Early-life exposure to PM$_{2.5}$ constituents and childhood asthma and wheezing: Findings from China, Children, Homes, Health study

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- Early life
- Quantile-based g-computation

ABSTRACT

Background: Emerging evidence suggests that early-life (in-utero and first-year since birth) exposure to ambient PM$_{2.5}$ is a risk factor for asthma onset and exacerbation among children, while the hazards caused by PM$_{2.5}$ compositions remain largely unknown.

Objective: To examine potential associations of early-life exposures to PM$_{2.5}$ mass and its major chemical constituents with childhood asthma and wheezing.

Methods: By conducting the Phase II of the China, Children, Homes, Health study, we investigated 30,325 preschool children aged 3–6 years during 2019–2020 in mainland China. Early-life exposure to PM$_{2.5}$ mass and its constituents (i.e., black carbon [BC], organic matter [OM], nitrate, ammonium, sulfate) were calculated based on monthly estimates at a 1 km $\times$ 1 km resolution from satellite-based models. We adopted a novel quantile-based g-computation approach to assess the effect of a mixture of PM$_{2.5}$ constituents on childhood asthma/wheezing.

Results: The average PM$_{2.5}$ concentrations during in-utero and the first year since birth were 64.7 $\pm$ 10.6 and 61.8 $\pm$ 10.5 $\mu g/m^3$, respectively. Early-life exposures to a mixture of major PM$_{2.5}$ constituents were significantly associated with increased risks of asthma and wheezing, while no evident compositions-wheezing associations were found in the first year. Each quintile increases in all five PM$_{2.5}$ components exposures in utero was accordingly associated with an odds ratio of 1.18 [95% confidence interval: 1.07–1.29] for asthma and 1.08 [1.01–1.16] for wheezing. BC, OM and SO$_4^{2-}$ contributed more to risks of asthma and wheezing than the other PM$_{2.5}$ constituents during early life, wherein the effects of BC were only observed during pregnancy. Sex subgroup analyses suggested stronger associations among girls of first-year exposures to PM$_{2.5}$ components with childhood asthma.

Conclusion: Early-life exposures to ambient PM$_{2.5}$, particularly compositions of BC, OM and SO$_4^{2-}$, are associated with an increased risk of childhood asthma.
1. Introduction

Asthma is the most common chronic disease among children and is responsible for great health burden worldwide over past decades (Yan et al. 2020). It was estimated that there were approximately 50 million asthmatic children across the globe in 2015 (Anenberg, 2018), and the high prevalence of pediatric asthma could be possibly triggered by gene-environment interactions (Von Mutius, 2009). Early childhood wheezing is often regarded as a predominant symptom associated with asthma later in life (Martinez 2009). Increasing epidemiological and experimental evidence indicated that early-life (in utero and first year since birth) exposures to ambient air pollution, fine particulate matter (PM$_{2.5}$, particles with aerodynamic diameter ≤ 2.5 μm) in particular, were linked to asthma or/and wheezing in children (Dick et al. 2014; Jung et al. 2019).

To date, most PM-asthma studies generally focused on the effect of PM$_{2.5}$ mass, overlooking that its chemical constituents, especially those derived from combustion, might play an important role in the toxicity (Adams et al. 2015; Khreis et al. 2017). Sporadic evidence has associated childhood exposure to carbonaceous constituents of PM$_{2.5}$ (i.e., black carbon [BC] and organic matter [OM]) with pediatric asthma/wheezing in developed countries (Khreis et al. 2017), such as the USA (Brunst et al. 2015), Canada (Clark et al. 2010) and Germany (Gehring et al. 2015b). To our knowledge, no prior research has examined the effects of early life exposures to other major PM$_{2.5}$ components (e.g., water-soluble inorganic ions), with the exception of a prospective cohort study of 1,130,855 singleton live births occurring in the province of Ontario, Canada during 2006–2014 (Lavigne et al. 2021). In the study, PM$_{2.5}$ concentration during pregnancy was merely averaged at 8.1 ± 1.6 μg/m$^3$. Hence, huge research gaps still exist with regard to the effects of PM$_{2.5}$ compositions in developing countries with high-level particulate air pollution (e.g., China) (Yang, 2018).

In most existing epidemiologic studies, researchers commonly adopted parametric regression approaches (e.g., logistic/Poisson model for cross-sectional design or Cox model for longitudinal cohort), aiming to investigate the effects of individual PM$_{2.5}$ chemical components on children’s respiratory health (Khreis et al. 2017; Zhang et al. 2021). Notably, given the high correlation among PM$_{2.5}$ components (Liang et al. 2016), these standard analytic models may largely fail to disentangle the real health effects of individual PM$_{2.5}$ constituents because of the potential collinearity (Keil et al. 2020). The quantile-based g-computation approach, a novel analytic method that combined the inferential simplicity of weighted quantile sum (WQS) regression and the flexibility of $g$-computation, could accurately estimate a joint effect of the mixture exposures with a less restrictive set of identification conditions (Keil et al. 2020). This new approach also allows a valid inference regarding the contribution of an individual component to the mixture, even in the absence of directional homogeneity (Araki et al. 2020).

Based on the Phase II of China, Children, Homes, Health study during 2019–2020, this study adopted generalized linear mixed-effects models and the quantile-based g-computation approach to investigate associations of childhood asthma and wheezing with early-life exposures to major PM$_{2.5}$ chemical constituents. We also aimed to explore potential effect modification by sex on PM-asthma/wheezing associations.

2. Methods

2.1. Study design and participants

The Phase II of the China, Children, Homes, Health (CCHH) study is a large-scale cross-sectional questionnaire survey conducted between 2019 and 2020 in seven capital cities (i.e., Changsha, Chongqing, Nanjing, Shanghai, Taiyuan, Urumqi and Wuhan) across divergent geographic regions of mainland China (Fig. 1). On the basis of parent-reported data, the CCHH survey is primarily designed to explore the associations of household environments with childhood asthma and rhinitis among Chinese preschool children. The CCHH questionnaire items were mainly designed according to the International Study of Asthma and Allergies (ISAAC) and the study of Dampness in Building and Health (DBH) in Sweden. This standard questionnaire has been validated by the pilot study and the Phase I of CCHH during 2010–2012. Our survey procedure followed methods in the Phase I of CCHH study (Cai et al. 2020; Zhang et al. 2013). In brief, standard questionnaires were distributed to the children’s caregivers (e.g., parents or grandparents) by the responsible teachers in the chosen kindergartens or daycare centers. Our research team gave guidance online and offline to ensure that respondents filled out questionnaires normatively.

This cross-sectional study investigated a total of 37,859 children aged 3–6 years, and we restricted participants by the following procedures. First, we excluded 604 preschoolers with missing information of pregnancy week, as well as 412 outside 28–40 weeks of gestation. Second, we further ruled out 2112 questionnaires with incomplete covariates of interest, e.g., parental atopy, maternal smoking status, etc. Finally, 4406 children were excluded since their in-utero or first-year addresses were out of the surveyed cities. Finally, we totally included 30,325 children in the analysis. The study was approved by the Medical Research Ethics Committee of School of Public Health, Fudan University, Shanghai. The participants and parents gave informed consent.

2.2. Health outcome and covariates

Childhood wheezing and asthma are defined by the following questions: 1) “Has ever had wheezing or whistling symptom from child’s birth to the survey?” and 2) “Has ever had doctor-diagnosed asthma from child’s birth to the survey?”

Following systematic reviews about factors affecting childhood asthma (Hehua et al. 2017; Yan et al. 2020) and previous CCHH publications (Cai et al. 2020; Zhang et al. 2013), we sorted out three sets of covariates in the regression analysis. These covariates included 1) children’s individual characteristics: sex (boy [versus] girl), birth season (spring vs. summer vs. autumn vs. winter), mode of delivery (cesarean vs. vaginal), preterm birth (<37 weeks, yes vs. no), low birth weight (<2500 g, yes vs. no) and ethnicity (Han vs. others); 2) parental variables: parental history of atopy (yes vs. no), duration of breastfeeding (<1 vs. 1–6 vs. 6–12 vs. ≥ 12 months), maternal smoking status (yes vs. no) and education attainment (senior high school or below vs. college vs. graduate school or higher); 3) household environment during early life: passive smoke exposure (yes vs. no), renovation (yes vs. no) and visible mould or damp (yes vs. no).

2.3. Exposure assessment for PM$_{2.5}$ constituents

For each child, monthly exposures of PM$_{2.5}$ and its chemical constituents at the residential address were assigned by the gridded estimates at a 1 km × 1 km spatial resolution from the V4.CH.02 (China Estimates) product, which was available from https://sites.wusl.edu/acag/datasets/surface-pm2-5/ (last accessed: April 22, 2022). The Dalhousie University Atmospheric Composition Analysis Group (DUCAG) developed the V4.CH.02 dataset, of which modelling details could be found in prior publications (Hammer, 2020; van Donkelaar, 2016; Van Donkelaar et al., 2019).

Briefly, aerosol optical depths (AODs) from multiple satellite products were combined and related to near-surface PM$_{2.5}$ concentrations based on geophysical relationships between PM$_{2.5}$ and AOD simulated by the GEOS-Chem chemical transport model (Hammer et al. 2020). The GEOS-Chem model is widely applied by research groups around the world to simulate the three-dimensional spatial and temporal distributions of various aerosol constituents using emission inventories and assimilated meteorology as major inputs (https://geos-chem.seas.harvard.edu/). Concentrations of PM$_{2.5}$ constituents were inferred by applying the simulated relative contribution of each component from GEOS-GEOS-Chem.
These initial estimates of PM$_{2.5}$ and its components (black carbon [BC], organic matter [OM], nitrate [NO$_3$], ammonium [NH$_4$], sulfate [SO$_4$], mineral dust and sea salt) were calibrated and validated with ground-based observations that were estimated by geographically weighted regression. Carbonaceous constituents and water-soluble inorganic ions accounted for over 90% of the total PM$_{2.5}$ mass in most surveyed cities (Fig. 1) and have been linked with respiratory morbidity and mortality outcomes from the insights of population-based evidence (Achilleos et al. 2017; Khreis et al. 2017). Primarily being emitted from natural sources (Tao et al. 2017), mineral dust and sea salt contributed a very small portion of PM$_{2.5}$ mass and had some uncertainty in exposure assessments by DUACAG (Zhao et al. 2021). In alignment with previous studies using the V4.CH.02 dataset (Liu et al. 2022; Shi et al. 2021; Zhao et al. 2020), we thus focused on the effects of main PM$_{2.5}$ components from combustion and did not include mineral dust and sea salt in the analysis.

Our study calculated average concentrations of the following exposure windows for each child: 1) in utero, mean exposure levels from their mothers’ conception to delivery; 2) the first year since birth, average exposure levels during birth to one-year-old. The in-utero period was divided into three pregnancy trimesters (trimester 1, trimester 2 and trimester 3) for stratified analysis.

### 2.4. Statistical analysis

This study adopted the Spearman correlation coefficient to measure the correlation between in-utero and first-year exposures to PM$_{2.5}$ and its constituents. Descriptive statistics for 3–6 years children included in our study were summarized as means (standard deviations [SD]) and counts (proportions), as appropriate. We performed t-tests and Pearson Chi-square tests to compare distributions of covariates between asthma/wheezing cases and children without asthma/wheezing.

We used a generalized linear mixed-effects model (GLMM) to evaluate single-pollutant effects on childhood asthma/wheezing and a quantile-based g-computation (g-comp) approach to assess the joint effect of main constituents and infer relative contributions of each component. All statistical analyses were conducted in R software (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria). Each test was conducted two-sided and the effect with $p < 0.05$ was considered statistically significant. The GLMM method and the g-computation approach were implemented using the R packages “lme4” and “gcomp”, respectively.

#### 2.4.1. Single-pollutant effects based on GLMM method

GLMM incorporated with a random effect for city was utilized to investigate the associations between asthma and wheezing incidence and early-life exposures to PM$_{2.5}$ and its five chemical constituents. We filled four regression models (Model 1–4) to control for possible confounders: 1) Model 1 was the basic model only including a single PM$_{2.5}$
constituent, with cities considered a random effect; 2) Model 2 added children’s individual characteristics to Model 1; 3) Model 3 were adjusted for covariates in Model 2 plus parental variables; 4) we additionally considered household environment during early life in Model 4. In each single-pollutant model, the estimated odds ratio (OR) and its 95% confidence interval (CI) were derived to report the associations of asthma and wheezing risk with per interquartile range (IQR) increase in specific PM$_{2.5}$ constituent. We performed two-sample z-tests between boys and girls to identify potential sex differences in vulnerability. We replaced the linear term of PM$_{2.5}$ constituents in the main analytic model with a natural cubic spline term with 3 degrees of freedom and used likelihood ratio tests to check the linearity of exposure-response curves.

2.4.2. Mixture effects using qg-computation approach

To address potential collinearity induced by high correlations between PM$_{2.5}$ constituents (Fig. S1), we adopted a qg-computation approach to estimate the joint effect of five PM$_{2.5}$ constituents on asthma and wheezing (Araki et al. 2020; Keil et al. 2020). The qg-computation method was developed by combining weighted quantile sum (WQS) regression models and g (generalized)-computation. The WQS regression has been widely applied to estimate joint effects of exposure to a mixture (Carrico et al. 2015; Deyssenroth et al. 2018). It could avoid the effects of potential collinearity exposures with a simple implementation (Keil et al. 2020). This approach starts by transforming a continued exposure ($X$) into a set of categorical variables using quantiles of each exposure as cut points ($X_i$). Here, we have five PM$_{2.5}$ constituents, i.e., $d = 5$. Uniting the weights for each exposure ($w_j$), a mixed-effect index ($S_i$) could be developed by Equation (1).

$$S_i = \sum_{j=1}^{d} w_j X_i^j$$

(1)

$X_i^j$ is the quantized representation of the $j^{th}$ exposure for the $i^{th}$ subject. Our study uses quintiles for constructing the index, then $X_i^j$ will equal 0, 1, 2, 3 or 4 for any child, corresponding to whether the exposure $X_i$ falls into the 0–20th, 20–40th, 40–60th, 60–80th or 80–100th percentile of that exposure. The mixed-effect index for each exposure was then used in a generalized linear model to estimate associations of the mixture exposure with health outcomes. The traditional WQS regression needs to meet a directional homogeneity assumption. When the effect of environmental complex exposures are not in the same direction, g-computation can be used by a generalized linear model to estimate causal effects (Keil et al. 2020). Hence, the qg-computation method can be treated as an extension of WQS, eliminating the restriction of directional homogeneity.

Given no significant violations of the linear pattern identified in dose-response analysis (Fig. S3), we selected linear function for each constituent to structure a mixed-effect index in the qg-computation approach. The overall mixture effect was presented as OR (95% CI) of asthma/wheezing per one quintile change in all exposures of interest. Simultaneously, some components in the mixture were identified as positive direction (association), and others were set in a negative direction (association) to ensure convergence of the qg-computation regression (Keil et al. 2020). The size of index weight of individual component exposure suggests relative contributions of each composition in the same (positive or negative) direction. Each directional weight is defined to sum to 1. In comparison to the GLMM analysis, we also constructed four qg-computation models adjusted for the same variables and performed sex subgroup analyses.

In sensitivity analyses, we first additionally adjusted for mean temperature exposure during early life in each qg-computation model to eliminate the potential confounding effects of weather on childhood

| Table 1 |
| Descriptive statistics of 3–6 years children included in the study. |

<table>
<thead>
<tr>
<th>Characteristics, n (%)</th>
<th>All children</th>
<th>Diagnosed with asthma</th>
<th>Ever had wheezing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>p-value</td>
</tr>
<tr>
<td>Total Child</td>
<td>30325 (100)</td>
<td>1205 (100)</td>
<td>29120 (100)</td>
</tr>
<tr>
<td>Age, year, mean ± SD</td>
<td>5.0 ± 1.0</td>
<td>5.0 ± 0.9</td>
<td>5.0 ± 1.0</td>
</tr>
<tr>
<td>Boys</td>
<td>15779 (52.0)</td>
<td>751 (62.3)</td>
<td>15028 (51.6)</td>
</tr>
<tr>
<td>Birth season</td>
<td>0.728</td>
<td>0.197</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>7673 (25.3)</td>
<td>296 (24.6)</td>
<td>7377 (25.3)</td>
</tr>
<tr>
<td>Summer</td>
<td>8492 (28.0)</td>
<td>327 (27.1)</td>
<td>8165 (28.0)</td>
</tr>
<tr>
<td>Autumn</td>
<td>6837 (22.6)</td>
<td>280 (23.2)</td>
<td>6557 (22.5)</td>
</tr>
<tr>
<td>Winter</td>
<td>7323 (24.1)</td>
<td>302 (25.1)</td>
<td>7021 (24.1)</td>
</tr>
<tr>
<td>Natural birth</td>
<td>15464 (51.0)</td>
<td>603 (50.0)</td>
<td>14861 (51.0)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1564 (5.2)</td>
<td>72 (6.0)</td>
<td>1472 (5.1)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1066 (3.5)</td>
<td>49 (4.1)</td>
<td>1017 (3.5)</td>
</tr>
<tr>
<td>Han ethnicity</td>
<td>28691 (94.6)</td>
<td>1147 (95.2)</td>
<td>27544 (94.6)</td>
</tr>
<tr>
<td>Parental</td>
<td>811 (27.7)</td>
<td>148 (12.3)</td>
<td>663 (2.3)</td>
</tr>
<tr>
<td>Parental atopy</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding (month)</td>
<td>200 (16.6)</td>
<td>4064 (13.9)</td>
<td>442 (17.0)</td>
</tr>
<tr>
<td>1–6</td>
<td>7116 (23.5)</td>
<td>345 (28.6)</td>
<td>6771 (23.3)</td>
</tr>
<tr>
<td>6–12</td>
<td>9891 (32.6)</td>
<td>366 (30.4)</td>
<td>9525 (32.7)</td>
</tr>
<tr>
<td>≥12</td>
<td>9072 (29.9)</td>
<td>294 (24.4)</td>
<td>8778 (30.1)</td>
</tr>
<tr>
<td>Maternal smoking a</td>
<td>595 (2.3)</td>
<td>45 (4.0)</td>
<td>550 (2.2)</td>
</tr>
<tr>
<td>Maternal education</td>
<td>0.006</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Senior high school or below</td>
<td>7455 (24.6)</td>
<td>253 (21.0)</td>
<td>7202 (24.7)</td>
</tr>
<tr>
<td>College</td>
<td>19749 (65.1)</td>
<td>810 (67.2)</td>
<td>18939 (65.0)</td>
</tr>
<tr>
<td>Graduate School or higher</td>
<td>3121 (10.3)</td>
<td>142 (11.8)</td>
<td>2979 (10.2)</td>
</tr>
<tr>
<td>Household environment during early life</td>
<td>30325 (100)</td>
<td>1205 (100)</td>
<td>29120 (100)</td>
</tr>
<tr>
<td>Passive smoke exposure a</td>
<td>7769 (29.4)</td>
<td>391 (34.9)</td>
<td>7318 (29.2)</td>
</tr>
<tr>
<td>Renovation b</td>
<td>5729 (23.6)</td>
<td>276 (27.5)</td>
<td>543 (23.5)</td>
</tr>
<tr>
<td>Visible mould or damp b</td>
<td>4576 (18.9)</td>
<td>286 (28.5)</td>
<td>4290 (18.5)</td>
</tr>
</tbody>
</table>

Notes:

a The variable information was not collected in Urumqi (n = 4138), whereas 83 asthma and 248 wheezing cases were included.

b The variable information was not collected in Urumqi (n = 4138) and Chongqing (n = 1926), whereas a total of 263 asthma and 454 wheezing cases were included. SD, standard deviation.
asthma/wheezing. Specifically, daily mean temperatures at a 10 km x 10 km spatial resolution during the study period were extracted from the atmospheric reanalysis dataset developed by the European Center for Medium-Range Weather Forecasts (https://cds.climate.copernicus.eu) and assigned to each mother according to their residential addresses (Zhang et al. 2021). Second, we restricted the analyses to Han-ethnicity and full-term (gestational age ≥ 37 weeks) children only. To explore the influence of preterm birth and low birth weight, we also compared associations between models with and without adjustment for them. Finally, our study performed stratified analyses by city to assess the heterogeneity of associations between cities. The effect differences between main and sensitivity analyses were examined through the z-tests.

3. Results

Table 1 summarizes the characteristics of all children and shows the prevalence of asthma/wheezing stratified by covariates. Included children aged 5.0 ± 1.0 years (mean ± SD). A total of 1205 (4.0%) children reported diagnosed asthma, and 2596 (8.6%) reported wheezing symptoms from child’s birth to the survey. Boys accounted for around half for all children but over 60% of asthma/wheezing cases. Significantly higher prevalence of asthma/wheezing were observed among children born prematurely and breastfed for < 6 months, as well as subjects whose parents suffered from atopy and mother had a higher-level education. Preschool children who lived in an environment with maternal smoke and early-life exposures to second-hand smoke, renoxivation work and visible dampness had more asthma and wheezing symptoms.

Table 2 shows the average PM$_{2.5}$ concentrations over all cities during in utero and the first year since birth. Carbonaceous constituents and water-soluble inorganic ions were positively correlated during pregnancy and first year of life (Fig. S1).

Table 3 lists the joint effect of in-utero and first-year mixture exposures on childhood asthma and wheezing, and four qq-computation models produced approximate risk estimates. During pregnancy, each quintile increases in exposure to all five PM$_{2.5}$ compositions was accordingly associated with an OR of 1.18 (1.07–1.29) for asthma and 1.08 (1.01–1.16) for wheezing in Model 3. Positive index weighted for BC, OM and SO$_{4}^{2-}$ during early life (Table 4), meaning these constituents were positively linked to asthma/wheezing incidence, wherein the harmful effects of BC were only observed during in utero. For instance, BC (index weight: 0.16), OM (0.48) and SO$_{4}^{2-}$ (0.36) exposures during pregnancy were positive associations with childhood asthma, while NO$_{3}$ (-0.10) and NH$_{4}^{+}$ (-0.90) were negatively weighted. Detailed index weights of PM$_{2.5}$ constituent exposures during trimester-specific periods were presented in Table S2.

![Fig. 3](image-url) illustrates single-pollutant ORs [95% CI] of childhood asthma stratified by sex, associated with per IQR increase of in-utero and first-year exposures to PM$_{2.5}$ constituents. We observed significantly higher risks of asthma associated with postnatal components exposures among girls (all p values for sex interaction < 0.05), while there is no evident sex difference during pregnancy. In terms of wheezing, we observed comparable in-utero and first-year associations between boys and girls (Fig. S5). Similar effect modification by sex was revealed in the joint analysis based on a qq-computation method (Table 5). Stronger associations with asthma were identified among girls in the first year only, with a mixture OR of 1.21 [1.06–1.39] for girls and 0.99 [0.90–1.10] for boys.

4. Discussion

To the best of our knowledge, this is the first population-based study to assess associations of childhood asthma/wheezing with early-life exposures to PM$_{2.5}$ constituents in China. Based on the China, Children, Homes, Health study, we observed that BC, OM and SO$_{4}^{2-}$ contributed more to asthma/wheezing risk than the other PM$_{2.5}$ constituents in early life, wherein BC effects were only observed during pregnancy. Sex analyses revealed that estimated effects were more significant for girls than for boys in the first year only. Our findings may have important implications in formulating intervention measures for specific partuculate matter components, so as to more effectively reduce asthma/wheezing risk caused by PM$_{2.5}$ air pollution.

A recent meta-analysis found that in developing countries, prenatal exposure to PM$_{2.5}$ mass significantly elevated the risk of childhood asthma and wheezing (OR = 1.19, 95% CI: 1.06–1.38, per 15-µg/m$^3$ increase) (Yan et al. 2020). Our multi-city study in China observed generally similar estimates (OR = 1.20, 95% CI: 1.05–1.37, per IQR, 14.6 µg/m$^3$, increase). Several systematic reviews have provided evidence that total PM$_{2.5}$ exposures in early life were associated with childhood asthma onset and exacerbation (Dick et al. 2014; Hehua et al.).

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Table 2

Summary distributions of in-utero and first-year exposures to ambient air pollutants among children included in the study.

<table>
<thead>
<tr>
<th>Variables, µg/m$^3$</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>Percentiles</th>
<th>Max</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P$_{25}$</td>
<td>P$_{50}$</td>
<td>P$_{75}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-utero</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>64.7 ± 10.6</td>
<td>24.0</td>
<td>56.1 65.8</td>
<td>72.7 99.8</td>
<td>16.6</td>
</tr>
<tr>
<td>BC</td>
<td>4.1 ± 0.8</td>
<td>1.0</td>
<td>3.5 4.1</td>
<td>4.6 6.9</td>
<td>1.1</td>
</tr>
<tr>
<td>OM</td>
<td>10.9 ± 4.6</td>
<td>0.6</td>
<td>7.8 11.5</td>
<td>14.9 22.8</td>
<td>7.1</td>
</tr>
<tr>
<td>NO$_{3}$</td>
<td>15.8 ± 4.0</td>
<td>2.2</td>
<td>12.5 16.0</td>
<td>18.8 30.2</td>
<td>6.2</td>
</tr>
<tr>
<td>NH$_{4}^{+}$</td>
<td>10.4 ± 1.9</td>
<td>3.8</td>
<td>8.4 9.4</td>
<td>11.3 15.0</td>
<td>2.9</td>
</tr>
<tr>
<td>SO$_{4}^{2-}$</td>
<td>15.8 ± 2.6</td>
<td>6.2</td>
<td>14.3 16.0</td>
<td>17.2 23.2</td>
<td>2.9</td>
</tr>
<tr>
<td>First-year</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PM$_{2.5}$</td>
<td>61.8 ± 10.5</td>
<td>25.5</td>
<td>54.2 60.8</td>
<td>70.5 93.0</td>
<td>16.3</td>
</tr>
<tr>
<td>BC</td>
<td>3.8 ± 0.8</td>
<td>1.2</td>
<td>3.2 3.8</td>
<td>4.5 6.4</td>
<td>1.3</td>
</tr>
<tr>
<td>OM</td>
<td>10.4 ± 4.1</td>
<td>1.0</td>
<td>7.4 11.1</td>
<td>13.4 19.1</td>
<td>6.0</td>
</tr>
<tr>
<td>NO$_{3}$</td>
<td>14.8 ± 3.6</td>
<td>4.0</td>
<td>12.3 14.6</td>
<td>17.6 26.7</td>
<td>5.3</td>
</tr>
<tr>
<td>NH$_{4}^{+}$</td>
<td>9.7 ± 1.9</td>
<td>6.8</td>
<td>12.4 15.4</td>
<td>16.8 21.7</td>
<td>2.9</td>
</tr>
<tr>
<td>SO$_{4}^{2-}$</td>
<td>14.7 ± 2.7</td>
<td>6.8</td>
<td>12.4 15.4</td>
<td>16.8 21.7</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation, IQR, interquartile range; PM$_{2.5}$, fine particulate matter; BC, black carbon; OM, organic matter; NO$_{3}$, nitrate; NH$_{4}^{+}$, ammonium; SO$_{4}^{2-}$, sulfate.
remain largely unknown. During the gestational period, PM life effect of particulate matter on childhood asthma development still (Yan et al. 2020). To date, the biological mechanisms of the early—life effect of particulate matter on childhood asthma development still are largely unknown. During the gestational period, PM might penetrate the alveoli and the placental barrier and act directly on the fetus (Korten et al. 2017). It also could trigger systemic inflammation in pregnant mother and decreases supply of fetal nutrients/oxygen, which indirectly influences fetal lung function (Jung et al. 2019; Korten et al. 2017). After birth, plausibly mechanisms included inducing oxidative stress and damage, remodeling airway wall, triggering inflammatory pathways and immunological effects, enhancing respiratory sensitization to allergens, etc. (Gowers et al. 2012; Lopes et al. 2018).

Health effects of ambient PM not only depend on total mass but also on its chemical components (Adams et al. 2015; Liang et al. 2016), while reported influence of individual particulate matter constituents are largely inconsistent (Rohr et al. 2012). PM is composed of various chemical substances, of which water-soluble inorganic ions (e.g., SO, NO, NH4+), nitrate; NH4, ammonium; SO2, sulfate.

Notes: \( p < 0.05, ** p < 0.01, *** p < 0.001. \)

Bold font face indicates a positive index weight. Abbreviations: qg-computation, quantile-based g-computation; OR, odds ratio; CI, confidence interval; PM, fine particulate matter; BC, black carbon; OM, organic matter; NO\(_2\), nitrate; NH\(_4\), ammonium; SO\(_2\).
OM, BC, NH, CI, confidence interval. Bold font face indicates a positive index weight. Abbreviations: OR, odds ratio; constituents. * p < 0.05, ** p < 0.01, *** p < 0.001. Bold font face indicates a positive index weight. Abbreviations: OR, odds ratio; CI, confidence interval.

Limited research studies have assessed the linkage of exposure to PM$_{2.5}$ constituents with asthma and wheezing (Lavigne et al. 2021; Ostro et al. 2009). In a population-based nested case-control study, Clark and colleagues found significant effects of prenatal and postnatal exposures to BC on asthma development, using land-use regression (LUR) for exposure assessment in southwestern British Columbia (Clark et al. 2010). Among children from birth to age 10 years in the greater Vancouver metropolitan region, another survey did not show elevated asthma risk associated with perinatal BC exposure, adopting the same study design and exposure assessment of LUR (Sibili et al. 2016). Considering spatiotemporal variations in the proportions of major PM$_{2.5}$ constituents, the component-adjusted model estimated positive coefficients related to childhood asthma onset for childhood exposures to OM, BC, NH$_4^+$ and NO$_3^-$ whereas negative coefficients for SO$_4^{2-}$ during 2006–2014 in the province of Ontario, Canada (Lavigne et al. 2021). Our study observed the largest positive weight index for SO$_4^{2-}$, BC and OM followed. Different effects of PM$_{2.5}$ components could be in part attributed to between-study differences, including PM$_{2.5}$ mass concentration (e.g., mean PM$_{2.5}$ concentration of 63.1 ± 9.2 μg/m$^3$ in China vs. 7.9 ± 1.5 μg/m$^3$ in Canada), socioeconomic levels, exposure periods as well as analytical methods and confounding control. More population-based and laboratory explorations are urgently warranted to better understand interactions between individual PM$_{2.5}$ chemical compositions and their adverse health effects.

This study found that adverse effects of ambient PM$_{2.5}$ on childhood asthma existed in pregnancy and the first year of birth, which was coherent with the Kaiser Air Pollution and Pediatric Asthma study including the 24,608 children from diverse races (Pennington et al. 2018). In terms of wheezing incidence, we identified gestational exposure to PM$_{2.5}$ constituents were related to it with either GLMM or qg-computation approach, while no evident PM-wheezing associations were observed in the first year. There is biological plausibility for the fetal period as an essential exposure window since it was a critical period of lung function development (Kajekar 2007; Schittny 2017). Developmental stages of the lungs include the embryonic (gestational weeks, 4–7), pseudoglandular (7–17), canalicular (17–26), saccular (27–36), and alveolar (after 36 gestational weeks and until adolescence) stages (Jung et al. 2019). Most vital tissues of the lung are fully developed in utero, such as forming all of the future airways mainly during the pseudoglandular stage (Kajekar 2007). A few epidemiological investigations subdivided pregnancy into specific trimesters (Lee et al. 2018) or sensitive weeks (Hu et al. 2015; Jung et al. 2019) to identify sensitivity windows for particulates’ effects. A Singapore birth cohort study in 953 children aged 2 years (Soh et al. 2018) showed PM$_{2.5}$ exposures in the first and third trimesters were associated with increased episodes of wheezing. However, Lavigne et al. conducted two large cohort studies in Canada (Lavigne et al. 2018) and Toronto (Lavigne et al. 2019), and both only identified an association between childhood asthma development (up to age 6) and the second-trimester exposure to PM$_{2.5}$. In line with a cross-sectional investigation of 2598 preschool children aged 3–6 years from part of the CCHH-I study (Deng et al. 2016), our whole CCHH-II results also did not capture the vulnerable trimester for childhood asthma development associated with particulate matter pollution. More large-scale research using daily/hourly exposure concentrations or considering the precise scope of activity and confounding influence requires further conducted to identify the sensitivity windows of early life.

In prenatal and postnatal exposure windows, differential effects of particulate air pollution on childhood asthma/wheezing among boys and girls may due to sex differences in lung development physiology and hormonal factors (De Marco et al. 2000). Because of delayed lung maturation in boys (Gortner et al. 2013), more investigations for

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**Table 5**

The joint effect of mixture exposures on childhood asthma and wheezing stratified by sex from quantile-based q-computation models.

<table>
<thead>
<tr>
<th></th>
<th>In-utero</th>
<th></th>
<th></th>
<th>First-year</th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Boy</td>
<td>Girl</td>
<td>Boy</td>
<td>Girl</td>
<td>Boy</td>
<td>Girl</td>
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<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mixture OR</td>
<td>1.20</td>
<td>1.16</td>
<td>0.99</td>
<td>1.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[1.08-1.33]</td>
<td>[1.02-1.33]</td>
<td>[0.90-1.10]</td>
<td>[1.06-1.39]</td>
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</tr>
<tr>
<td>P for interaction</td>
<td>0.694</td>
<td></td>
<td></td>
<td>0.020</td>
<td></td>
<td></td>
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<tr>
<td><strong>Wheezing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixture OR</td>
<td>1.12</td>
<td>1.08</td>
<td>0.99</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[1.04-1.21]</td>
<td>[0.98-1.18]</td>
<td>[0.93-1.07]</td>
<td>[0.95-1.13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.552</td>
<td></td>
<td></td>
<td>0.302</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: The models were adjusted for random effects of city, sex, birth season, mode of delivery, preterm birth, low birth weight, ethnicity, duration of breastfeeding, parental atopy, maternal smoking status, and education attainment. * Risk effects associated with one quintile increase in exposures to five constituents. ** p < 0.05, *** p < 0.01, **** p < 0.001. Bold font face indicates a positive index weight. Abbreviations: OR, odds ratio; CI, confidence interval.
pregnancy suggested boys are more susceptible to particle exposures effect on asthma risks (Lavigne et al. 2019; Lee et al. 2018; Zhang et al. 2021). A case of point is that Hsu and colleagues found that the associations in urban children were significantly stronger in boys from 14 to 20 weeks gestation (Hsu et al. 2015). Objectively measured surveys have found negative associations between lung function and exposures to outdoor air pollution during early years since birth, especially for girls (Oftedal et al. 2008). In this study, we observed that boys’ risks of asthma with in-utero exposures to PM2.5 constituents were elevated but no significant difference with girls, whereas significantly higher post-natal risks were among girls. The same findings of sex differences during pregnancy and first year since birth were shown in a cross-sectional study of 2490 children aged 3–6 years occurring in Changsha, China between 2011 and 2012 (Deng et al. 2015). Nevertheless, whether in-utero or first-year exposure to particles pollutions, effect sizes for boys were consistently larger than for girls reported in the City of Toronto, Canada (Lavigne et al. 2019). The totally converse sex trend was found in southwestern British Columbia (Clark et al. 2010), although sex differences in these two studies were not significant. Inconsistent sex findings in different regions may cause by the differences in age of studied population, pollution levels, study design as well as methods of exposure assessment. We call for more laboratory explorations for sex differences stratified by age to reveal possible biological mechanisms.

Several limitations should also be acknowledged. First, the health outcomes and covariates in our study were self-reported rather than measured values, thus recall and parents-reported bias may exist in this cross-sectional investigation. However, modified from the ISAAC and the DBH, our standard questionnaire had been confirmed by the pilot survey in 2010 and widely applied in previous CCHH-I studies. Second, our analyses failed to account for the contributing effects of gaseous pollutants (e.g., ozone) and crustal constituents (e.g., Ca, Al, Si, K), as well as the potential confounding influence of pregnancy-related characteristics (e.g., fetal parity, gravidity and maternity diseases). Nevertheless, four models in our study adjusted for different variables produced approximative risk estimates, which indicated our results were not largely affected by a single covariate. Third, the estimates from the V4.CH.02 (China Estimates) product are not verified by real values due to a lack of regular monitoring data of PM2.5 constitutes in China. Given the professionalism and effectiveness of the predicted method and the extensive verification around other countries (Hammer et al. 2020; van Donkelaar et al. 2016), this product can be used to assess health effects to some extent. Forth, in alignment with previous epidemiological studies (Hvidtfeldt, 2019; Zheng, 2021), we used the 1 km × 1 km resolution of PM2.5 constituents for analysis, which may fail to sufficiently capture small-scale variations in traffic-related pollutants such as BC. A relatively coarse resolution could hamper the accuracy of exposure assessments, our analysis might thus have underestimated the health effects of some components (Meng, 2018). Finally, because the children from our study lived concentratedly in urban regions (about 80%) and suffered from high levels of fine particulate matter (mean of 63.1 μg/m³, minimum of 27.9 μg/m³), our multi-center findings should be carefully generalized to other rural populations and low-polluted countries.

5. Conclusion

In conclusion, this multi-center study provides brand-new evidence on childhood asthma development associated with early-life exposures to specific PM2.5 constituents from fossil combustion, SO2, BC and OM in particular. Stronger PM-asthma associations were among girls in the first year since birth. Identifying harmful chemical components of PM2.5 and a more susceptible population could help policymakers to prioritize the treatment of air pollution and conduct more effective and targeted measures of preventing asthma onset and exacerbation.

CRediT authorship contribution statement

Yuanyuan Zhang: Conceptualization, Methodology, Software, Visualization, Data curation, Writing – original draft, Writing – review & editing. Zhourui Yin: Software, Visualization, Writing – review & editing. Peixuan Zhou: Software, Visualization, Data curation, Writing – review & editing. Liansheng Zhang: Writing – review & editing, Supervision. Zhuohui Zhao: Conceptualization, Investigation, Data curation. Dan Norback: Conceptualization, Investigation, Data curation. Xin Zhang: Investigation, Data curation. Chan Lu: Investigation, Data curation. Wei Yu: Investigation, Data curation. Tingting Wang: Investigation, Data curation. Xiaohong Zheng: Investigation, Data curation. Ling Zhang: Investigation, Data curation, Writing – review & editing, Supervision, Funding acquisition. Yunqian Zhang: Conceptualization, Methodology, Software, Visualization, Data curation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107297.

References

Cai, J., et al., 2020. Damp indicators in different areas of residence in different periods are strongly associated with childhood asthma and wheeze. Build. Environ. 182, 107131.
Deyssenroth, M.A., et al., 2018. Intratracheal multi-metal exposure is associated with reduced fetal growth through modulation of the placental gene network. Environ. Int. 120, 373–381.


Lopes, T.D.M., et al., 2018. Pre- and postnatal exposure of mice to concentrated urban PM2.5 decreases the number of alveoli and leads to altered lung function at an early stage of life. Environ. Pollut. 241, 511–520.


