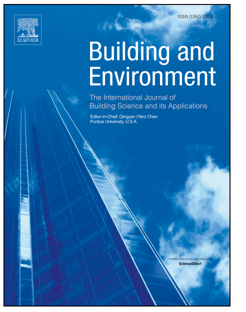
Journal Pre-proof



Impacts of intrauterine and postnatal exposure to air pollution on preschool children's asthma: A key role in cumulative exposure

Chan Lu, Lin Wang, Hongsen Liao, Bin Li, Qin Liu, Qin Li, Faming Wang

PII: S0360-1323(23)00901-0

DOI: https://doi.org/10.1016/j.buildenv.2023.110874

Reference: BAE 110874

To appear in: *Building and Environment*

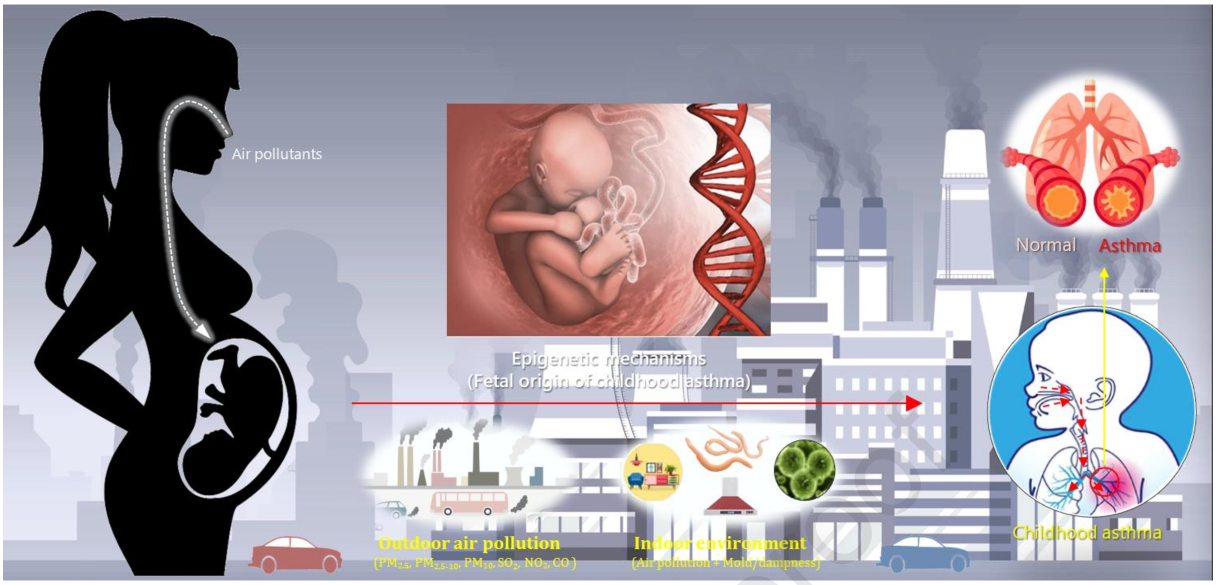
Received Date: 2 August 2023

Revised Date: 16 September 2023

Accepted Date: 24 September 2023

Please cite this article as: Lu C, Wang L, Liao H, Li B, Liu Q, Li Q, Wang F, Impacts of intrauterine and postnatal exposure to air pollution on preschool children's asthma: A key role in cumulative exposure, *Building and Environment* (2023), doi: https://doi.org/10.1016/j.buildenv.2023.110874.

GRAPHICAL ABSTRACT



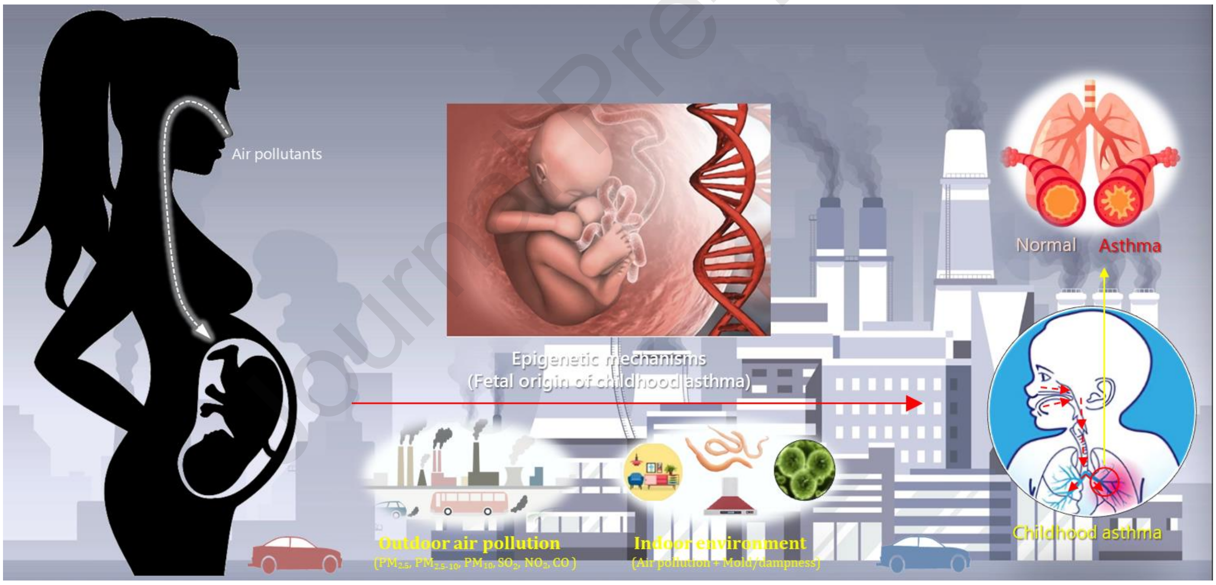
Impacts of intrauterine and postnatal exposure to air pollution on preschool children's asthma: A key role in cumulative exposure

Chan Lu [a,*] Lin Wang [a], Hongsen Liao [a], Bin Li [b], Qin Liu [a], Qin Li [a], Faming Wang [c,*]

[a] XiangYa School of Public Health, Central South University, Changsha, China
[b] School of Psychology, Central China Normal University, Wuhan, China
[c] Division of Animal and Human Health Engineering, Department of Biosystems, KU Leuven, Leuven, Belgium

Word count: 5806 words (references, figures and tables excluded)

GRAPHICAL ABSTRACT



HIGHLIGHTS

- Traffic-related air pollution (TRAP) exposure was related with childhood asthma
- Pregnancy, 2nd trimester, and postnatal period were critical widows for PM exposure
- Daytime and nighttime TRAP exposure played an important role in the risk of asthma
- There were cumulative effects of $PM_{2.5}$ and NO_2 over gestation in relation to asthma
- Our study supports and develops the “fetal origin of childhood asthma” hypothesis

* Corresponding authors. Email address: chanlu@csu.edu.cn (C. Lu); Faming.Wang@kuleuven.be (F. Wang).

Impacts of intrauterine and postnatal exposure to air pollution on preschool children's asthma: A key role in cumulative exposure

Chan Lu [a,*] Lin Wang [a], Hongsen Liao [a], Bin Li [b], Qin Liu [a], Qin Li [a], Faming Wang [c,*]

A B S T R A C T

Background: Despite mounting evidence linking asthma to air pollution, it remains unclear which specific pollutant(s) exposure during critical time window(s) plays a pivotal role in the development of asthma.

Objective: The objective of this study is to investigate the effects of intrauterine and postnatal air pollution exposure on children's asthma.

Methods: From 2019 to 2020, a retrospective cohort study was conducted in Changsha, China. The inverse distance weighted (IDW) method was used to estimate each child's personal exposure to outdoor air pollutants at their home address. Associations between personal air pollution exposure and asthma were comprehensively examined.

Results: The occurrence of children's asthma was found to be linked to exposure to $PM_{2.5}$ and NO_2 during both the intrauterine and current periods, with significant ORs (95% CI) of 1.44 (1.08-1.93) and 1.29 (1.00-1.68) for IQR increase in intrauterine exposure particularly during the 2nd trimester, and 1.26 (1.01-1.57) and 1.26 (1.04-1.51) for exposure in previous year. Post-natal PM_{10} exposure was linked to asthma, with an OR (95% CI) of 1.28 (1.01-1.62). Higher risks of asthma were associated with intrauterine exposure to $PM_{2.5}$ and postnatal exposure to PM_{10}. The critical time windows for $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} exposure were identified as the entire pregnancy, the second trimester, and the entire postnatal period, respectively. Cumulative exposure to $PM_{2.5}$ and NO_2 during gestational weeks had a notable impact on asthma. Additionally, exposure to traffic-related air pollution (TRAP) at all timing stages, as well as $PM_{2.5-10}$ and SO_2 at night, increased the risk of asthma. Certain subgroups were more vulnerable to asthma risk due to air pollution.

Conclusion: Children's asthma was predominantly influenced by exposure to particulate matters and TRAP during both the intrauterine and postnatal periods.

Keywords: Childhood asthma; Pregnancy; Early life exposure; Particulate matters; Accumulation effect

Introduction

Asthma is one of the most prevalent chronic conditions during childhood and remains a significant contributor to paediatric hospitalisations worldwide. In 2015, 358 million people worldwide had asthma (an increase of nearly 100% from 183 million in 1990),[1] resulting in 397,100 deaths.[2] Furthermore, asthmatic symptoms can reoccur in children, causing significant and long-term burdens on social economy and public health.[3] As of now, there is no exact cure for asthma, and it is expected that significant burden of childhood asthma will continue to rise. This increase is being driven primarily by an increase in asthma cases, particularly in low- and middle-income countries.[4] The rapid increase in the prevalence of childhood asthma cannot be attributed to genetic factors, but rather to environmental changes.[5] Nonetheless, the specific air pollutant(s) and time window(s) that have the greatest impact on asthma development are unknown.[6] Therefore, it is crucial to investigate the primary environmental factors that are contributing to the rapid rise in childhood asthma. This allows for the implementation of effective measures to reduce and prevent its occurrence in its early stages.

Air pollutants have been shown to have an important influence on the occurrence and development of children's asthma as a major environmental factor affecting children's asthma.[7] Numerous studies, mostly conducted in high-income countries, have found a link between the occurrence and progression of childhood asthma and traffic-related air pollution (TRAP) (i.e., NO_2).[8-10] As a developing country, China has a more complex and mixed pattern in both the nature and composition of air pollutants. One the one hand, rapid economic growth in many Chinese cities has resulted in a significant increase in the number of private cars and traffic emissions. On the other hand, a large number of infrastructure constructions and industrial activities have resulted in high concentrations of particulate matters (PMs) and SO_2. According to a recent analysis of air quality data from China's major cities in 2017, 26 cities experienced high levels of PMs ($PM_{2.5}$ and PM_{10}) and NO_2 at the same time.[11] Therefore, it's essential to conduct research on the effect of long-term exposure to high levels of air pollution on childhood asthma, taking into account the precise home address of each subject in China.

It has been proposed that early-life exposure to air pollution is likely to be the cause of asthma development.[12] Furthermore, early life has been identified as the critical time frame during which outdoor and indoor environmental factors, as well as climatic exposures, play a key role in the development of childhood asthma and allergies.[13] Previous research has shown that fetal lung growth can be affected by maternal particulate matter exposure.[14] Peak expiratory flow in children aged 6-11 is affected by maternal PM_{10} exposure during pregnancy, and peak expiratory flow is a very important indicator associated with asthma.[15] Yang et al. found that prenatal exposure to PM_{10} has a significant effect on airway hyperresponsiveness (AHR), which correlates with the risk of newly diagnosed childhood asthma.[16] Another recent study found that exposure for $PM_{2.5}$, PM_{10}, SO_2, and NO_2 was positively correlated with hospitalization rates for childhood asthma.[17] An investigation conducted in the USA discovered that the annual $PM_{2.5}$ concentration in areas with high asthma incidence was significantly higher than that in areas with low asthma incidence.[18] Therefore, more research is needed to determine the specific roles of PMs, TRAP, and other pollutants exposure during different windows of early life in relation to the occurrence and progression of children's asthma.

We hypothesized in this study that early-life exposure to outdoor air pollution during the intrauterine and early post-natal periods was associated with childhood doctor-diagnosed asthma. Besides, some critical time window(s) and specific time stages of the day may play an important role in the risk of children's asthma. In order to identify the main air pollutant(s) and their critical exposure time windows and specific time stage(s) during prenatal and postnatal periods in relation to the risk of childhood asthma, a cross-sectional study was conducted in Changsha, China,[19] as part of the 2nd-round national CCHH (China, Children, Homes, Health) study.[20]

Methods

Study design and participants

This is a large-scale retrospective cohort study that was conducted in Changsha, Hunan Province, China, with kindergarten children serving as research subjects. Additionally, we have incorporated a cross-sectional study to supplement our research. The survey period was extended from November 2019 to June 2020. The study protocol, as described in our recent work,[19] This study has received approval from the Ethics Committee of Fudan University (IRB#2019-09-0778). Additionally, we received assistance from kindergarten administrators and obtained informed consent from the guardians of the children involved in the study. Initially, we utilized the internationally recognized questionnaire from the "International Study of Asthma and Allergies in Childhood (ISAAC)."[21] and a Swedish questionnaire on "Dampness in Buildings and Health (DBH)"[22] to collect data on state of health, residential environmental exposures, lifestyle patterns of family members, and Personal Basic Information (using cross-sectional design). Following that, the personal exposure of each child to outdoor air pollutants at their respective home addresses across various time windows in both the prenatal and postnatal stages was calculated (using a retrospective cohort design).

A random survey of 36 kindergartens in all six administrative districts of Changsha was conducted, and the kindergarten children from chosen schools were invited to participate. (Figure 1). A total of 13,609 questionnaires were distributed to the children enrolled in the 36 kindergartens, and parents were asked to complete the within 7 days. Subsequently, we conducted systematic training sessions for the teachers in charge of the survey to ensure careful and accurate completion of the questionnaires. Next, the family members residing with the child will receive the designated survey questionnaire distributed by teachers, and they are required to finish the questionnaire within a 7-day timeframe. We excluded questionnaires from children who were either too old or too young, focusing on children between the ages of 3 and 6 as the research subjects. We also removed questionnaires that lacked health information, as this could have an impact on the accuracy of the results. In the end, we collected 8,846 questionnaires that met the study criteria, and these Samples from these questionnaires were included in the research. (Figure S1).

Ascertainment of asthma

The health outcomes, including doctor-diagnosed asthma (DDA), were ascertained through the following inquiries: (1) "Has your child ever received a doctor's diagnosis of asthma?" (2) "At what age was your child first diagnosed with asthma?" (Options: 1 year old / 2 years old / 3 years old / 4 years old / 5 years old / 6 years old / 7 years old). We defined doctor-diagnosed lifetime asthma (DDLA) as a positive response to the first question. Additionally, we further defined doctor-diagnosed asthma onset (DDAO) at each age as a response to the corresponding option in the second question. To account for the timing of DDA in early life, the surveyed children were categorized into five subgroups based on the trajectory of DDAO between the ages of 0 and 6 years: no DDAO, DDAO for the first time at 1 year old / 2 years old / 3 years old / ≥4 years old (combining ages 4-7 years due to a limited number of cases during these ages).

Exposure time windows

We divided the time of exposure into two categories for this study: the intrauterine period and the postnatal period. The intrauterine period included the first, second, and third trimesters, as well as 40 weeks of gestational age, and the entirety of the pregnancy period (from the last menstruation day [LMD] of the pregnant mother to the child's day of birth). The postnatal period consisted of three phases: the first year after birth (From birth until the twelfth month of age), the preceding year (12 months before filling out the questionnaire), and the entire postnatal period (from the date of birth to the day of questionnaire completion). Additionally, the 24-hour day was divided into four sub-time windows: (1) morning peak, lasting from 07:00 am to 9:00 am; (2) working hours, lasting from 10:00 am to 16:00 pm; (3) evening peak, lasting from 17:00 pm to 19:00 pm; and (4) night hours, lasting from 20:00 pm to 06:00 am. Moreover, we combined the time stages of morning peak, working hours, and evening peak into a single daytime period (07:00-19:00).

Exposure assessment

Data on daily and hourly levels of ambient $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO in Changsha were gathered from ten municipal air quality monitoring stations. The data covers the years from 2013 to 2020. The $PM_{2.5-10}$ concentration was derived by computing the difference between $PM_{2.5}$ and PM_{10} concentrations. Each monitoring station utilized the conventional methods as stipulated by the Chinese Environmental Protection Agency (EPA) for the measurements.[23,24] In this present investigation, SO_2 was recognized to air pollutants associated with industrial activities. PM_{10} has been identified as a surrogate for a complex mixture of air pollutants.[25,26] $PM_{2.5-10}$ was classified as conventional air pollution originating from soil/dust sources, whereas $PM_{2.5}$, NO_2, and CO were regarded as representative surrogates of TRAP in this context.[19,27]

We calculated the daily levels of six major air pollutants at each child's residential address using an inverse distance weighted (IDW) method, with the accuracy of each home address's latitude and longitude reserved to six decimal places, using data from the four closest monitoring stations.[19] The weighting function employed the inverse ($1/d^2$) of the squared distance between each home address and the nearest station.[23] The average distance (d) was either equal to or less than 5 km.

We calculated the pregnant mothers' exposure by determining the mean daily levels of six air pollutants (PM_{10}, $PM_{2.5-10}$, $PM_{2.5}$, NO_2, SO_2, and CO) during the first, second, and third trimesters, as well as the entire duration of pregnancy. These time frames corresponded to the 1^{st} to 12^{th} gestational week, 13^{th} to 27^{th} gestational week, 28^{th} week until the last gestational week, and from the LMD of the pregnant mother until the child's day of birth, respectively.[28] We also calculated the mother's exposure to air pollutants over the course of her 40-week pregnancy. The post-natal periods included the first year after birth (from birth until the twelfth month of age), the previous year (12 months prior to filling out the questionnaire), and the entire postnatal period (from the date of birth to the day of questionnaire completion).

Covariates

This study concentrated on three groups of potential confounding covariates. These confounding covariates included (1) personal factors: sex (male / female), age (3-4 years / 5-6 years), birth season (spring [from March to May] / summer [from June to August] / autumn [from September to November] / winter [from December to next February]), number of people living with child (≤3 / 4-5 / >5), parasitic infection (yes / no), parental atopy (yes / no), and staying with child every day (yes / no); (2) socio economic status (SES): level of parental education (low / middle / high), level of parental annual income (low / middle / high), and house size (<100 m^2 / ≥100 m^2); and (3) living environmental factors: new furniture (yes / no), house redecoration (yes / no), mold/damp stains (yes / no), damp clothing or bedding (yes / no), kitchen ventilation type (no / only natural / only mechanical / both natural and mechanical), opening windows in four seasons (yes / no), and living near traffic main road or highway (yes / no) (Table 1). Each of the confounding covariates mentioned above was related to children's asthma.[28]

Statistical Analysis

In this study, we presented descriptive statistics, including counts (percentages), mean ± SD, and interquartile range (IQR). we used the Pearson chi-square test and t-test to compare differences in confounding covariates between the control and asthma cases subgroups. In order to assess the association between children's DDA and air pollution exposure during both intrauterine and post-natal periods, we utilized multiple logistic regression models while adjusting for covariates. Individual exposure to air pollutants measured daily and time stages of the day were used as continuous variables in the logistic regression model. The relationship between asthma and air pollutants was assessed by measuring their exposure increment per interquartile range (IQR). The associations were evaluated using odds ratios (ORs) and 95% confidence intervals (CIs) for each interquartile range (IQR) increase in exposure to various air pollutants. A single-pollutant model was used to investigate the independent relationships between childhood asthma and levels of outdoor air pollutants within specific time windows. When adjusting the single-pollutant model, all covariates listed in Table 1 were considered. The multi-pollutant model was used to identify the air pollutant(s) that had the greatest impact on children's asthma. The multi-pollutant model was also adjusted for the other pollutants within the same time window, expanding on the findings of the single-pollutant model. The Multi-pollutant + window model was employed to identify the primary pollutant(s) exposure during critical time window(s) that had a notable and statistically significant impact on childhood asthma. The Multi-pollutant + window model was tweaked further, adjusting the same air pollutant during the other time window(s) indicated by the multi-pollutant model. Furthermore, Subgroup analyses were conducted to identify those groups that were more vulnerable to the effects of air pollution on DDA. The statistical analyses were performed using SPSS statistical software (version 22.0, SPSS Inc., Chicago, USA). All analyses were conducted as two-tailed tests, and a risk with a *p*-value of 0.05 was considered statistically significant. Individual air pollution exposures were calculated using Python 3.10 software on the PyCharm platform (version 2020.2.3 Community Edition, JetBrains, s.r.o., Czech Republic).

Results

Of the 8,689 children studied, 372 (4.3%) had a reported experiencing doctor-diagnosed asthma (DDA). Table 1 presents the demographic characteristics and lifetime prevalence of DDA, categorized by the considered covariates. Sex, the number of people living with the child, parental atopy, parental annual income, new furniture, house redecoration, visible mold/damp stains, and damp clothing and bedding were found to have a significant association with children's DDA ($p<0.05$). For example, the lifetime prevalence of DDA was significantly higher among boys, families with fewer people living with the child (n≤3), children with parental atopy, families with high parental annual income, families with new furniture, house redecoration, visible mold/damp stains, and damp clothing and bedding. However, no correlation was found between DDA and age group, birth season, parasitic infection, staying with child every day, parental education level, house size, kitchen ventilation styles, opening windows in all four seasons, or living near a busy main road or highway.

Table S1 illustrates the distributions of individual exposure to outdoor air pollutants during the intrauterine and post-natal periods. Throughout the pregnancy, the mean maternal exposure levels (mean ± SD) for $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, SO_2, NO_2, and CO were 68±13, 30±5, 82±11, 22±6, and 41±6 μg/m^3, with CO at1.03±0.17 mg/m^3. Individual exposure to both air pollutants decreased throughout the complete post-natal period compared to the entire pregnancy. Throughout the entire postnatal period, the mean individual exposure levels for the six pollutants were 50±3, 26±3, 63±6, 12±2, 36±3 μg/m^3, and 0.82±0.52 mg/m^3, respectively. Moreover, Pearson correlations among outdoor air pollutants within different time windows were relatively low and/or moderate (<0.7) (Table S2), supporting the use of a multi-pollutant model in the present analysis.

Table 2 presents the correlation between prenatal and postnatal exposure to outdoor air pollutants and children's DDA. Within the single-pollutant model, we found a significant link between childhood asthma and $PM_{2.5}$ and NO_2, as evidenced by ORs (95% CI) of 1.44 (1.08-1.93) and 1.29 (1.00-1.68) for per IQR increment during entire intrauterine exposure, and 1.26 (1.01-1.57) and 1.26 (1.04-1.51) for current exposure in previous year, respectively. Children's DDA was also linked to postnatal

PM_{10} exposure, with a significant OR (95% CI) = 1.28 (1.01-1.62). DDA has significant odds ratios (ORs) in relation to exposure to two types of particulate matter ($PM_{2.5}$ and $PM_{2.5-10}$) and NO_2 during the second trimester. $PM_{2.5}$ exposure during the second trimester was associated with persistent and statistically significant ORs, which were evident in both the multi-pollutant and multi-pollutant + window models. Furthermore, persistent and statistically significant ORs for PM_{10} exposure were found throughout the post-natal period. Remarkably significant ORs were observed for $PM_{2.5-10}$ exposure during the second trimester. Notably, our findings show that prenatal exposure to fine particles ($PM_{2.5}$) influenced the risk of children's DDA the most, while postnatal exposure to coarse (inhalable) particles (PM_{10}) also played a significant role. Moreover, we observed a similar trend in asthma risk associated with exposure to both PMs (Figure S2) and gaseous air pollutants (Figure S3) during the 40 gestational weeks, compared to exposure during each trimester.

Table 3 presents the relationship between intrauterine and post-natal exposure to outdoor air pollution and the first occurrence of childhood DDA at different ages. Our findings indicate that exposure to air pollution during the first two trimesters of pregnancy, particularly during intrauterine development, was primarily associated with the DDA onset for the first time at 3 years old. In comparison, exposure to outdoor air pollution during pregnancy, especially during the first two trimesters and the first year of postnatal life, was associated with the onset of DDA at an older age (≥4 years old). This finding suggests that early-life exposure may have a cumulative effect. Nonetheless, we found no significant positive correlation between outdoor air pollution and the first occurrence of DDA under the age of three (1 year or 2 years old). The evidence indicates that air pollution exposure, especially during early life, played a greater role in the onset of childhood DDA at older ages than at younger ages.

Table 4 displays the correlation between prenatal and postnatal exposure to air pollution at different time windows throughout the day and childhood asthma. Our findings revealed a remarkable relationship between daytime exposure (07:00-19:00), which includes the morning peak (07:00-09:00), working hours (10:00-16:00), and evening peak (17:00-19:00), and TRAP encompassing $PM_{2.5}$, PM_{10}, NO_2, and CO. This exposure, particularly during the second trimester and the previous year, had a significant influence on the onset of children's DDA. In comparison, we observed that not only TRAP, but also coarse fraction of PM ($PM_{2.5-10}$) and industry-related pollutant (SO_2) exposure in the second trimester and previous year significantly increased DDA risk.

Table S3 shows a subgroup analysis of the correlation between air pollutants and DDA, stratified by personal factors. Our findings revealed that children aged 3-4 years old, as well as those living in households with more than three people, were more vulnerable to the impact of intrauterine and postnatal exposure to outdoor air pollutants on DDA. Furthermore, children from higher socioeconomic status (SES) families, as indicated by a larger house size (≥100 m^2), higher parental annual income, and middle/high parental education levels, were more likely to develop DDA linked to outdoor air pollution (Table S4). Additionally, children living in homes that were redecorated and had open windows during all four seasons were found to be more susceptible to DDA due to intrauterine and postnatal exposure to outdoor air pollutants (Table S5).

This study investigated the cumulative effect of air pollutant exposure during the nine gestational months and the first three years after birth on childhood asthma (Figure 2). The cumulative exposure to $PM_{2.5}$ and NO_2 during the gestational months was linked to an increased risk of DDA. However, no significant cumulative effect was observed for postnatal exposure.

Discussion

As far as we know, this is the first study to evaluate the links between exposure to various air pollutants at each child's precise home address during the intrauterine period, including 40 gestational weeks, three trimesters, post-natal period including the first year of life and the previous year, and their accumulated exposure. Furthermore, the study investigated how exposure at different times of the day during different time windows of the prenatal and postnatal periods influenced the risk of DDA in preschool children. Our findings revealed that both prenatal and postnatal exposure to PMs and TRAP had a significant impact on children's DDA. Notably, exposure to fine particles ($PM_{2.5}$) during the prenatal period was found to be more important, whereas exposure to inhalable particles (PM_{10}) was found to be more influential during the postnatal period. Moreover, our investigation revealed that the entire gestation period, the second trimester, and the entire postnatal duration were critical time periods for exposure to $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10}, respectively, in relation to the increased risk of DDA. Furthermore, we discovered that both daytime and nighttime exposure to TRAP during specific time windows had a negative effect on DDA, with nighttime exposure having a greater impact. The subgroup analysis revealed that several subsets were more vulnerable to the risk of DDA due to exposure to air pollution. These findings support the "fetal origin of asthma" hypothesis, particularly during the second trimester.

Our remarkable discovery showed a link between intrauterine and current exposure to TRAP, specifically fine particles ($PM_{2.5}$) and NO_2, and children's DDA. This finding supports the theory of the "fetal origin of asthma." Exposure to air pollution during the prenatal and early postnatal periods is more important than exposure later in life due to the increased vulnerability of crucial organs and target systems during these pivotal stages of life development.[29] A birth cohort study in the Netherlands, for example, found significant links between pollutants from traffic sources and non-infectious cough during the first year of life. Nonetheless, these effects decreased or vanished in the second year of life.[30] The results of our study are consistent with the scant evidence available on the impact of early-life air pollution exposure on the occurrence of childhood asthma. A Swedish cohort study found a link between exposure to nitrogen monoxide (NO) during the first year of life and an increased risk of asthma at the age of four.[31] One of our recent studies found that early exposure to outdoor air pollution was not associated with the early onset of allergic symptoms, including asthma in children,[32] which is consistent with the present study finding no relationship between outdoor air pollution exposure and the early onset of asthma in children under the age of three. This could be because: (1) the diagnosis of asthma for children under the age of three is complicated; (2) exposure to indoor environmnetal factors such as window condensation during pregnancy and new furniture during the first year played a key role in the early asthmatic symptom (wheeze) before the age of two.[32]

In addition, our other study found that prenatal industrial air pollutant (SO_2) exposure was associated with the onset of respiratory infection (otitis media) in children aged 3-4 years.[33] Previous studies have found that early life exposure to outdoor air pollution is associated with respiratory infection (e.g., otitis media) but not with the early onset of allergic symptoms (e.g., wheeze). A study conducted in Germany found a higher risk of asthma in children exposed to NO_2 and $PM_{2.5}$ at the age of one year.[34] A study conducted in the USA found that higher NO_2 exposure during the first year of life was associated with an increased risk of asthma (OR =1.17, 95% CI: 1.04-1.31).[35] According to a Canadian study, an increase of 10 μg/m^3 in NO_2 exposure during pregnancy was linked to an adjusted odds ratio (OR) of 1.12 (95% CI: 1.07-1.17) for asthma in children aged 3-4 years.[36] One of our previous studies found that every 15 μg/m^3 increase in utero NO_2 exposure was associated with an increased risk of asthma in children aged 3-6 years, with an adjusted OR of 1.74 (95% CI: 1.15-2.62).[23] A systematic review study discovered a statistically significant correlation between prenatal exposure to nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) and the risk of asthma and wheezing development in children.[37]

We recently discovered that the pregnancy and postnatal periods are critical time windows for exposure to fine particles ($PM_{2.5}$) and inhalable particles (PM_{10}), which have a significant impact on the onset of children's asthma. Evidence from relevant epidemiological studies indicates that maternal PM exposure is linked to decreased lung function in children, suggesting that maternal PM exposure can influence fetal lung growth.[14] In Canada, a recent study found evidence to support a link between second-trimester exposure to ultrafine particulate matter and the development of childhood asthma.[38] A recent study conducted in six Chinese cities found that prenatal exposure to outdoor $PM_{2.5}$ and PM_{10} was linked to a higher occurrence of wheezing in children aged 3 to 6 years.[39] A study in the USA revealed that higher levels of $PM_{2.5}$ exposure in mothers between 16 and 25 weeks of gestation may contribute to the development of asthma in 6-year-old boys,[40] which is consistent with our results. Several studies from Shanghai[41] and Hong Kong[42] found no asthmatic risk for PM_{10} exposure after birth. Despite we have identified a relatively greater importance for various types of PMs exposure in relation to asthma during both the intrauterine and postnatal periods, the underlying mechanisms remain unknown, necessitating further research.

Next, there have only been a few studies that assessed the relative importance of intrauterine, gestational weeks, trimesters, and postnatal exposures to air pollutants, and their findings have been inconclusive. Clark et al. found that first-year exposures to TRAP ($PM_{2.5}$, NO_2, and CO) was more harmful than intrauterine exposures, with the exception of PM_{10}, SO_2, or O_3 exposure, where no significant difference was observed.[36] They did not specify which time window was more important, but they did state that intrauterine PM_{10} and NO_2 exposure would have an impact independent of postnatal exposure. The current study, on the other hand, observed that exposure to $PM_{2.5}$ and NO_2 during the second trimester of pregnancy had a relatively significant impact on the occurrence of DDA in offspring, which is consistent with our previous findings.[43] We also discovered that $PM_{2.5}$ and NO_2 exposure during the 21st weeks of gestation played a critical role in the development of asthma in children. As a result, we advise pregnant women to avoid PMs, particularly TRAP exposure, during this period in utero.

We conducted a groundbreaking investigation into the impact of exposure to various ambient air pollutants during the prenatal and postnatal periods at various time intervals throughout the day, specifically at each child's precise home address, on asthma. We observed that early-life exposure to TRAP during both day and nighttime significantly influenced children's DDA, with nighttime exposure exhibiting a more pronounced negative effect. Few studies have looked at the impact of air pollutant exposure on children's asthma at different times of day. Previous research has found that PMs and SO_2 can significantly increase the risk of childhood asthma.[44-46] In addition, large-scale-industrial pollutants in Chinese cities can only be discharged at a specific time at night. On the other hand, the temperature at night is lower than during the day, while the relative humidity is higher, making it easier for pollutants to accumulate and difficult to diffuse.[47] We found that the influence of $PM_{2.5-10}$ and NO_2 in the morning rush hour on asthma is significant, which may be related to increased automobile exhaust emissions and road dust due to high traffic volume during the rush hours. [48-50]

Our research has numerous significant strengths. First, a large number of kindergarten children participated in the study, which utilized a combination of cross-sectional and retrospective research methods. This methodology ensured the accuracy, validity, and representativeness of our data and outcomes. Second, this study is the first to comprehensively evaluate the associations between DDA levels in children and individual exposure to various outdoor air pollutants. The evaluation encompasses three distinct categories of particulate matters (PMs) and diverse gaseous air pollutants from a variety of pollution sources, spanning both the prenatal and postnatal stages. Thirdly, a high level of precision was attained in evaluating individual exposure to six air pollutants at each child's precise residential address, achieved by setting the longitude and latitude to six decimal places. This methodology produced accurate and precise individual exposure estimations. Regarding children's DDA, we also considered cumulative personal exposure to air pollution during gestational months and postnatal years. Fourthly, this study is the first to conduct a comprehensive and comparative examination of the DDA risk associated with children's exposure to ambient air pollution across a wide range of time windows. Through our remarkable discoveries and analysis, it is possible to identify the key air pollutant(s) exposure, during specific vulnerable time windows and periods of the day, associated with specific pollution source(s), that have the most significant impact on the development of DDA in early childhood.

This study has several limitations that must be acknowledged. First, the collection of data was based on a questionnaire survey, which could potentially introduce recall bias. It is essential to not, however, that the majority of the questionnaires were completed by parents of young children, who typically have excellent recall, particularly when recalling events from their child's early years. In addition, all enrolled families maintained accurate medical records containing vital information, such as regular prenatal exams, birth-related information, and the health status of family members, obtained from hospitals or routine health screenings in kindergartens. This should have reduced the significant recall bias present in our study. Second, we were unable to accurately measure indoor pollutant concentrations. Notably, in Chinese cities, the ratio of indoor to outdoor air pollution is nearly equal due to the frequent opening of windows and doors, which allows for adequate indoor natural ventilation. Therefore, the exposure levels in both indoor and outdoor environments are comparable.

The concentration of outdoor air pollution should closely resemble that of indoor air pollution. Thus, the absence of indoor air pollution data is unlikely to have a substantial impact on the conclusions regarding the association between outdoor pollution exposure and childhood asthma. Thirdly, it is essential to recognize that this study was carried out in a single city, which may not be representative of the situation in other regions of China. The levels of air pollutants and climate characteristics vary from region to region, necessitating multi-center research for a complete understanding. Fourthly, we lacked information on lifestyle habits, dietary habits, and medical history in this study, which may have had an impact on the findings. Therefore, future research should take these into account.

Conclusions

This research represents a pioneering effort to comprehensively evaluate the links between exposure to various outdoor air pollutants at various crucial time windows. It includes the intrauterine phase, 40 gestational weeks (including three trimesters), the postnatal period encompassing the first year after birth and the year preceding the completion of questionnaires, as well as cumulative exposure over gestational months and early years after birth. In addition, this study investigated DDA exposure throughout the entire day and at various time intervals. The remarkable results indicate that both prenatal and postnatal exposure to PMs and TRAP have a substantial impact on childhood DDA. Specifically, prenatal exposure to fine particles ($PM_{2.5}$) and postnatal exposure to inhalable particles (PM_{10}) were identified as the more significant factors for asthma. Recent research identified the entire duration of pregnancy, the second trimester, and the entire postnatal period as critical exposure windows for $PM_{2.5}$, $PM_{2.5\text{-}10}$, and PM_{10} exposure, respectively. Both daytime and nighttime exposure to TRAP exerted a significant influence on children's asthma for the first time in our observations, with nighttime exposure exhibiting relatively greater significance. Our findings support the "fetal origin of asthma" hypothesis. Moreover, our study could aid policymakers in formulating environmental protection and public health policies, particularly for vulnerable subgroups. On one hand, it is recommended that the Environmental Protection Bureau enact pertinent policies centered on energy conservation and reducing emissions. These measures could include restricting vehicle traffic, conducting road cleaning, promoting the use of cleaner gasoline and green transportation alternatives, and reducing industrial emissions and improving desulfurization processes. Furthermore, pregnant women and children should avoid exposure to significant air pollutants, particularly PMs and TRAP. It is also recommended that they reside far from major roads and highways. Moreover, young children are encouraged to avoid inhaling inhalable PM (PM_{10}), especially those originating from heavy industry, during their early years. Lastly, our study calls for coordinated action (e.g., pediatricians should collaborate with children and parents) to make pediatric healthcare more resource-efficient, recommending the implementation of specific strategies for the effective reduction and early prevention of asthma risk, particularly in vulnerable populations.[51]

■ ACKNOWLEDGMENTS

Our study was supported by the National Natural Science Foundation of China (No. 42007391, 42277432) and the Natural Science Foundation of Hunan Province (No. 2021JJ30813). We thank all the participated kindergartens, their children and their families for contributions and participation. We also appreciate the helps from the collaborated teachers and students at Central South University in the Database establishment and data arrangement.

AUTHOR INFORMATION

First author

Chan Lu — *XiangYa School of Public Health, Central South University, Changsha 410078, Hunan, China*

Co-corresponding authors

Chan Lu — *XiangYa School of Public Health, Central South University, Changsha 410078, Hunan, China;*
ID: orcid.org/0000-0002-0110-9492;
Email: chanlu@csu.edu.cn

Faming Wang — *Division of Animal and Human Health Engineering, Department of Biosystems, KU Leuven, Leuven, 3001, Belgium*
Email: Faming.Wang@kuleuven.be

Authors' information

Chan Lu (Distinguished Professor, FISBE; co-first author, corresponding author) — *XiangYa School of Public Health, Central South University, Changsha 410028, Hunan, China*

Lin Wang — *XiangYa School of Public Health, Central South University, Changsha 410028, Hunan, China*

Hongsen Liao — *XiangYa School of Public Health, Central South University, Changsha 410028, Hunan, China*

Bin Li — *School of Psychology, Central China Normal University, Wuhan 430070, Hubei, China*

Qin Liu — *XiangYa School of Public Health, Central South University, Changsha 410028, Hunan, China*

Qin Li — *XiangYa School of Public Health, Central South University, Changsha 410028, Hunan, China*

Faming Wang (Co-first author) — *Division of Animal and Human Health Engineering, Department of Biosystems, KU Leuven, Leuven, 3001, Belgium*

DECLARATIONS

Ethics approval and consent to participate

This work has received approval for research from Fudan University and a proof/certificate of approval (IRB#2019-09-0778) is available upon request. A written consent was obtained from all the surveyed kindergartens, parents or guardians for all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare no competing financial interest.

Authors' contributions

Chan Lu conducted the study, conceptualized, designed, and performed the study, collected the data, supervised the data analysis, and drafted the initial manuscript and revised the manuscript. **Lin Wang** collected and analyzed the data and drafted some parts of the initial manuscript. **Hongsen Liao** collected and analyzed the data and drafted some parts of the initial manuscript. **Bin Li** collected the data and reviewed the manuscript. **Qin Liu** reviewed the manuscript. **Qin Li** reviewed the manuscript. **Faming Wang** conceptualized, designed, supervised the data analysis, reviewed, and revised the manuscript.

REFERENCES

[1] WHO. 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: A systematic analysis for the global burden of disease study 2015. Lancet 388: 1545-1602.
[2] WHO. 2016. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the global burden of disease study 2015. Lancet 388: 1459-1544.
[3] Masoli M, Fabian D, Holt S, Beasley R. 2004. The global burden of asthma: Executive summary of the GINA Dissemination Committee report. Allergy 59: 469-478.
[4] Eder W, Ege MJ, von Mutius E. 2006. The asthma epidemic. N Engl J Med 355: 2226-2235.
[5] Martinez FD. 2007. Genes, environments, development and asthma: A reappraisal. Eur Respir J 29: 179-184.
[6] De Sario M, Katsouyanni K, Michelozzi P. 2013. Climate change, extreme weather events, air pollution and respiratory health in Europe. Eur Respir J 42: 826-843.

[7] Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. 2011. Acute effects of air pollution on pediatric asthma exacerbation: Evidence of association and effect modification. Environ Res 111: 418-424.

[8] Gauderman WJ, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J, et al. 2005. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology 16: 737-743.

[9] McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, et al. 2006. Traffic, susceptibility, and childhood asthma. Environ Health Perspect 114: 766-772.

[10] Zmirou D, Gauvin S, Pin I, Momas I, Sahraoui F, Just J, et al. 2004. Traffic related air pollution and incidence of childhood asthma: Results of the vesta case-control study. J Epidemiol Community Health 58: 18-23.

[11] Feng Y, Ning M, Lei Y, Sun Y, Liu W, Wang J. 2019. Defending blue sky in China: Effectiveness of the "Air Pollution Prevention and Control Action Plan" on air quality improvements from 2013 to 2017. J Environ Manage 252: 109603.

[12] Jung CR, Chen WT, Tang YH, Hwang BF. 2019. Fine particulate matter exposure during pregnancy and infancy and incident asthma. J Allergy Clin Immunol 143: 2254-2262.

[13] Sheffield PE, Weinberger KR, Kinney PL. 2011. Climate change, aeroallergens, and pediatric allergic disease. Mt Sinai J Med 78: 78-84.

[14] Mölter A, Agius RM, de Vocht F, Lindley S, Gerrard W, Lowe L, et al. 2013. Long-term exposure to PM_{10} and NO_2 in association with lung volume and airway resistance in the MAAS birth cohort. Environ. Health Perspect 121: 1232-1238.

[15] Mortimer K, Neugebauer R, Lurmann F, Alcorn S, Balmes J, Tager I. 2008. Air pollution and pulmonary function in asthmatic children: Effects of prenatal and lifetime exposures. Epidemiology 19: 550-557.

[16] Yang SI, Lee SY, Kim HB, Kim HC, Leem JH, Yang HJ, et al. 2019. Prenatal particulate matter affects new asthma via airway hyperresponsiveness in schoolchildren. Allergy 74: 675-684.

[17] Kuo CY, Chan CK, Wu CY, Phan DV, Chan CL. 2019. The short-term effects of ambient air pollutants on childhood asthma hospitalization in Taiwan: A national study. Int J Environ Res Public Health 16: 203-215.

[18] Lovinsky-Desir S, Acosta LM, Rundle AG, Miller RL, Goldstein IF, Jacobson JS, et al. 2019. Air pollution, urgent asthma medical visits and the modifying effect of neighborhood asthma prevalence. Pediatr Res 85: 36-42.

[19] Lu C, Li Q, Qiao Z, Liu Q, Wang F. 2023. Effects of pre-natal and post-natal exposures to air pollution on onset and recurrence of childhood otitis media. J Hazard Mater 459: 132254.

[20] Wu C, Zhang Y, Wei J, Zhao Z, Norbäck D, Zhang X, et al. 2022. Associations of early-life exposure to submicron particulate matter with childhood asthma and wheeze in China. JAMA Netw Open 5: e2236003.

[21] Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 368: 733-743.

[22] Bornehag CG, Sundell J, Sigsgaard T. 2004. Dampness in buildings and health (DBH): Report from an ongoing epidemiological investigation on the association between indoor environmental factors and health effects among children in Sweden. Indoor Air 14: 59-66.

[23] Deng Q, Lu C, Norbäck D, Bornehag CG, Zhang Y, Liu W, et al. 2015. Early life exposure to ambient air pollution and childhood asthma in China. Environ Res 143: 83-92.

[24] Lu C, Yang W, Liu Z, Liao H, Li Q, Liu Q. 2022. Effect of preconceptional, prenatal and postnatal exposure to home environmental factors on childhood pneumonia: A key role in early life exposure. Environ Res 214: 114098.

[25] Deng Q, Lu C, Li Y, Sundell J, Norbäck D. 2016. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. Environ Res 150: 119-127.

[26] Kan H, Chen R, Tong S. 2012. Ambient air pollution, climate change, and population health in China. Environ Int 42: 10-19.

[27] Lu C, Liu Z, Liao H, Yang W, Li Q, Liu Q. 2022. Effects of early life exposure to home environmental factors on childhood allergic rhinitis: modifications by outdoor air pollution and temperature. Ecotoxicol Environ Saf 244: 114076.

[28] Lu C, Liao H, Liu Z, Yang W, Liu Q, Li Q. 2022. Association between early life exposure to indoor environmental factors and childhood asthma. Build Environ 226: 109740.

[29] Nordling E, Berglind N, Melén E, Emenius G, Hallberg J, Nyberg F, et al. 2008. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology 19: 401-408.

[30] Gehring U, Cyrys J, Sedlmeir G, Brunekreef B, Bellander T, Fischer P, et al. 2002. Traffic-related air pollution and respiratory health during the first 2 yrs of life. Eur Respir J 19: 690-698.

[31] Gruzieva O, Bergström A, Hulchiy O, Kull I, Lind T, Melén E, et al. 2013. Exposure to air pollution from traffic and childhood asthma until 12 years of age. Epidemiology 24: 54-61.

[32] Lu C, Liu Z, Yang W, Liao H, Liu Q, Li Q, et al. 2023. Early life exposure to outdoor air pollution and indoor environmental factors on the development of childhood allergy from early symptoms to diseases. Environ Res 216: 114538.

[33] Deng Q, Lu C, Jiang W, Zhao J, Deng L, Xiang Y. 2017. Association of outdoor air pollution and indoor renovation with early childhood ear infection in China. Chemosphere 169: 288-296.

[34] Morgenstern V, Zutavern A, Cyrys J, Brockow I, Gehring U, Koletzko S, et al. 2007. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. Occup Environ Med 64: 8-16.

[35] Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, et al. 2013. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. Am J Respir Crit Care Med 188: 309-318.

[36] Clark NA, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, et al. 2010. Effect of early life exposure to air pollution on development of childhood asthma. Environ Health Perspect 118: 284-290.

[37] Zhang H, Chang Q, Gao S, Wu Q, Zhao Y. 2017. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. Environ Res 159: 519-530.

[38] Lavigne E, Donelle J, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, et al. 2019.

Spatiotemporal variations in ambient ultrafine particles and the incidence of childhood asthma. Am J Respir Crit Care Med 199: 1487-1495.
[39] Norbäck D, Lu C, Zhang Y, Li B, Zhao Z, Huang C, et al. 2019. Onset and remission of childhood wheeze and rhinitis across China - associations with early life indoor and outdoor air pollution. Environ Int 123: 61-69.
[40] Leon Hsu HH, Mathilda Chiu YH, Coull BA, Kloog I, Schwartz J, Lee A, et al. 2015. Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. Am J Respir Crit Care Med 192: 1052-1059.
[41] Liu W, Huang C, Hu Y, Fu Q, Zou Z, Sun C, et al. 2016. Associations of gestational and early life exposures to ambient air pollution with childhood respiratory diseases in Shanghai, China: A retrospective cohort study. Environ Int 92: 284-293.
[42] He B, Huang JV, Kwok MK, Au Yeung SL, Hui LL, Li AM, et al. 2019. The association of early-life exposure to air pollution with lung function at ~17.5 years in the "Children of 1997" Hong Kong Chinese birth cohort. Environ Int 123: 444-450.
[43] Lu C, Deng L, Ou C, Yuan H, Chen X, Deng Q. 2017. Preconceptional and perinatal exposure to traffic-related air pollution and eczema in preschool children. J Dermatol Sci 85: 85-95.
[44] Jassal MS. 2015. Pediatric asthma and ambient pollutant levels in industrializing nations. Int Health 7: 7-15.
[45] Kravitz-Wirtz N, Teixeira S, Hajat A, Woo B, Crowder K, Takeuchi D. 2018. Early-life air pollution exposure, neighborhood poverty, and childhood asthma in the United States, 1990-2014. Int J Environ Res Public Health 15: 1114-1127.
[46] Shakerkhatibi M, Benis KZ, Asghari-Jafarabadi M, Sadeghi-Bazarghani H, Allahverdipour H, Oskouei DS, et al. 2021. Air pollution-related asthma profiles among children/adolescents: A multi-group latent class analysis. Ecotoxicol Environ Saf 219: 112344.
[47] Deng Q, Lu C, Ou C, Chen L, Yuan H. 2016. Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children. Chemosphere 152: 459-467.
[48] Cassidy BE, Alabanza-Akers MA, Akers TA, Hall DB, Ryan PB, Bayer CW, et al. 2007. Particulate matter and carbon monoxide multiple regression models using environmental characteristics in a high diesel-use area of baguio city, philippines. Sci Total Environ 381: 47-58.
[49] Tunno BJ, Michanowicz DR, Shmool JLC, Tripathy S, Kinnee E, Cambal L, et al. 2018. Spatial patterns in rush-hour vs. Work-week diesel-related pollution across a downtown core. Int J Environ Res Public Health 15: 1968-1982.
[50] Xu H, Chen H. 2021. Impact of urban morphology on the spatial and temporal distribution of $PM_{2.5}$ concentration: A numerical simulation with WRF/CMAQ model in Wuhan, China. J Environ Manage 290: 112427.
[51] Gozderesi Y, Tsagkaris C, Eleftheriades A, Pervanidou P. 2022. To pollute or not to pollute? Decreasing the ecological footprint of pediatrics in the COVID-19 era. J Clim Chang Health 8: 100141.

Table 1 Demographic information and prevalence of doctor-diagnosed asthma among children aged 3-6 years (n=8,689)

	Total	Childhood asthma	p-value
	Number (%)	Case (n) (%)	
Total	8,689 (100.0)	372 (4.3)	
Sex			**<0.001**
Boys	4,667 (53.7)	240 (5.1)	
Girls	4,022 (46.3)	132 (3.3)	
Age (years)			0.861
3-4	4,820 (55.5)	208 (4.3)	
5-6	3,869 (44.5)	164 (4.2)	
Birth season			0.154
Spring	2,168 (25.0)	95 (4.4)	
Summer	2,378 (27.4)	90 (3.8)	
Autumn	2,089 (24.0)	106 (5.1)	
Winter	2,054 (23.6)	81 (3.9)	
Parasitic infection			0.316
No	6,658 (76.6)	259 (3.9)	
Yes	275 (3.2)	14 (5.1)	
Number of people living with child			**0.008**
≤3	2,739 (31.5)	140 (5.1)	
4-5	4,740 (54.6)	174 (3.7)	
>5	1,210 (13.9)	58 (4.8)	
Parental atopy			**<0.001**
No	6,032 (69.4)	172 (2.9)	
Yes	2,657 (30.6)	199 (7.5)	
Staying with child everyday			0.083
No	1,122 (12.9)	59 (5.3)	
Yes	7,567 (87.1)	313 (4.1)	
Parental education level			0.223
Low [a]	1,538 (17.7)	54 (3.5)	
Middle [b]	5,926 (68.2)	260 (4.4)	
High [c]	1,225 (14.1)	58 (4.7)	
Parental annual income			**0.001**
Low	1,405 (16.2)	74 (5.3)	
Middle	7,025 (80.8)	277 (3.9)	
High	259 (3.0)	21 (8.1)	
House size (m^2)			0.290
<100	2,792 (32.1)	128 (4.6)	
≥100	5,767 (66.4)	236 (4.1)	
New furniture			**0.026**
No	5,708 (65.7)	224 (3.9)	
Yes	2,972 (34.2)	147 (4.9)	
House redecoration			**0.003**
No	6,868 (79.0)	271 (3.9)	
Yes	1,812 (20.9)	100 (5.5)	
Mold/damp stains			**<0.001**
No	6,514 (75.0)	225 (3.5)	
Yes	2,166 (24.9)	146 (6.7)	
Damp clothing or bedding			**<0.001**
No	7,325 (84.3)	287 (3.9)	
Yes	1,355 (15.6)	84 (6.2)	
Kitchen ventilation styles			0.588
No	12 (0.1)	0 (0.0)	
Only natural [d]	171 (2.0)	8 (4.7)	
Only mechanical [e]	3,613 (41.6)	144 (4.0)	
Both natural and mechanical	4,893 (56.3)	220 (4.5)	
Opening windows in four seasons			0.065
No	392 (4.5)	24 (6.1)	
Yes	8,297 (95.5)	348 (4.2)	
Living near traffic main road or highway			0.174
No	7,306 (84.1)	54 (0.7)	
Yes	1,011 (11.6)	318 (31.5)	

Sum of the number is not 8,689 due to missing data.

The prevalence of childhood asthma was calculated by the formula: (number of case / number of total children) * 100%.

Parental education level: [a] Low level was indicated as primary school, junior high school, high school, or vocational high school; [b] Middle level was indicated as undergraduate or junior college; [c] High level was indicated as master's or PhD.

Kitchen ventilation styles: [d] Natural ventilation was indicated as opening windows; [e] Mechanical ventilation was indicated as using smoke exhaust ventilator, exhaust fan, air cleaner, or others.

The p-values <0.05 in bold was indicated as statistically significant.

Table 2 Odds ratio (95% CI) of children's asthma for exposure to outdoor air pollutants during intrauterine and post-natal periods (n=8,689)

	Single-pollutant model #	Multi-pollutant model †	Multi-pollutant + window model §
1st trimester			
$PM_{2.5}$	1.18 (0.91, 1.53)	1.20 (0.91, 1.58)	1.27 (0.94, 1.71)
$PM_{2.5-10}$	1.03 (0.89, 1.19)	1.08 (0.90, 1.29)	1.01 (0.84, 1.22)
PM_{10}	0.94 (0.76, 1.16)	0.84 (0.65, 1.09)	0.86 (0.66, 1.12)
SO_2	1.15 (0.90, 1.46)	1.15 (0.85, 1.55)	1.01 (0.72, 1.43)
NO_2	1.10 (0.83, 1.46)	0.91 (0.59, 1.38)	0.84 (0.55, 1.29)
CO	1.10 (0.89, 1.37)	1.05 (0.80, 1.37)	1.02 (0.76, 1.37)
2nd trimester			
$PM_{2.5}$	1.27 (1.00, 1.63)*	1.28 (1.00, 1.64)*	1.27 (0.99, 1.63)
$PM_{2.5-10}$	1.17 (1.03, 1.33)*	1.23 (1.07, 1.43)**	1.24 (1.04, 1.46)*
PM_{10}	1.07 (0.87, 1.33)	0.82 (0.63, 1.06)	0.82 (0.63, 1.07)
SO_2	1.16 (0.93, 1.45)	1.12 (0.86, 1.46)	1.04 (0.75, 1.45)
NO_2	1.41 (1.06, 1.87)*	1.27 (0.85, 1.91)	1.24 (0.80, 1.91)
CO	1.04 (0.92, 1.17)	0.93 (0.70, 1.24)	0.80 (0.54, 1.17)
3rd trimester			
$PM_{2.5}$	1.11 (0.85, 1.46)	1.13 (0.85, 1.50)	1.22 (0.89, 1.69)
$PM_{2.5-10}$	1.07 (0.91, 1.27)	1.03 (0.83, 1.27)	1.01 (0.81, 1.26)
PM_{10}	1.12 (0.92, 1.38)	1.06 (0.81, 1.38)	1.03 (0.78, 1.36)
SO_2	1.00 (0.80, 1.24)	0.97 (0.74, 1.27)	0.83 (0.62, 1.13)
NO_2	1.12 (0.85, 1.49)	1.04 (0.70, 1.53)	0.90 (0.59, 1.36)
CO	1.04 (0.83, 1.30)	1.02 (0.76, 1.37)	0.89 (0.61, 1.29)
Entire pregnancy			
$PM_{2.5}$	1.44 (1.08, 1.93)*	1.42 (1.06, 1.91)*	1.45 (1.06, 1.98)*
$PM_{2.5-10}$	1.11 (0.91, 1.35)	1.10 (0.84, 1.45)	1.09 (0.82, 1.43)
PM_{10}	1.01 (0.85, 1.20)	0.90 (0.72, 1.14)	0.92 (0.73, 1.16)
SO_2	1.13 (0.87, 1.47)	1.10 (0.82, 1.48)	1.04 (0.74, 1.45)
NO_2	1.29 (1.00, 1.68)*	1.13 (0.82, 1.57)	1.11 (0.77, 1.59)
CO	1.09 (0.88, 1.35)	0.95 (0.74, 1.24)	0.95 (0.73, 1.23)
First year			
$PM_{2.5}$	1.05 (0.78, 1.40)	0.94 (0.67, 1.33)	0.86 (0.60, 1.22)
$PM_{2.5-10}$	1.04 (0.91, 1.19)	0.99 (0.81, 1.20)	0.97 (0.77, 1.20)
PM_{10}	1.23 (0.98, 1.53)	1.23 (0.93, 1.63)	1.25 (0.94, 1.67)
SO_2	1.09 (0.84, 1.43)	1.04 (0.76, 1.43)	1.03 (0.69, 1.54)
NO_2	1.00 (0.85, 1.16)	0.98 (0.81, 1.18)	0.87 (0.71, 1.07)
CO	0.93 (0.81, 1.06)	0.95 (0.80, 1.12)	0.95 (0.79, 1.16)
Past year			
$PM_{2.5}$	1.26 (1.01, 1.57)*	1.28 (0.98, 1.67)	1.24 (0.94, 1.62)
$PM_{2.5-10}$	1.08 (0.95, 1.23)	1.48 (0.97, 2.26)	1.48 (0.96, 2.26)
PM_{10}	1.14 (0.96, 1.35)	0.53 (0.26, 1.07)	0.53 (0.26, 1.07)
SO_2	1.16 (0.96, 1.40)	1.40 (0.98, 2.00)	1.43 (0.99, 2.06)
NO_2	1.26 (1.04, 1.51)*	1.29 (0.97, 1.72)	1.24 (0.87, 1.76)
CO	0.97 (0.87, 1.08)	0.96 (0.84, 1.09)	0.96 (0.82, 1.12)
Entire postnatal			
$PM_{2.5}$	1.04 (0.83, 1.31)	0.70 (0.49, 1.00)	0.73 (0.50, 1.06)
$PM_{2.5-10}$	1.14 (0.97, 1.35)	0.72 (0.44, 1.17)	0.72 (0.44, 1.17)
PM_{10}	1.28 (1.01, 1.62)*	2.43 (1.09, 5.44)*	2.60 (1.16, 5.81)*
SO_2	1.16 (0.95, 1.42)	1.10 (0.79, 1.53)	1.02 (0.67, 1.55)
NO_2	1.08 (0.95, 1.24)	1.04 (0.88, 1.23)	1.00 (0.84, 1.20)
CO	1.01 (0.94, 1.07)	0.96 (0.70, 1.31)	0.96 (0.70, 1.31)

OR (95%CI) was estimated for per IQR increase in each outdoor air pollutant during each time window.

Single-pollutant model was adjusted for all covariates in Table 1.

† Multi-pollutant model was further adjusted for the other pollutants during the same time window based on single-pollutant model.

§ Multi-pollutant + window model was further adjusted for the same air pollutant during the other time window(s) based on multi-pollutant model.

* $p<0.05$. ** $p<0.01$.

Table 3 Odds ratio (95% CI) of first episode of doctor-diagnosed asthma for exposure to outdoor air pollution during intrauterine and post-natal periods among children aged 3-6 years using multinomial model (n=8,689)

	First episode of doctor-diagnosed asthma				
	No (n=8,317)	1 year (n=97)	2 years (n=115)	3 years (n=89)	≥4 years (n=71)
1st trimester					
$PM_{2.5}$	1.00	0.83 (0.50, 1.37)	0.98 (0.62, 1.54)	1.68 (0.96, 2.95)	1.91 (1.08, 3.37)*
$PM_{2.5-10}$	1.00	0.98 (0.74, 1.31)	0.95 (0.72, 1.25)	1.11 (0.81, 1.53)	1.07 (0.80, 1.45)
PM_{10}	1.00	1.18 (0.78, 1.79)	0.81 (0.56, 1.19)	0.90 (0.57, 1.40)	0.94 (0.62, 1.44)
SO_2	1.00	0.88 (0.55, 1.40)	1.30 (0.86, 1.97)	1.31 (0.79, 2.19)	1.28 (0.76, 2.14)
NO_2	1.00	0.97 (0.56, 1.68)	0.81 (0.49, 1.32)	2.11 (1.19, 3.75)*	1.15 (0.61, 2.17)
CO	1.00	0.71 (0.44, 1.14)	1.01 (0.68, 1.50)	1.00 (0.62, 1.62)	1.92 (1.31, 2.80)***
2nd trimester					
$PM_{2.5}$	1.00	1.10 (0.69, 1.76)	1.32 (0.86, 2.02)	1.08 (0.64, 1.82)	1.74 (1.02, 2.94)*
$PM_{2.5-10}$	1.00	1.02 (0.79, 1.31)	1.06 (0.85, 1.33)	1.37 (1.05, 1.77)*	1.25 (0.97, 1.61)
PM_{10}	1.00	0.92 (0.62, 1.39)	0.85 (0.59, 1.23)	1.03 (0.65, 1.63)	1.60 (0.99, 2.58)
SO_2	1.00	1.10 (0.73, 1.68)	1.16 (0.79, 1.71)	1.14 (0.72, 1.82)	1.29 (0.81, 2.06)
NO_2	1.00	1.42 (0.83, 2.44)	1.43 (0.88, 2.32)	1.40 (0.77, 2.54)	1.32 (0.71, 2.46)
CO	1.00	0.97 (0.64, 1.47)	1.05 (0.84, 1.31)	0.91 (0.56, 1.48)	1.05 (0.94, 1.18)
3rd trimester					
$PM_{2.5}$	1.00	1.04 (0.62, 1.75)	0.87 (0.52, 1.45)	1.13 (0.64, 1.99)	1.58 (0.92, 2.71)
$PM_{2.5-10}$	1.00	1.06 (0.77, 1.47)	1.10 (0.82, 1.48)	1.10 (0.76, 1.57)	1.02 (0.72, 1.46)
PM_{10}	1.00	0.96 (0.65, 1.40)	1.06 (0.74, 1.52)	1.51 (0.96, 2.37)	1.10 (0.72, 1.67)
SO_2	1.00	1.16 (0.78, 1.74)	0.80 (0.52, 1.24)	0.86 (0.53, 1.38)	1.19 (0.76, 1.87)
NO_2	1.00	1.32 (0.79, 2.22)	0.78 (0.47, 1.32)	1.31 (0.74, 2.33)	1.24 (0.67, 2.27)
CO	1.00	0.87 (0.56, 1.33)	0.92 (0.61, 1.39)	1.02 (0.63, 1.64)	1.51 (0.98, 2.34)
Entire pregnancy					
$PM_{2.5}$	1.00	0.94 (0.54, 1.63)	1.09 (0.65, 1.81)	1.81 (0.99, 3.31)	3.82 (1.97, 7.42)***
$PM_{2.5-10}$	1.00	1.12 (0.77, 1.62)	1.05 (0.74, 1.49)	1.29 (0.84, 1.96)	1.02 (0.66, 1.55)
PM_{10}	1.00	0.97 (0.70, 1.35)	0.86 (0.63, 1.17)	1.15 (0.80, 1.67)	1.06 (0.74, 1.51)
SO_2	1.00	1.04 (0.63, 1.71)	1.11 (0.69, 1.77)	1.16 (0.67, 2.01)	1.35 (0.78, 2.32)
NO_2	1.00	1.29 (0.79, 2.11)	0.97 (0.62, 1.52)	2.09 (1.23, 3.53)**	1.26 (0.70, 2.27)
CO	1.00	0.79 (0.51, 1.22)	1.02 (0.69, 1.51)	0.98 (0.61, 1.58)	1.76 (1.24, 2.48)***
First year					
$PM_{2.5}$	1.00	0.89 (0.50, 1.59)	1.23 (0.71, 2.13)	0.70 (0.37, 1.32)	1.39 (0.83, 2.35)
$PM_{2.5-10}$	1.00	0.98 (0.76, 1.27)	1.15 (0.93, 1.43)	0.86 (0.63, 1.15)	1.12 (0.86, 1.47)
PM_{10}	1.00	0.98 (0.65, 1.47)	1.11 (0.77, 1.60)	1.30 (0.82, 2.06)	2.17 (1.24, 3.81)**
SO_2	1.00	0.97 (0.58, 1.62)	0.94 (0.57, 1.56)	1.29 (0.75, 2.24)	1.32 (0.78, 2.22)
NO_2	1.00	0.93 (0.69, 1.25)	0.98 (0.75, 1.28)	1.05 (0.76, 1.45)	1.09 (0.78, 1.53)
CO	1.00	0.84 (0.64, 1.12)	0.93 (0.73, 1.20)	0.88 (0.65, 1.20)	1.08 (0.84, 1.40)
Past year					
$PM_{2.5}$	1.00	1.25 (0.82, 1.92)	1.17 (0.79, 1.72)	1.35 (0.85, 2.16)	1.30 (0.80, 2.10)
$PM_{2.5-10}$	1.00	1.00 (0.78, 1.28)	1.12 (0.90, 1.41)	0.97 (0.74, 1.27)	1.30 (0.97, 1.74)
PM_{10}	1.00	1.01 (0.73, 1.40)	1.23 (0.92, 1.63)	1.09 (0.77, 1.55)	1.24 (0.86, 1.79)
SO_2	1.00	1.06 (0.75, 1.51)	1.31 (0.95, 1.82)	1.14 (0.77, 1.67)	1.06 (0.71, 1.58)
NO_2	1.00	0.99 (0.80, 1.22)	0.83 (0.70, 0.98)*	1.12 (0.88, 1.42)	1.08 (0.84, 1.40)
CO	1.00	1.25 (0.82, 1.92)	1.17 (0.79, 1.72)	1.35 (0.85, 2.16)	1.30 (0.80, 2.10)
Entire postnatal					
$PM_{2.5}$	1.00	0.98 (0.62, 1.54)	0.94 (0.61, 1.45)	0.86 (0.52, 1.42)	1.43 (0.97, 2.10)
$PM_{2.5-10}$	1.00	0.94 (0.68, 1.30)	1.12 (0.84, 1.49)	0.99 (0.69, 1.42)	1.74 (1.23, 2.45)**
PM_{10}	1.00	0.95 (0.61, 1.49)	1.16 (0.78, 1.75)	1.11 (0.67, 1.83)	2.84 (1.63, 4.95)***
SO_2	1.00	1.00 (0.64, 1.57)	0.99 (0.65, 1.53)	1.20 (0.79, 1.81)	1.32 (1.04, 1.67)*
NO_2	1.00	1.07 (0.83, 1.38)	1.00 (0.79, 1.26)	1.19 (0.91, 1.56)	1.13 (0.84, 1.51)
CO	1.00	1.00 (0.89, 1.13)	0.88 (0.60, 1.30)	0.99 (0.73, 1.35)	1.01 (0.95, 1.08)

OR (95%CI) was estimated for IQR increase in each outdoor air pollutant during each time window.
Model was adjusted for all covariates in Table 1.
* $p<0.05$. ** $p<0.01$. *** $p<0.001$.

Table 4 Odds ratio (95% CI) of children's asthma for intrauterine and post-natal exposure to outdoor air pollution during different timing stages of a day (n=8,689).

	Daytime (08:00-19:00)	Morning peak (07:00-09:00)	Working hours (10:00-16:00)	Evening peak (17:00-19:00)	Night hours (20:00-6:00)
1st trimester					
$PM_{2.5}$	1.18 (0.92, 1.51)	1.15 (0.92, 1.43)	1.21 (0.92, 1.58)	1.19 (0.94, 1.51)	1.14 (0.93, 1.39)
$PM_{2.5-10}$	0.96 (0.76, 1.21)	0.95 (0.76, 1.19)	0.97 (0.77, 1.22)	1.02 (0.77, 1.35)	0.93 (0.74, 1.16)
PM_{10}	1.10 (0.91, 1.33)	1.11 (0.89, 1.39)	1.12 (0.92, 1.37)	1.13 (0.93, 1.37)	1.11 (0.88, 1.41)
SO_2	1.16 (0.91, 1.48)	1.19 (0.94, 1.51)	1.19 (0.92, 1.55)	1.22 (0.92, 1.61)	1.19 (0.93, 1.53)
NO_2	1.16 (0.83, 1.61)	1.07 (0.78, 1.45)	1.18 (0.86, 1.62)	1.23 (0.89, 1.72)	1.10 (0.82, 1.48)
CO	1.22 (0.94, 1.58)	1.19 (0.93, 1.53)	1.24 (0.96, 1.59)	1.26 (0.96, 1.67)	1.22 (0.93, 1.59)
2nd trimester					
$PM_{2.5}$	1.43 (1.10, 1.86)**	1.41 (1.10, 1.79)**	1.45 (1.10, 1.91)**	1.37 (1.09, 1.73)**	1.31 (1.09, 1.58)**
$PM_{2.5-10}$	1.19 (0.95, 1.49)	1.18 (1.07, 1.31)**	1.12 (0.90, 1.40)	1.10 (0.86, 1.40)	1.37 (1.13, 1.65)***
PM_{10}	1.34 (1.10, 1.63)**	1.40 (1.13, 1.73)**	1.34 (1.09, 1.64)**	1.30 (1.09, 1.55)**	1.39 (1.13, 1.70)***
SO_2	1.26 (1.01, 1.58)*	1.20 (0.96, 1.50)	1.29 (1.01, 1.65)*	1.26 (0.98, 1.62)	1.30 (1.01, 1.68)*
NO_2	1.37 (1.04, 1.81)*	1.48 (1.12, 1.96)**	1.37 (1.03, 1.82)*	1.29 (0.97, 1.72)	1.36 (1.06, 1.76)*
CO	1.27 (1.05, 1.53)*	1.26 (1.05, 1.51)*	1.27 (1.04, 1.56)*	1.29 (1.05, 1.58)*	1.26 (1.05, 1.50)*
3rd trimester					
$PM_{2.5}$	1.17 (0.94, 1.47)	1.14 (0.93, 1.41)	1.19 (0.94, 1.49)	1.18 (0.96, 1.44)	1.14 (0.94, 1.38)
$PM_{2.5-10}$	1.06 (0.87, 1.28)	1.08 (0.94, 1.25)	1.05 (0.87, 1.27)	1.06 (0.84, 1.33)	1.06 (0.84, 1.33)
PM_{10}	1.16 (0.94, 1.44)	1.17 (0.94, 1.45)	1.16 (0.94, 1.43)	1.16 (0.96, 1.40)	1.17 (0.93, 1.49)
SO_2	1.12 (0.92, 1.37)	1.08 (0.89, 1.31)	1.13 (0.92, 1.38)	1.14 (0.95, 1.37)	1.08 (0.90, 1.30)
NO_2	1.17 (0.90, 1.51)	1.13 (0.87, 1.46)	1.16 (0.90, 1.49)	1.24 (0.94, 1.65)	1.07 (0.85, 1.33)
CO	1.11 (0.92, 1.35)	1.11 (0.93, 1.33)	1.12 (0.92, 1.36)	1.14 (0.93, 1.41)	1.10 (0.90, 1.35)
Entire pregnancy					
$PM_{2.5}$	1.17 (0.96, 1.42)	1.15 (0.97, 1.38)	1.19 (0.97, 1.47)	1.15 (0.98, 1.35)	1.11 (0.98, 1.26)
$PM_{2.5-10}$	1.16 (0.88, 1.54)	1.10 (0.98, 1.24)	1.15 (0.78, 1.68)	1.15 (0.90, 1.47)	1.09 (0.95, 1.26)
PM_{10}	1.18 (0.96, 1.45)	1.19 (0.98, 1.44)	1.20 (0.95, 1.51)	1.17 (0.99, 1.38)	1.14 (0.98, 1.33)
SO_2	1.20 (0.94, 1.53)	1.20 (0.92, 1.56)	1.18 (0.94, 1.48)	1.21 (0.98, 1.48)	1.16 (0.94, 1.44)
NO_2	1.09 (0.94, 1.26)	1.10 (0.96, 1.25)	1.09 (0.94, 1.27)	1.09 (0.96, 1.23)	1.08 (0.93, 1.24)
CO	1.16 (0.94, 1.43)	1.15 (0.94, 1.40)	1.17 (0.93, 1.46)	1.16 (0.97, 1.39)	1.11 (0.95, 1.30)
First year					
$PM_{2.5}$	1.14 (0.87, 1.51)	1.21 (0.88, 1.64)	1.13 (0.88, 1.45)	1.14 (0.88, 1.48)	1.16 (0.90, 1.49)
$PM_{2.5-10}$	1.04 (0.94, 1.15)	1.05 (0.91, 1.22)	1.03 (0.94, 1.12)	1.08 (0.92, 1.26)	1.02 (0.94, 1.11)
PM_{10}	1.06 (0.90, 1.25)	1.14 (0.88, 1.46)	1.05 (0.92, 1.21)	1.08 (0.90, 1.29)	1.08 (0.91, 1.29)
SO_2	1.27 (0.90, 1.81)	1.43 (0.93, 2.20)	1.29 (0.89, 1.86)	1.32 (0.89, 1.97)	1.42 (0.93, 2.18)
NO_2	1.05 (0.86, 1.27)	1.03 (0.82, 1.30)	1.08 (0.84, 1.37)	1.03 (0.91, 1.16)	1.00 (0.84, 1.20)
CO	1.00 (0.92, 1.09)	1.01 (0.93, 1.10)	1.00 (0.94, 1.07)	0.99 (0.93, 1.06)	1.01 (0.93, 1.10)
Past year					
$PM_{2.5}$	1.30 (1.02, 1.66)*	1.36 (1.01, 1.82)*	1.32 (1.03, 1.68)*	1.28 (1.00, 1.65)*	1.30 (1.01, 1.67)*
$PM_{2.5-10}$	1.20 (0.96, 1.49)	1.31 (1.00, 1.71)**	1.16 (0.93, 1.44)	1.39 (0.96, 2.02)	1.28 (1.01, 1.61)*
PM_{10}	1.28 (1.01, 1.63)*	1.30 (1.01, 1.68)*	1.30 (1.02, 1.66)*	1.27 (1.00, 1.60)*	1.39 (1.03, 1.88)*
SO_2	1.09 (0.89, 1.34)	1.04 (0.77, 1.41)	1.05 (0.88, 1.25)	1.42 (1.02, 1.97)*	1.37 (1.02, 1.85)*
NO_2	1.43 (1.07, 1.92)*	1.36 (1.05, 1.77)*	1.45 (1.07, 1.98)*	1.39 (1.06, 1.82)*	1.35 (1.05, 1.75)*
CO	1.31 (1.00, 1.71)*	1.31 (1.02, 1.68)*	1.27 (0.98, 1.64)	1.34 (1.00, 1.79)*	1.39 (1.02, 1.91)*
Entire postnatal					
$PM_{2.5}$	1.07 (0.85, 1.34)	1.06 (0.87, 1.30)	1.08 (0.84, 1.39)	1.10 (0.83, 1.46)	1.09 (0.87, 1.39)
$PM_{2.5-10}$	1.14 (0.99, 1.31)	1.21 (0.99, 1.47)	1.09 (0.98, 1.20)	1.26 (1.00, 1.60)*	1.06 (0.97, 1.15)
PM_{10}	1.20 (0.89, 1.63)	1.21 (0.90, 1.63)	1.21 (0.89, 1.64)	1.27 (0.90, 1.80)	1.22 (0.90, 1.66)
SO_2	1.45 (0.94, 2.24)	1.32 (0.98, 1.76)	1.45 (0.95, 2.21)	1.30 (0.95, 1.79)	1.39 (0.98, 1.99)
NO_2	1.10 (0.90, 1.33)	1.06 (0.90, 1.27)	1.12 (0.89, 1.40)	1.11 (0.90, 1.35)	1.07 (0.90, 1.26)
CO	0.96 (0.88, 1.05)	1.04 (0.88, 1.23)	0.96 (0.85, 1.07)	0.95 (0.83, 1.08)	1.00 (0.82, 1.21)

OR (95%CI) was estimated for IQR increase in each air pollutant.
ORs were adjusted for all covariates in Table 1.
* $p<0.05$. ** $p<0.01$. *** $p<0.001$.

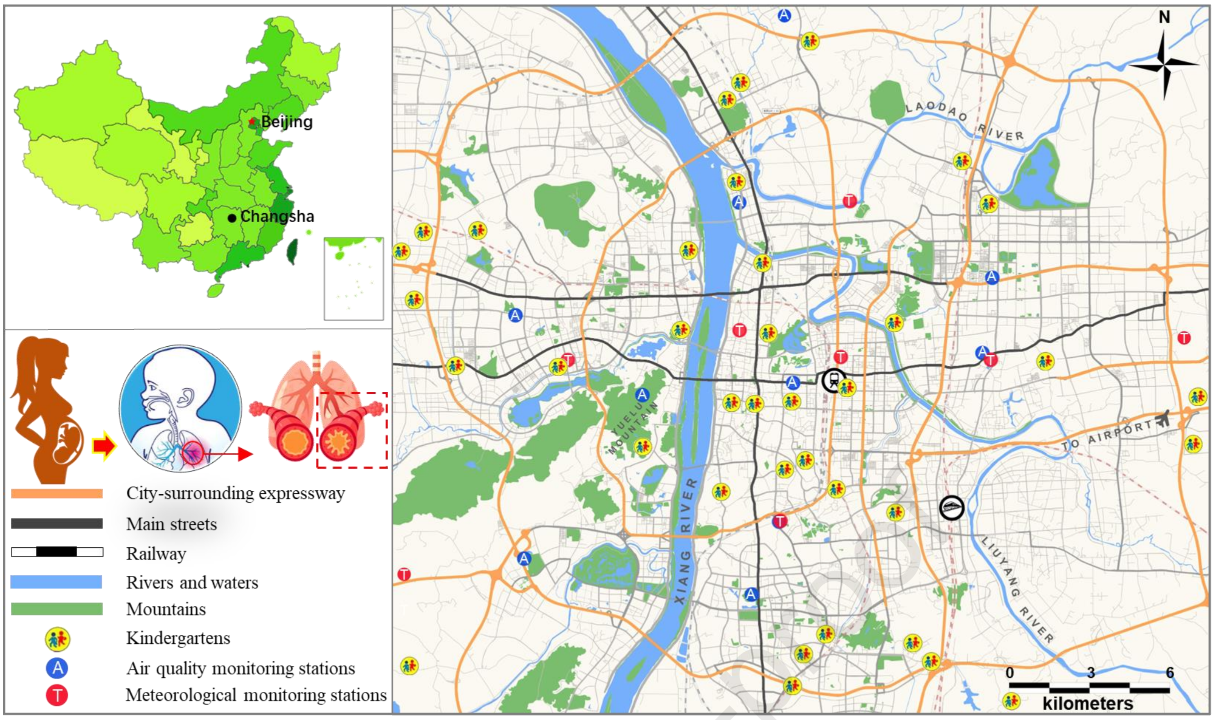


Figure 1. Map for the locations of 36 participating kindergartens, 10 ambient air quality monitoring stations, and 8 meteorological monitoring stations in Changsha, China (n=8,689).

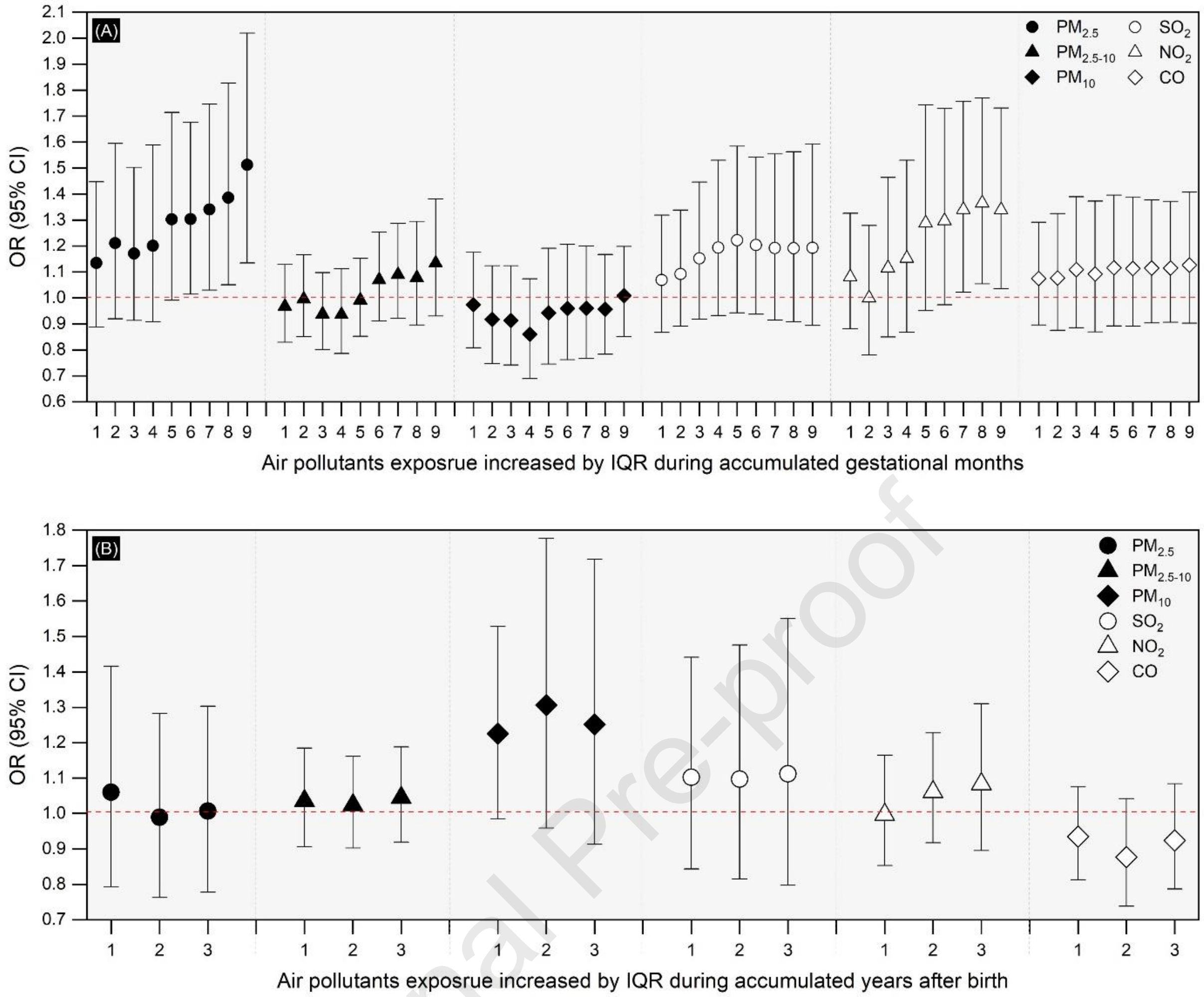


Figure 2. Odds ratio (95% CI) of children's doctor-diagnosed asthma (DDA) for accumulated exposure to outdoor air pollution during accumulated 9 months of gestational age (A) and accumulated first 3 years after birth (B).
ORs (95%CI) were estimated for IQR increase in each air pollutant during each time window.
Models were adjusted for all covariates in Table 1.

Supplemental materials

Table S1 Statistics of intrauterine and post-natal personal exposure to outdoor air pollution among children aged 3-6 years (n=8,689)

	Mean	SD	25%	50%	75%	IQR
1st trimester						
$PM_{2.5}$	69	25	50	65	84	34
$PM_{2.5-10}$	29	8	24	28	33	9
PM_{10}	79	19	65	80	93	28
SO_2	23	8	16	21	28	12
NO_2	42	12	32	40	49	17
CO	1.05	0.28	0.85	1.00	1.21	0.36
2nd trimester						
$PM_{2.5}$	67	23	51	64	79	28
$PM_{2.5-10}$	29	7	25	28	32	7
PM_{10}	80	18	67	81	93	26
SO_2	22	8	16	20	26	10
NO_2	41	10	33	40	49	16
CO	1.02	0.36	0.85	0.98	1.16	0.31
3rd trimester						
$PM_{2.5}$	66	24	48	62	79	31
$PM_{2.5-10}$	29	7	24	28	33	9
PM_{10}	79	18	66	80	93	27
SO_2	21	8	15	18	25	10
NO_2	40	11	32	39	48	16
CO	1.00	0.24	0.81	0.95	1.13	0.32
Entire pregnancy						
$PM_{2.5}$	68	13	58	67	76	18
$PM_{2.5-10}$	30	5	27	30	34	7
PM_{10}	82	11	75	82	89	14
SO_2	22	6	17	21	26	9
NO_2	41	6	37	41	46	9
CO	1.03	0.17	0.91	0.98	1.14	0.23
First year						
$PM_{2.5}$	59	9	52	55	66	14
$PM_{2.5-10}$	30	4	28	29	32	4
PM_{10}	79	10	73	81	86	13
SO_2	18	4	15	17	21	6
NO_2	40	4	37	39	42	5
CO	0.95	0.11	0.88	0.93	0.99	0.11
Past year						
$PM_{2.5}$	44	2	43	44	47	4
$PM_{2.5-10}$	23	2	22	23	24	2
PM_{10}	57	2	55	56	58	3
SO_2	6.9	0.5	6.5	6.9	7.3	0.8
NO_2	31	2	30	31	33	3
CO	0.86	0.03	0.85	0.87	0.88	0.03
Entire postnatal						
$PM_{2.5}$	50	3	48	50	52	4
$PM_{2.5-10}$	26	3	24	26	28	4
PM_{10}	63	6	58	62	68	10
SO_2	12	2	11	12	13	2
NO_2	36	3	34	35	37	3
CO	0.82	0.52	0.64	0.89	0.93	0.29

$PM_{2.5}$ (μg/m^3) = particulate matter ≤ 2.5μm in aerodynamic, $PM_{2.5-10}$ (μg/m^3) = 2.5μm ≤ particulate matter particulate matter ≤ 10μm in aerodynamic, PM_{10} (μg/m^3) = particulate matter ≤ 10μm in aerodynamic, SO_2 (μg/m^3) = sulphur dioxide, NO_2 (μg/m^3) = nitrogen dioxide, CO (mg/m^3) = carbon monoxide. SD = standard deviation, IQR: Inter quartile range.

652 **Table S2** Pearson correlations between outdoor air pollutants within different time windows (n=8,689).

Air pollutants	$PM_{2.5}$	$PM_{2.5-10}$	PM_{10}	SO_2	NO_2	CO
1st trimester						
$PM_{2.5}$	1	0.22**	0.26**	0.74**	0.86**	0.76**
$PM_{2.5-10}$		1	0.55**	0.08**	0.23**	0.24**
PM_{10}			1	0.04**	0.33**	0.12**
SO_2				1	0.68**	0.57**
NO_2					1	0.66**
CO						1
2nd trimester						
$PM_{2.5}$	1	0.13**	0.27**	0.74**	0.85**	0.48**
$PM_{2.5-10}$		1	0.53**	-0.07**	0.18**	0.01
PM_{10}			1	0.01	0.35**	-0.01
SO_2				1	0.64**	0.52**
NO_2					1	0.49**
CO						1
3rd trimester						
$PM_{2.5}$	1	0.14**	0.32**	0.82**	0.85**	0.78**
$PM_{2.5-10}$		1	0.53**	-0.02	0.19**	0.08**
PM_{10}			1	0.13**	0.38**	0.10**
SO_2				1	0.71**	0.60**
NO_2					1	0.68**
CO						1
Entire pregnancy						
$PM_{2.5}$	1	0.38**	0.01	0.75**	0.72**	0.66**
$PM_{2.5-10}$		1	0.51**	0.04**	0.40**	0.21**
PM_{10}			1	-0.21**	0.18**	-0.20**
SO_2				1	0.51**	0.48**
NO_2					1	0.48**
CO						1
First year						
$PM_{2.5}$	1	0.36**	0.69**	0.86**	0.51**	0.45**
$PM_{2.5-10}$		1	0.47**	0.12**	0.43**	0.04**
PM_{10}			1	0.63**	0.38**	0.06**
SO_2				1	0.43**	0.29**
NO_2					1	0.29**
CO						1
Last year						
$PM_{2.5}$	1	-0.08**	0.21**	0.28**	0.64**	0.18**
$PM_{2.5-10}$		1	0.85**	0.24**	0.14**	-0.51**
PM_{10}			1	0.62**	0.34**	-0.47**
SO_2				1	0.16**	-0.20**
NO_2					1	0.16**
CO						1
Entire postnatal						
$PM_{2.5}$	1	0.37**	0.71**	0.77**	0.48**	0.14**
$PM_{2.5-10}$		1	0.85**	0.22**	0.35**	0.24**
PM_{10}			1	0.55**	0.45**	0.16**
SO_2				1	0.46**	0.32**
NO_2					1	0.13**
CO						1

653 ** Correlation is significant at the 0.01 level (2-tailed).

Table S3 Odds ratio (95% CI) of children's asthma for exposure to outdoor air pollution during intrauterine and post-natal periods stratified by personal factors (n=8,689).

	Age (years)		Number of people living with child	
	3-4 (n=4,820)	5-6 (n=3,869)	≤3 (n=2,739)	>3 (n=5,950)
1st trimester				
$PM_{2.5}$	1.35 (0.85, 2.13)	0.84 (0.57, 1.23)	1.25 (0.82, 1.89)	1.14 (0.82, 1.60)
$PM_{2.5-10}$	1.03 (0.80, 1.34)	1.04 (0.86, 1.25)	0.96 (0.75, 1.22)	1.08 (0.89, 1.31)
PM_{10}	1.13 (0.78, 1.64)	0.94 (0.72, 1.24)	0.71 (0.50, 1.00)	1.15 (0.87, 1.50)
SO_2	1.30 (0.88, 1.91)	0.95 (0.68, 1.33)	1.33 (0.91, 1.96)	1.04 (0.76, 1.43)
NO_2	1.49 (0.99, 2.26)	0.73 (0.48, 1.10)	0.95 (0.61, 1.49)	1.22 (0.85, 1.76)
CO	1.02 (0.69, 1.53)	0.97 (0.72, 1.31)	1.02 (0.72, 1.46)	1.15 (0.87, 1.51)
2nd trimester				
$PM_{2.5}$	1.13 (0.74, 1.75)	1.41 (1.01, 1.95)*	1.32 (0.89, 1.95)	1.22 (0.89, 1.68)
$PM_{2.5-10}$	1.14 (0.88, 1.48)	1.13 (0.98, 1.32)	1.08 (0.89, 1.31)	1.24 (1.05, 1.46)**
PM_{10}	1.20 (0.81, 1.79)	1.13 (0.82, 1.54)	1.03 (0.73, 1.44)	1.10 (0.84, 1.46)
SO_2	1.45 (1.03, 2.04)*	1.11 (0.82, 1.50)	1.19 (0.83, 1.70)	1.13 (0.86, 1.50)
NO_2	1.42 (0.95, 2.12)	1.45 (0.95, 2.21)	1.20 (0.73, 1.95)	1.50 (1.06, 2.14)*
CO	0.91 (0.62, 1.34)	1.04 (0.90, 1.19)	1.24 (0.87, 1.77)	0.99 (0.79, 1.25)
3rd trimester				
$PM_{2.5}$	1.44 (0.90, 2.29)	1.06 (0.74, 1.52)	0.99 (0.62, 1.59)	1.16 (0.83, 1.62)
$PM_{2.5-10}$	0.97 (0.70, 1.35)	0.98 (0.78, 1.23)	1.04 (0.79, 1.37)	1.08 (0.87, 1.34)
PM_{10}	1.07 (0.73, 1.58)	0.93 (0.69, 1.24)	1.04 (0.74, 1.46)	1.14 (0.88, 1.47)
SO_2	1.28 (0.87, 1.87)	1.05 (0.78, 1.42)	0.83 (0.56, 1.23)	1.09 (0.83, 1.43)
NO_2	1.21 (0.81, 1.82)	1.19 (0.78, 1.81)	0.97 (0.59, 1.60)	1.19 (0.84, 1.68)
CO	0.99 (0.67, 1.48)	1.10 (0.84, 1.45)	1.13 (0.78, 1.64)	0.99 (0.74, 1.30)
Entire pregnancy				
$PM_{2.5}$	1.36 (0.93, 2.00)	1.35 (0.81, 2.25)	1.47 (0.91, 2.37)	1.41 (0.97, 2.04)
$PM_{2.5-10}$	1.05 (0.74, 1.47)	0.94 (0.71, 1.25)	0.85 (0.62, 1.18)	1.29 (1.00, 1.65)*
PM_{10}	1.15 (0.84, 1.57)	0.90 (0.71, 1.13)	0.84 (0.63, 1.12)	1.11 (0.89, 1.38)
SO_2	1.52 (1.01, 2.28)*	1.02 (0.72, 1.45)	1.17 (0.76, 1.80)	1.11 (0.80, 1.55)
NO_2	1.47 (1.05, 2.05)*	1.07 (0.70, 1.64)	1.02 (0.65, 1.59)	1.46 (1.06, 2.02)*
CO	0.96 (0.65, 1.41)	1.06 (0.81, 1.40)	1.18 (0.83, 1.69)	1.03 (0.78, 1.37)
First year				
$PM_{2.5}$	2.28 (0.98, 5.29)	0.92 (0.67, 1.28)	0.93 (0.57, 1.50)	1.12 (0.77, 1.61)
$PM_{2.5-10}$	1.15 (0.95, 1.39)	1.00 (0.82, 1.22)	0.86 (0.68, 1.09)	1.12 (0.96, 1.31)
PM_{10}	1.29 (0.99, 1.69)	1.12 (0.73, 1.71)	1.08 (0.75, 1.54)	1.28 (0.97, 1.70)
SO_2	1.49 (0.88, 2.54)	0.96 (0.68, 1.37)	0.97 (0.62, 1.51)	1.17 (0.83, 1.64)
NO_2	1.08 (0.87, 1.33)	0.90 (0.71, 1.15)	0.81 (0.62, 1.06)	1.11 (0.92, 1.35)
CO	0.82 (0.64, 1.03)	1.02 (0.87, 1.21)	0.92 (0.74, 1.16)	0.94 (0.79, 1.12)
Past year				
$PM_{2.5}$	1.20 (0.89, 1.64)	1.24 (0.89, 1.73)	1.32 (0.91, 1.91)	1.20 (0.90, 1.59)
$PM_{2.5-10}$	1.03 (0.87, 1.22)	1.13 (0.92, 1.38)	1.00 (0.80, 1.24)	1.13 (0.96, 1.34)
PM_{10}	1.09 (0.87, 1.36)	1.17 (0.91, 1.51)	1.03 (0.78, 1.36)	1.21 (0.98, 1.49)
SO_2	1.06 (0.82, 1.38)	1.24 (0.95, 1.62)	1.16 (0.86, 1.56)	1.15 (0.91, 1.45)
NO_2	1.33 (1.04, 1.70)*	1.12 (0.84, 1.49)	1.06 (0.77, 1.47)	1.35 (1.07, 1.70)*
CO	0.95 (0.82, 1.10)	1.01 (0.86, 1.20)	0.93 (0.78, 1.10)	0.99 (0.86, 1.14)
Entire postnatal				
$PM_{2.5}$	1.04 (0.70, 1.55)	1.02 (0.76, 1.38)	0.96 (0.65, 1.43)	1.07 (0.80, 1.43)
$PM_{2.5-10}$	1.08 (0.87, 1.34)	1.19 (0.91, 1.55)	0.99 (0.75, 1.31)	1.21 (0.99, 1.49)
PM_{10}	1.18 (0.87, 1.60)	1.33 (0.90, 1.97)	1.10 (0.74, 1.61)	1.36 (1.01, 1.84)*
SO_2	1.52 (1.04, 2.21)*	0.98 (0.70, 1.37)	1.14 (0.75, 1.71)	1.15 (0.92, 1.44)
NO_2	1.17 (0.98, 1.39)	0.97 (0.78, 1.19)	0.90 (0.71, 1.14)	1.18 (1.00, 1.38)*
CO	0.98 (0.73, 1.32)	1.01 (0.93, 1.08)	1.13 (0.76, 1.67)	1.00 (0.91, 1.10)

ORs were adjusted for all covariates in Table 1.

* $p<0.05$. ** $p<0.01$.

Table S4 Odds ratio (95% CI) of children's asthma for exposure to outdoor air pollution during intrauterine and post-natal periods stratified by socio economic status (SES) (n=8,689).

	House size (m^2)		Parental annual income		Parental education level	
	<100 (n=2,792)	≥100 (n=5,767)	Low (n=1,405)	High (n=7,284)	Low (n=1,538)	Middle/high (n=7,151)
1st trimester						
$PM_{2.5}$	1.19 (0.77, 1.82)	1.17 (0.85, 1.63)	1.20 (0.66, 2.20)	1.17 (0.87, 1.55)	1.49 (0.77, 2.89)	1.11 (0.84, 1.48)
$PM_{2.5-10}$	1.17 (0.91, 1.49)	0.97 (0.80, 1.17)	1.17 (0.83, 1.64)	1.00 (0.85, 1.19)	0.79 (0.55, 1.15)	1.08 (0.92, 1.27)
PM_{10}	0.88 (0.62, 1.25)	0.99 (0.76, 1.30)	0.85 (0.51, 1.40)	0.96 (0.76, 1.21)	0.84 (0.50, 1.42)	0.96 (0.76, 1.21)
SO_2	1.22 (0.82, 1.80)	1.09 (0.80, 1.49)	1.15 (0.68, 1.95)	1.13 (0.86, 1.49)	1.12 (0.61, 2.05)	1.15 (0.88, 1.50)
NO_2	1.04 (0.65, 1.68)	1.13 (0.79, 1.61)	0.94 (0.48, 1.83)	1.12 (0.82, 1.54)	1.05 (0.50, 2.21)	1.10 (0.81, 1.49)
CO	1.14 (0.81, 1.62)	1.07 (0.81, 1.42)	1.03 (0.62, 1.69)	1.12 (0.88, 1.43)	1.47 (0.94, 2.31)	1.03 (0.80, 1.32)
2nd trimester						
$PM_{2.5}$	1.46 (0.98, 2.17)	1.14 (0.84, 1.56)	1.36 (0.76, 2.43)	1.24 (0.95, 1.62)	1.36 (0.71, 2.60)	1.24 (0.96, 1.62)
$PM_{2.5-10}$	1.08 (0.87, 1.33)	1.22 (1.04, 1.42)*	1.22 (0.89, 1.66)	1.16 (1.01, 1.33)*	1.29 (0.95, 1.75)	1.15 (1.00, 1.32)*
PM_{10}	1.16 (0.81, 1.65)	1.02 (0.78, 1.34)	1.10 (0.66, 1.83)	1.06 (0.84, 1.34)	1.06 (0.60, 1.88)	1.08 (0.85, 1.36)
SO_2	1.03 (0.72, 1.48)	1.24 (0.93, 1.63)	0.81 (0.49, 1.34)	1.26 (0.99, 1.62)	0.86 (0.50, 1.48)	1.23 (0.97, 1.57)
NO_2	1.45 (0.91, 2.29)	1.34 (0.93, 1.92)	1.42 (0.73, 2.78)	1.39 (1.02, 1.91)*	1.13 (0.54, 2.40)	1.43 (1.05, 1.95)*
CO	1.01 (0.82, 1.25)	1.11 (0.84, 1.46)	0.97 (0.57, 1.63)	1.04 (0.92, 1.17)	1.55 (0.86, 2.80)	1.01 (0.86, 1.20)
3rd trimester						
$PM_{2.5}$	0.77 (0.49, 1.22)	1.36 (0.97, 1.92)	0.97 (0.50, 1.91)	1.15 (0.85, 1.55)	0.98 (0.50, 1.89)	1.16 (0.86, 1.56)
$PM_{2.5-10}$	0.92 (0.69, 1.22)	1.18 (0.95, 1.45)	1.08 (0.71, 1.64)	1.08 (0.89, 1.29)	1.00 (0.64, 1.57)	1.09 (0.90, 1.31)
PM_{10}	0.96 (0.70, 1.33)	1.24 (0.95, 1.61)	1.44 (0.87, 2.38)	1.07 (0.85, 1.34)	1.00 (0.60, 1.65)	1.15 (0.92, 1.44)
SO_2	0.88 (0.60, 1.28)	1.06 (0.80, 1.39)	0.85 (0.50, 1.45)	1.03 (0.80, 1.32)	0.72 (0.43, 1.21)	1.07 (0.84, 1.38)
NO_2	0.90 (0.56, 1.45)	1.24 (0.87, 1.77)	0.72 (0.35, 1.50)	1.22 (0.90, 1.66)	0.75 (0.37, 1.53)	1.21 (0.89, 1.66)
CO	1.00 (0.69, 1.45)	1.06 (0.80, 1.40)	0.88 (0.50, 1.55)	1.07 (0.84, 1.37)	0.90 (0.50, 1.59)	1.07 (0.84, 1.37)
Entire pregnancy						
$PM_{2.5}$	1.37 (0.84, 2.23)	1.45 (1.01, 2.08)*	1.51 (0.74, 3.08)	1.41 (1.02, 1.94)*	1.50 (0.74, 3.02)	1.40 (1.02, 1.93)*
$PM_{2.5-10}$	1.34 (0.96, 1.86)	0.99 (0.77, 1.26)	1.01 (0.61, 1.66)	1.13 (0.91, 1.40)	1.00 (0.60, 1.67)	1.12 (0.90, 1.38)
PM_{10}	1.10 (0.83, 1.46)	0.95 (0.77, 1.19)	1.12 (0.73, 1.70)	0.98 (0.81, 1.19)	0.89 (0.59, 1.35)	1.03 (0.85, 1.25)
SO_2	1.04 (0.68, 1.60)	1.17 (0.84, 1.63)	0.86 (0.48, 1.55)	1.20 (0.90, 1.62)	0.76 (0.41, 1.42)	1.24 (0.92, 1.66)
NO_2	1.24 (0.81, 1.91)	1.29 (0.93, 1.80)	1.03 (0.56, 1.92)	1.35 (1.01, 1.80)*	0.84 (0.43, 1.65)	1.38 (1.04, 1.84)*
CO	1.10 (0.77, 1.58)	1.08 (0.82, 1.41)	0.94 (0.55, 1.60)	1.12 (0.89, 1.42)	1.35 (0.88, 2.08)	1.04 (0.82, 1.33)
First year						
$PM_{2.5}$	0.79 (0.49, 1.25)	1.28 (0.88, 1.87)	0.41 (0.19, 0.90)	1.28 (0.93, 1.76)	0.54 (0.26, 1.13)	1.20 (0.87, 1.65)
$PM_{2.5-10}$	0.88 (0.70, 1.12)	1.12 (0.96, 1.30)	0.68 (0.47, 0.98)	1.11 (0.97, 1.27)	0.75 (0.51, 1.10)	1.10 (0.95, 1.28)
PM_{10}	0.97 (0.67, 1.40)	1.39 (1.05, 1.84)*	0.79 (0.47, 1.32)	1.33 (1.04, 1.70)*	0.95 (0.55, 1.67)	1.28 (1.01, 1.63)*
SO_2	1.15 (0.73, 1.80)	1.07 (0.76, 1.49)	0.70 (0.37, 1.34)	1.21 (0.90, 1.62)	0.66 (0.34, 1.27)	1.23 (0.91, 1.66)
NO_2	0.95 (0.74, 1.23)	1.01 (0.83, 1.24)	0.66 (0.44, 0.98)	1.08 (0.91, 1.28)	1.07 (0.71, 1.61)	0.99 (0.83, 1.17)
CO	0.88 (0.69, 1.12)	0.95 (0.80, 1.13)	0.96 (0.69, 1.35)	0.92 (0.79, 1.08)	1.02 (0.72, 1.46)	0.91 (0.78, 1.07)
Past year						
$PM_{2.5}$	0.97 (0.67, 1.39)	1.45 (1.09, 1.93)*	1.23 (0.72, 2.10)	1.26 (0.98, 1.61)	2.80 (1.51, 5.19)***	1.12 (0.88, 1.42)
$PM_{2.5-10}$	1.07 (0.86, 1.33)	1.09 (0.92, 1.28)	1.23 (0.89, 1.71)	1.05 (0.91, 1.22)	1.12 (0.77, 1.63)	1.07 (0.93, 1.23)
PM_{10}	1.19 (0.89, 1.58)	1.11 (0.90, 1.37)	1.51 (1.01, 2.27)*	1.08 (0.90, 1.31)	1.39 (0.87, 2.22)	1.10 (0.92, 1.32)
SO_2	1.17 (0.87, 1.58)	1.15 (0.91, 1.46)	1.63 (1.05, 2.55)*	1.09 (0.89, 1.34)	1.57 (0.95, 2.60)	1.10 (0.90, 1.34)
NO_2	1.01 (0.75, 1.35)	1.44 (1.12, 1.84)**	1.06 (0.67, 1.68)	1.30 (1.05, 1.60)*	1.25 (0.76, 2.04)	1.27 (1.03, 1.56)*
CO	0.92 (0.77, 1.09)	1.00 (0.87, 1.15)	0.89 (0.68, 1.17)	0.98 (0.87, 1.11)	1.16 (0.85, 1.60)	0.95 (0.85, 1.07)
Entire postnatal						
$PM_{2.5}$	0.77 (0.53, 1.12)	1.25 (0.95, 1.65)	0.72 (0.40, 1.30)	1.12 (0.87, 1.44)	0.95 (0.52, 1.73)	1.06 (0.82, 1.36)
$PM_{2.5-10}$	0.87 (0.64, 1.17)	1.30 (1.07, 1.59)**	1.06 (0.70, 1.60)	1.16 (0.96, 1.39)	1.39 (0.87, 2.23)	1.12 (0.93, 1.34)
PM_{10}	0.84 (0.55, 1.27)	1.58 (1.18, 2.11)**	1.07 (0.60, 1.90)	1.33 (1.02, 1.72)*	1.68 (0.90, 3.12)	1.23 (0.95, 1.59)
SO_2	0.95 (0.64, 1.42)	1.24 (1.01, 1.52)*	0.68 (0.38, 1.21)	1.23 (1.02, 1.49)*	0.74 (0.41, 1.34)	1.22 (1.01, 1.48)*
NO_2	0.94 (0.76, 1.17)	1.19 (1.00, 1.41)*	0.76 (0.55, 1.07)	1.16 (1.00, 1.34)*	1.02 (0.72, 1.43)	1.10 (0.95, 1.28)
CO	0.70 (0.48, 1.03)	1.01 (0.97, 1.06)	1.09 (0.64, 1.87)	1.00 (0.93, 1.08)	1.25 (0.71, 2.22)	1.00 (0.93, 1.09)

ORs were adjusted for all covariates in Table 1.

* p<0.05. ** p<0.01. *** p<0.001.

Table S5 Odds ratio (95% CI) of children's asthma for exposure to outdoor air pollution during intrauterine and post-natal periods stratified by living environmental factors (n=8,689).

	Redecoration		Opening windows in four seasons	
	No (n=6,868)	Yes (n=1,812)	No (n=392)	Yes (n=8,297)
1st trimester				
$PM_{2.5}$	1.04 (0.77, 1.40)	1.77 (1.03, 3.05)*	0.55 (0.16, 1.86)	1.25 (0.95, 1.63)
$PM_{2.5-10}$	1.03 (0.87, 1.23)	1.05 (0.77, 1.44)	0.52 (0.23, 1.17)	1.06 (0.91, 1.24)
PM_{10}	0.93 (0.73, 1.18)	1.00 (0.64, 1.54)	0.50 (0.19, 1.34)	0.98 (0.79, 1.22)
SO_2	1.10 (0.83, 1.46)	1.25 (0.78, 2.02)	0.60 (0.18, 2.02)	1.16 (0.91, 1.49)
NO_2	1.06 (0.76, 1.47)	1.23 (0.71, 2.13)	0.78 (0.23, 2.61)	1.11 (0.83, 1.49)
CO	1.11 (0.86, 1.44)	1.05 (0.68, 1.60)	1.53 (0.55, 4.22)	1.11 (0.89, 1.39)
2nd trimester				
$PM_{2.5}$	1.20 (0.91, 1.59)	1.53 (0.91, 2.57)	1.25 (0.52, 3.00)	1.27 (0.98, 1.64)
$PM_{2.5-10}$	1.23 (1.06, 1.42)**	1.02 (0.79, 1.32)	1.03 (0.61, 1.72)	1.18 (1.03, 1.34)*
PM_{10}	1.10 (0.86, 1.41)	1.01 (0.65, 1.55)	0.70 (0.27, 1.81)	1.10 (0.88, 1.37)
SO_2	1.11 (0.86, 1.43)	1.39 (0.88, 2.19)	0.82 (0.30, 2.24)	1.17 (0.93, 1.47)
NO_2	1.31 (0.95, 1.82)	1.97 (1.08, 3.60)*	1.23 (0.37, 4.16)	1.41 (1.05, 1.89)*
CO	0.97 (0.76, 1.23)	1.58 (1.01, 2.47)*	2.14 (0.91, 5.02)	1.02 (0.88, 1.19)
3rd trimester				
$PM_{2.5}$	1.16 (0.85, 1.58)	0.90 (0.51, 1.60)	2.84 (0.79, 10.19)	1.03 (0.78, 1.37)
$PM_{2.5-10}$	1.03 (0.85, 1.25)	1.13 (0.81, 1.59)	0.95 (0.48, 1.89)	1.09 (0.91, 1.29)
PM_{10}	1.07 (0.84, 1.35)	1.24 (0.82, 1.89)	0.85 (0.37, 1.95)	1.16 (0.94, 1.43)
SO_2	0.97 (0.75, 1.25)	1.12 (0.71, 1.77)	2.03 (0.64, 6.43)	0.96 (0.76, 1.21)
NO_2	1.18 (0.86, 1.63)	0.93 (0.50, 1.73)	1.92 (0.56, 6.57)	1.07 (0.80, 1.44)
CO	1.01 (0.78, 1.31)	1.12 (0.70, 1.79)	2.34 (0.95, 5.79)	0.97 (0.76, 1.22)
Entire pregnancy				
$PM_{2.5}$	1.28 (0.92, 1.79)	2.06 (1.10, 3.86)*	1.34 (0.38, 4.80)	1.44 (1.06, 1.94)*
$PM_{2.5-10}$	1.12 (0.89, 1.41)	1.08 (0.73, 1.58)	0.66 (0.29, 1.51)	1.17 (0.95, 1.44)
PM_{10}	1.02 (0.84, 1.24)	0.95 (0.66, 1.37)	0.59 (0.29, 1.21)	1.06 (0.88, 1.27)
SO_2	1.07 (0.79, 1.44)	1.38 (0.81, 2.34)	0.85 (0.23, 3.14)	1.13 (0.86, 1.48)
NO_2	1.26 (0.93, 1.69)	1.54 (0.88, 2.69)	1.24 (0.37, 4.23)	1.28 (0.98, 1.67)
CO	1.02 (0.79, 1.32)	1.31 (0.84, 2.04)	2.60 (1.03, 6.58)*	1.05 (0.84, 1.32)
First year				
$PM_{2.5}$	1.07 (0.77, 1.49)	0.97 (0.53, 1.77)	0.55 (0.14, 2.18)	1.05 (0.78, 1.41)
$PM_{2.5-10}$	1.07 (0.92, 1.24)	0.89 (0.66, 1.20)	0.95 (0.52, 1.74)	1.03 (0.90, 1.18)
PM_{10}	1.21 (0.93, 1.56)	1.18 (0.75, 1.86)	0.67 (0.28, 1.59)	1.26 (1.00, 1.58)*
SO_2	1.04 (0.76, 1.43)	1.28 (0.75, 2.17)	0.13 (0.02, 0.74)*	1.16 (0.88, 1.53)
NO_2	1.00 (0.83, 1.19)	0.99 (0.72, 1.35)	0.73 (0.34, 1.55)	1.00 (0.85, 1.18)
CO	0.95 (0.81, 1.12)	0.88 (0.67, 1.15)	1.52 (0.83, 2.78)	0.90 (0.77, 1.04)
Past year				
$PM_{2.5}$	1.10 (0.85, 1.43)	1.83 (1.14, 2.93)*	1.47 (0.58, 3.77)	1.22 (0.97, 1.54)
$PM_{2.5-10}$	1.13 (0.97, 1.31)	0.94 (0.71, 1.24)	1.61 (0.88, 2.93)	1.05 (0.92, 1.20)
PM_{10}	1.17 (0.97, 1.42)	1.05 (0.73, 1.49)	1.66 (0.82, 3.36)	1.10 (0.92, 1.31)
SO_2	1.22 (0.99, 1.51)	0.96 (0.66, 1.41)	2.02 (0.87, 4.70)	1.12 (0.92, 1.35)
NO_2	1.14 (0.92, 1.41)	1.69 (1.14, 2.49)**	1.20 (0.52, 2.76)	1.24 (1.02, 1.51)*
CO	0.93 (0.82, 1.05)	1.08 (0.86, 1.37)	0.94 (0.57, 1.56)	0.97 (0.87, 1.09)
Entire postnatal				
$PM_{2.5}$	1.03 (0.79, 1.33)	1.04 (0.64, 1.71)	0.82 (0.30, 2.24)	1.03 (0.81, 1.31)
$PM_{2.5-10}$	1.16 (0.96, 1.41)	1.05 (0.73, 1.50)	1.62 (0.77, 3.41)	1.11 (0.93, 1.32)
PM_{10}	1.28 (0.98, 1.68)	1.20 (0.73, 1.96)	1.38 (0.51, 3.69)	1.24 (0.97, 1.59)
SO_2	1.10 (0.87, 1.39)	1.47 (0.88, 2.45)	0.37 (0.11, 1.23)	1.19 (0.98, 1.45)
NO_2	1.05 (0.90, 1.23)	1.14 (0.87, 1.50)	0.80 (0.41, 1.56)	1.09 (0.95, 1.25)
CO	0.99 (0.84, 1.17)	1.43 (0.88, 2.33)	1.07 (0.34, 3.38)	1.00 (0.94, 1.08)

ORs were adjusted for all covariates in Table 1.

* p<0.05. ** p<0.01.

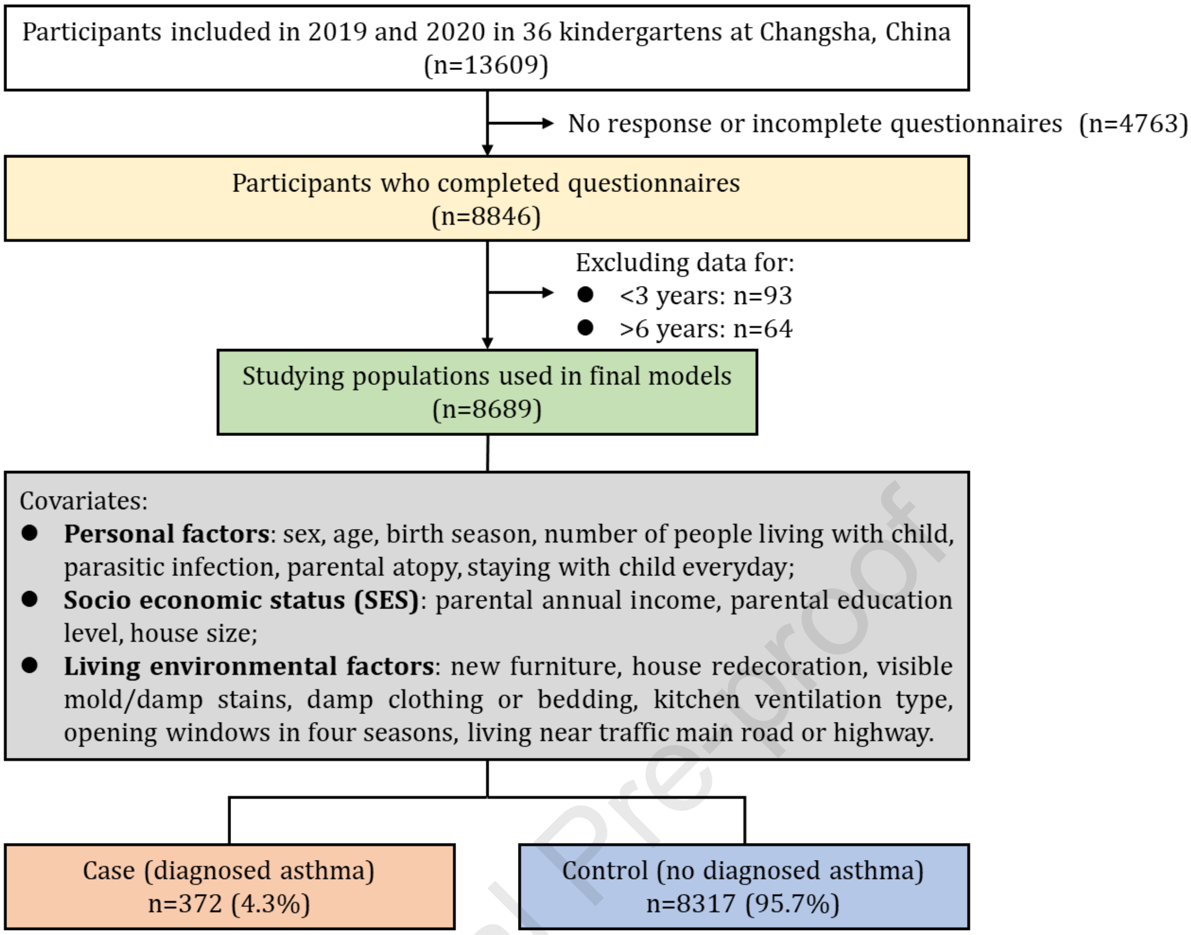


Figure S1. Flow chart of number and proportion as well as prevalence of doctor-diagnosed asthma among studying populations.

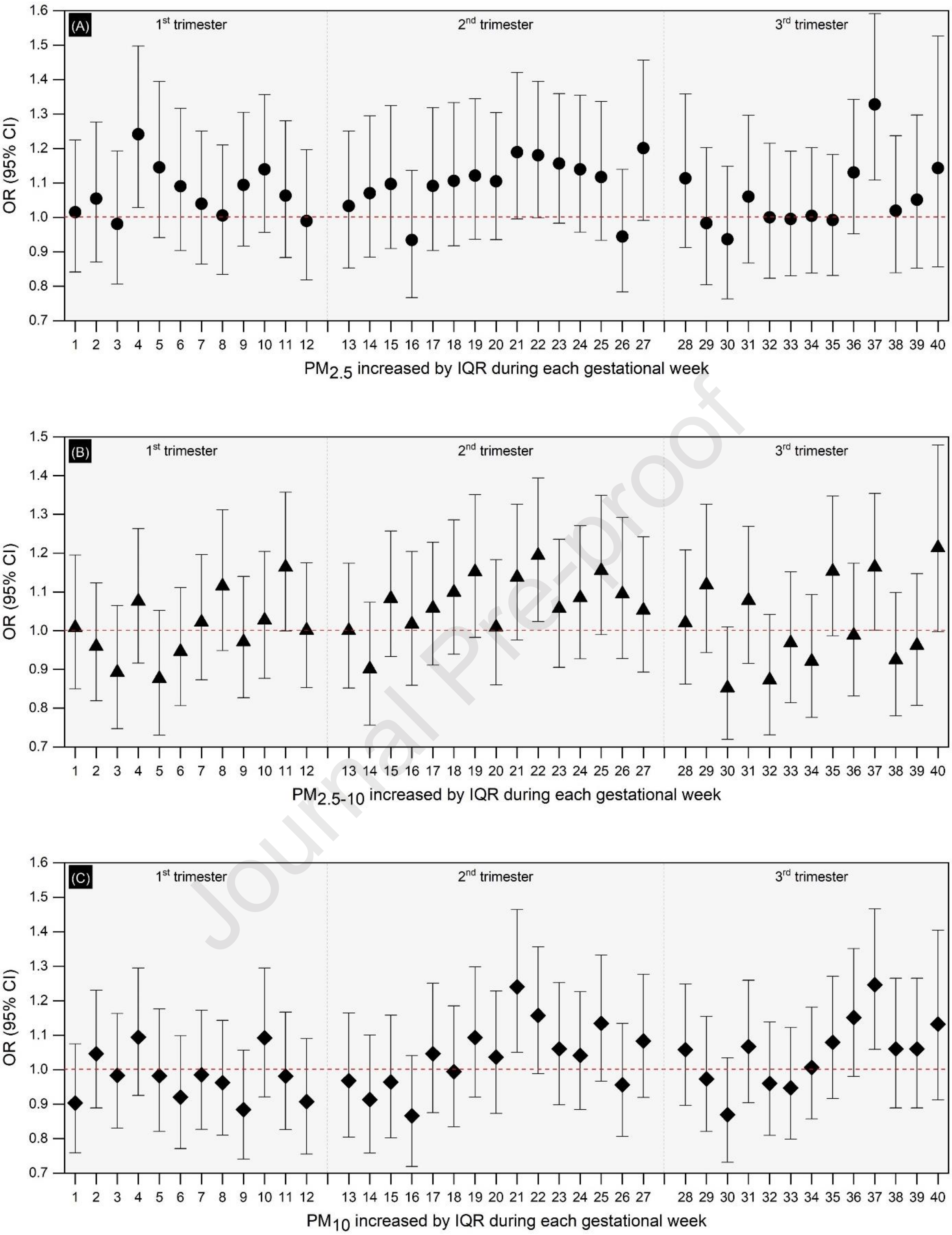


Figure S2. Odds ratio (95% CI) of children's doctor-diagnosed asthma for $PM_{2.5}$ (A), $PM_{2.5-10}$ (B), and PM_{10} (C) exposure in 40 gestational weeks.

Models were adjusted for all covariates in Table 1.

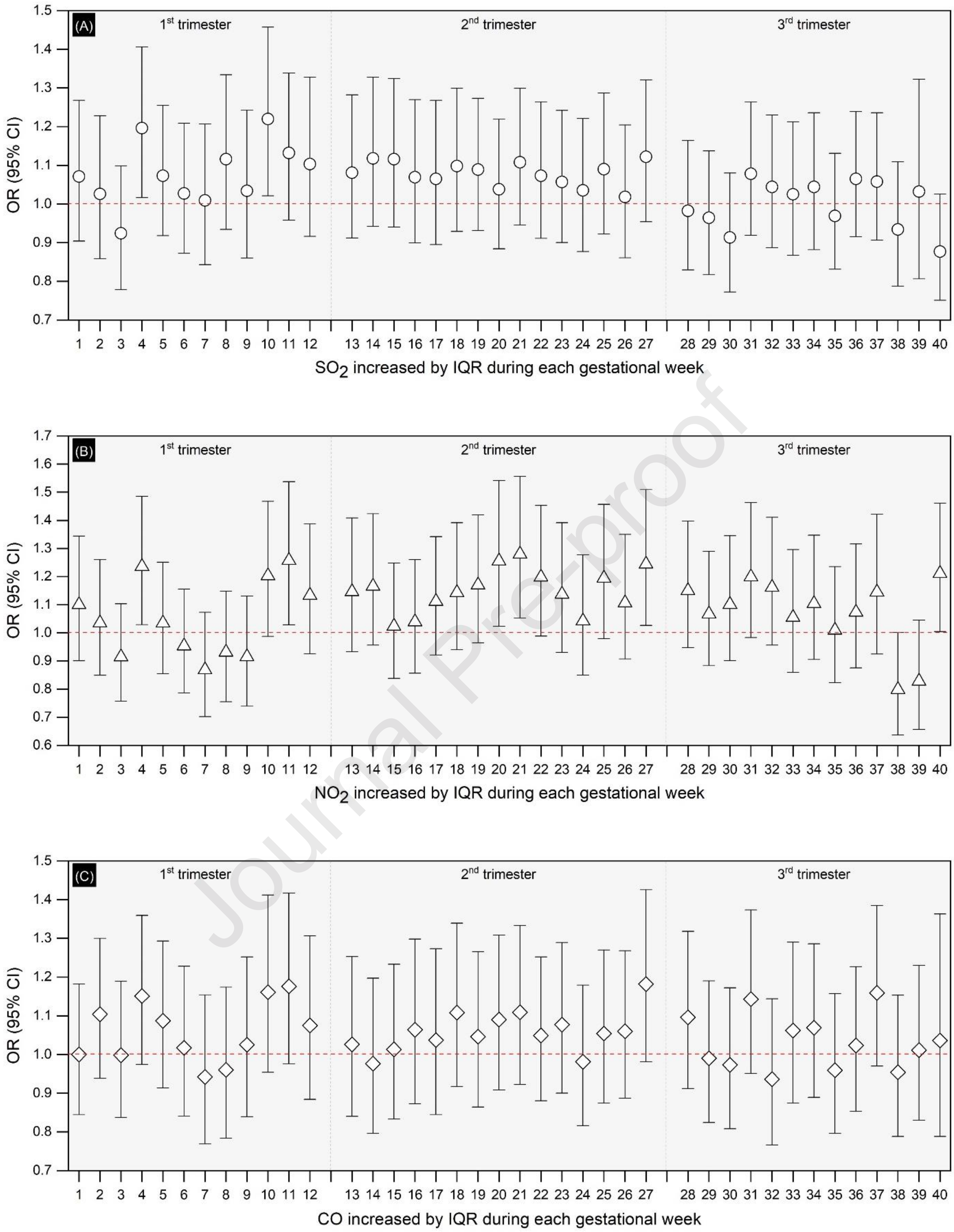


Figure S3. Odds ratio (95% CI) of children's doctor-diagnosed asthma for SO_2 (A), NO_2 (B), and CO (C) exposure in 40 gestational weeks.

Models were adjusted for all covariates in Table 1.

HIGHLIGHTS

- Traffic-related air pollution (TRAP) exposure was related with childhood asthma
- Pregnancy, 2nd trimester, and postnatal period were critical widows for PM exposure
- Daytime and nighttime TRAP exposure played an important role in the risk of asthma
- There were cumulative effects of $PM_{2.5}$ and NO_2 over gestation in relation to asthma
- Our study supports and develops the "fetal origin of childhood asthma" hypothesis

7

Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: