancy and incident asthma. *J Allergy Clin Immunol*. 2019;143(6):2254–2262 e5.
- Hsu H-HL, Chiu Y-HM, Coull BA, et al. Prenatal particulate air pollution and asthma onset in Urban children. Identifying sensitive windows and sex differences. *Am J Respir Crit Care Med*. 2015;192(9):1052–1059.

11. Yan W, Wang X, Dong T, et al. The impact of prenatal exposure to PM_{2.5} on childhood asthma and wheezing: a meta-analysis of observational studies. *Environ Sci Pollut Res Int*. 2020;27(23):29280-29290.
12. Carraro S, Scheltema N, Bont L, Baraldi E. Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing. *Eur Respir J*. 2014;44(6):1682-1696.
13. Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Ther*. 2007;114(2):129-145.
14. Liu X, Ye Y, Chen Y, et al. Effects of prenatal exposure to air particulate matter on the risk of preterm birth and roles of maternal and cord blood LINE-1 methylation: A birth cohort study in Guangzhou, China. *Environ Int*. 2019;133:105177.
15. Dong M, Liu X, Xiao J, et al. Associations between prenatal exposure to fine particulate matter and birth weight and modifying effects of birth order related to a new baby boom: a prospective birth cohort study in Guangzhou, China. *Atmos Environ*. 2020;231:117523.
16. Chen G, Sun X, Wang J, et al. The association between maternal exposure to fine Particulate Matter (PM_{2.5}) and Gestational Diabetes Mellitus (GDM): a prospective birth cohort study in China. *Environ Res Lett*. 2021;16(5):055004.
17. Massoth L, Anderson C, McKinney KA. Asthma and chronic rhinosinusitis: diagnosis and medical management. *Med Sci (Basel)*. 2019;7(4):53.
18. Martinez J, Martinez J. Not all that wheezes is asthma! *J Bras Pneumol*. 2013;39(4):518-520.
19. Liu T, Chen X, Xu Y, et al. Gut microbiota partially mediates the effects of fine particulate matter on type 2 diabetes: Evidence from a population-based epidemiological study. *Environ Int*. 2019;130:104882.
20. Zhou X, Cai J, Zhao Y, et al. Estimation of residential fine particulate matter infiltration in Shanghai, China. *Environ Pollut*. 2018;233:494-500.
21. Smith LJ, McKay KO, van Asperen PP, et al. Normal development of the lung and premature birth. *Paediatr Respir Rev*. 2010;11(3):135-142.
22. Hazlehurst MF, Carroll KN, Loftus CT, et al. Maternal exposure to PM_{2.5} during pregnancy and asthma risk in early childhood: consideration of stages of fetal lung development. *Environ Epidemiol*. 2021;5(2):e130.
23. Clark NA, Demers PA, Karr CJ, et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect*. 2010;118(2):284-290.
24. Zhang Y, Wei J, Shi Y, et al. Early-life exposure to submicron particulate air pollution in relation to asthma development in Chinese preschool children. *J Allergy Clin Immunol*. 2021;148(3):771-782 e12.
25. Korten I, Ramsey K, Latzin P. Air pollution during pregnancy and lung development in the child. *Paediatr Respir Rev*. 2017;21:38-46.
26. Xu X, Zhang J, Yang X, Zhang Y, Chen Z. The role and potential pathogenic mechanism of particulate matter in childhood asthma: a review and perspective. *J Immunol Res*. 2020;2020:8254909.
27. Bowatte G, Lodge C, Lowe AJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy*. 2015;70(3):245-256.
28. Tzivian L. Outdoor air pollution and asthma in children. *J Asthma*. 2011;48(5):470-481.
29. de Barros Mendes Lopes T, Groth EE, Veras M, et al. Pre- and post-natal exposure of mice to concentrated urban PM decreases the number of alveoli and leads to altered lung function at an early stage of life. *Environ Pollut*. 2018;241:511-520.
30. Sbihi H, Tamburic L, Koehoorn M, Brauer M. Perinatal air pollution exposure and development of asthma from birth to age 10 years. *Eur Respir J*. 2016;47(4):1062-1071.
31. Norbäck D, Lu C, Zhang Y, et al. Onset and remission of childhood wheeze and rhinitis across China - Associations with early life indoor and outdoor air pollution. *Environ Int*. 2019;123:61-69.
32. Lee P, Tan ZY, Pham T. All that wheezes is not asthma. *Thorax*. 2018;73(8):792.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Chen G, Zhou H, He G, et al.. Effect of early-life exposure to PM_{2.5} on childhood asthma/ wheezing: a birth cohort study. *Pediatr Allergy Immunol*. 2022;33:e13822. doi:[10.1111/pai.13822](https://doi.org/10.1111/pai.13822)