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Intrauterine and early postnatal exposures to submicron particulate matter and childhood allergic rhinitis: A multicity cross-sectional study in China

Yachen Li [a], Lifeng Zhu [a], Jing Wei [b], Chuansha Wu [c], Zhuohui Zhao [d], Dan Norbäck [e], Xin Zhang [f], Chan Lu [g], Wei Yu [h], Tingting Wang [i], Xiaohong Zheng [j], Ling Zhang [c,**], Yunquan Zhang [a,*]

[a] Institute of Social Development and Health Management, Hubei Province Key Laboratory of Occupational Hazard Identification and Control, School of Public Health, Wuhan University of Science and Technology, Wuhan 430065, China
[b] Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, MD 20740, USA
[c] Department of Environmental Hygiene and Occupational Medicine, School of Public Health, Wuhan University of Science and Technology, Wuhan 430065, China
[d] Department of Environmental Health, School of Public Health, Fudan University, Shanghai 200030, China
[e] Department of Medical Sciences, Uppsala University, Uppsala SE 75185, Sweden
[f] Research Centre for Environmental Science and Engineering, Shanxi University, Taiyuan 030006, China
[g] Department of Occupational and Environmental Health, School of Public Health, Xiangya Medical College, Central South University, Changsha 410078, China
[h] Joint International Research Laboratory of Green Buildings and Built Environments (Ministry of Education), Chongqing University, Chongqing 400045, China
[i] School of Nursing and Health Management, Shanghai University of Medicine and Health Sciences, Shanghai 201318, China
[j] School of Energy and Environment, Southeast University, Nanjing 210096, China

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ABSTRACT

Background: Airborne particulate matter pollution has been linked to occurrence of childhood allergic rhinitis (AR). However, the relationships between exposure to particulate matter with an aerodynamic diameter ≤1 μm (PM_1) during early life (in utero and first year of life) and the onset of childhood AR remain largely unknown. This study aims to investigate potential associations of in utero and first-year exposures to size-segregated PMs, including PM_1, $PM_{1-2.5}$, $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10}, with childhood AR.

Methods: We investigated 29286 preschool children aged 3–6 years in 7 Chinese major cities during 2019–2020 as the Phase II of the China Children, Families, Health Study. Machine learning-based space-time models were utilized to estimate early-life residential exposure to PM_1, $PM_{2.5}$, and PM_{10} at 1 × 1-km resolutions. The concentrations of $PM_{1-2.5}$ and $PM_{2.5-10}$ were calculated by subtracting PM_1 from $PM_{2.5}$ and $PM_{2.5}$ from PM_{10}, respectively. Multiple mixed-effects logistic models were used to assess the odds ratios (ORs) and 95% confidence intervals (CIs) of childhood AR associated with per 10-μg/m^3 increase in exposure to particulate air pollution during in utero period and the first year of life.

Results: Among the 29286 children surveyed (mean ± standard deviation, 4.9 ± 0.9 years), 3652 (12.5%) were reported to be diagnosed with AR. Average PM_1 concentrations during in utero period and the first year since birth were 36.3 ± 8.6 μg/m^3 and 33.1 ± 6.9 μg/m^3, respectively. Exposure to PM_1 and $PM_{2.5}$ during pregnancy and the first year of life was associated with an increased risk of AR in children, and the OR estimates were higher for each 10-μg/m^3 increase in PM_1 than for $PM_{2.5}$ (e.g., 1.132 [95% CI: 1.022–1.254] *vs.* 1.079 [95% CI: 1.014–1.149] in pregnancy; 1.151 [95% CI: 1.014–1.306] *vs.* 1.095 [95% CI: 1.008–1.189] in the first year of life). No associations were observed between AR and both pre- and post-natal exposure to $PM_{1-2.5}$, indicating that PM_1 rather than $PM_{1-2.5}$ contributed to the association between $PM_{2.5}$ and childhood AR. In trimester-stratified analysis, childhood AR was only found to be associated with exposure to PM_1 (OR = 1.077, 95% CI: 1.027–1.128), $PM_{2.5}$ (OR = 1.048, 95% CI: 1.018–1.078), and PM_{10} (OR = 1.032, 95% CI: 1.007–1.058) during the third trimester of pregnancy. Subgroup analysis suggested stronger PM-AR associations among younger (<5 years old) and winter-born children.

* Corresponding author. School of Public Health, Wuhan University of Science and Technology, #2 Huangjiahu West Road, Qingling Street, Hongshan District, Wuhan 430065, China.
** Corresponding author.
E-mail addresses: zhangling@wust.edu.cn (L. Zhang), YunquanZhang@wust.edu.cn (Y. Zhang).

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Conclusions: Prenatal and postnatal exposures to ambient PM_1 and $PM_{2.5}$ were associated with an increased risk of childhood AR, and $PM_{2.5}$-related hazards could be predominantly attributed to PM_1. These findings highlighted public health significance of formulating air quality guideline for ambient PM_1 in mitigating children's AR burden caused by particulate air pollution.

1. Introduction

As one of the most common chronic respiratory allergies, allergic rhinitis (AR) has been recognized as a global health threat that is affecting up to 40% of children, severely impairing life-course quality of life and posing considerable healthcare burden (Bousquet et al., 2020). The incidence of childhood AR has been gradually increasing in developed countries during recent decades (Genuneit et al., 2017), and this trend was mirrored in developing nations such as China due to exacerbated air pollution along with rapid economic growth (Soriano et al., 2020; Zhang and Zhang, 2019). Genetic vulnerability and ambient risks, e.g., particulate air pollution (PAP), may jointly trigger the occurrence and development of childhood AR, while evolution of genetic variation cannot fully explain the dramatic rise of AR cases in children in past decades (Greiner et al., 2011). Large bodies of population-based investigations suggested strong evidence for underlying causal nexus between intrauterine and early postnatal PAP exposures and childhood AR, in both high-exposure populations and less polluted locations (Lin et al., 2023).

Early-life exposures played pivotal roles in determining the risk of allergic diseases throughout childhood and into adulthood (Gluckman et al., 2008). Due to the rapid and immature development of the immune and respiratory systems during this period, fetuses and infants were particularly vulnerable to the adverse effects of air pollution (Bowatte et al., 2015). Researches had indicated that exposures during both the prenatal and early postnatal periods could alter immune responses and cellular functions, thereby influencing the risk of allergies and other immune-related diseases later in life (Aithal et al., 2023; Murrison et al., 2019). Thus, targeting critical PAP exposure window could contribute to the formulation of effective strategies for the prevention and intervention of AR in children. Emerging evidence linked PAP exposure during prenatal and first-year periods to asthma and allergies in later life (Liu et al., 2023), mostly in North American and European populations being exposed to low PAP levels (Bousquet et al., 2008). Under high-PAP-exposure scenarios in Chinese cities, recent cross-sectional or cohort investigations focused on analyzing the effects of particulate matter (PM) with aerodynamic diameters of $\leq$10 μm (PM_{10}) or $\leq$2.5 μm ($PM_{2.5}$) on childhood AR (Li et al., 2022; Lin et al., 2021a), whereas its nexus with smaller particles (e.g., PM with an aerodynamic diameter $\leq$1 μm, PM_1) remained largely unstudied. Existing epidemiological studies indicated that smaller particles typically may exhibit more adverse health effects on children in both short-term and long-term exposures (Wu et al., 2022; Zhang et al., 2019). To our knowledge, no prior single- or multi-city studies have examined the associations of AR in Chinese children with early-life PM_1 exposure, due to the wide lack of routine monitoring for ground PM_1, even in densely-populated urban locations (Chen et al., 2017; Yin et al., 2020).

In this study, motivated by recent advances in both machine learning and satellite remote technologies, we linked high-resolution (1 × 1-km) spatiotemporal PM_1 estimates (Wei et al., 2019) to multicity cross-sectional surveys as the Phase II of the China, Children, Homes, Health (CCHH) study in 2019–2020 (Wu et al., 2022; Zhang et al., 2022). The primary purpose was to investigate the associations of childhood AR with in utero and first-year exposures to size-segregated PMs (e.g., PM_1, $PM_{2.5}$, and PM_{10}). We also aimed to explore trimester-specific associations to identify potential windows of susceptibility and effect modification by child's sex, age, and season of birth in PM-AR associations.

2. Methods

2.1. Study design and participants

A large-scale cross-sectional questionnaire survey was conducted in 7 major cities in China from 2019 to 2020, spanning across northern (n = 1, Taiyuan), central (n = 2, Wuhan & Changsha), eastern (n = 2, Shanghai & Nanjing), northwestern (n = 1, Urumqi), and southwestern (n = 1, Chongqing) provinces, as the Phase II of the China, Children, Homes, Health (CCHH) study (Fig. 1). The CCHH questionnaires were designed based on the International Study of Asthma and Allergies (ISAAC) and the Dampness in Building and Health (DBH) study in Sweden. The main goal of the survey was to explore the associations between household environments and asthma and rhinitis in Chinese preschool children. The standard questionnaires were validated through the pilot study and the CCHH Phase-I study during 2010–2012, and we followed the same survey procedures as in the Phase-I study (Cai et al., 2020; Zhang et al., 2013). Specifically, we distributed the standard questionnaire to the child's caregivers (e.g., parents or grandparents) through the kindergarten or nursery teacher, and provided both online and offline guidance to ensure standardized completion of the questionnaire survey.

Initially, 30466 children aged 3–6 years were enrolled in the CCHH Phase-II study. We excluded ineligible records with unreported AR information (n = 88) and incomplete covariates (n = 1092), leaving a total of 29286 children included in the analysis (Fig. 1).

2.2. Exposure assessment

Air pollution estimates in this study were derived from ChinaHighAirPollutants dataset (CHAP, https://weijing-rs.github.io/product.html, accessed on August 31, 2023), which provided long-term, high-resolution, and full-coverage gridded estimates ground-level air pollutants for China. A mature machine learning-based approach (the space-time extremely randomized trees model) was applied to estimate the spatiotemporal concentrations of ground-level PM_1 (Wei et al., 2019), $PM_{2.5}$ (Wei et al., 2021a, 2023a), and PM_{10} (Wei et al., 2021b) at an spatial resolution of 0.01° × 0.01° (approximately 1 × 1-km). Daily predicted estimates showed a high agreement with ground monitoring measurements for PM_1 (cross-validation coefficient of determination, CV-R^2 = 0.83; root-mean square error, RMSE = 9.50 μg/m^3), $PM_{2.5}$ (CV-R^2 = 0.92, RMSE = 10.76 μg/m^3), and PM_{10} (CV-R^2 = 0.90, RMSE = 21.12 μg/m^3) across China. For each 0.01° × 0.01° grid, daily estimates of $PM_{1-2.5}$ (PM with an aerodynamic diameter of 1–2.5 μm) and $PM_{2.5-10}$ (PM with an aerodynamic diameter of 2.5–10 μm) were calculated by subtracting the concentration of PM_1 from $PM_{2.5}$ and the concentration of $PM_{2.5}$ from PM_{10}, respectively.

In accordance with our recent CCHH study (Wu et al., 2022), for each mother-child pair, we first retrieved the monthly average concentrations of particles with different sizes from 2013 to 2018 based on their residential address during maternal pregnancy and the first year of child's life, using spatially resolved PM estimates available from CHAP dataset. Monthly estimates were then used to calculate mean exposures from the onset of pregnancy to the first year of child's life, via being matched with the dates of delivery and conception for each mother-child pair. To minimize misclassification of exposure, in utero and first-year ambient PM concentrations were assessed separately according to the recorded address information for each period. Aligning with prior air pollution epidemiology studies (Cai et al., 2023; Wang et al., 2018b; Yang et al.,

2021), we divided the in utero period into three pregnancy trimesters (the first: 1–13 weeks' gestation, the second: 14–26 weeks' gestation, and the third: 27 weeks to delivery) and also calculated the mean exposure concentrations during each stage of pregnancy.

2.3. Health outcomes and covariates

Childhood AR was ascertained through questionnaire survey by asking the child's caregivers (e.g., parents or grandparents) the following question: "Has the child had any doctor-diagnosed allergic rhinitis from birth to the investigation?". In line with prior CCHH publications (Wu et al., 2022; Zhang et al., 2022), we sorted out three sets of covariates: (1) characteristics of the child, including sex (boy [versus] *vs.* girl), age, ethnicity (Han *vs.* others), mode of delivery (vaginal *vs.* cesarean), birth season (spring *vs.* summer *vs.* autumn *vs.* winter), and breastfeeding duration (<1 *vs.* 1–<6 *vs.* 6–<12 *vs.* ≥12 months); (2) characteristics of the parents, including maternal education attainment (high school or below *vs.* university *vs.* postgraduate or above), maternal smoking status (never *vs.* former *vs.* current) and parental history of atopy (yes *vs.* no); and (3) characteristics of the household environment, including passive smoke exposure, air pollution from solid fuel, house renovation, and visible mold or dampness. These household environmental variables were categorized as: none, prenatal exposure, first year exposure or both.

2.4. Statistical analysis

Multiple mixed-effects logistic regression models with a random intercept for the survey city, were fitted to evaluate the associations between childhood AR and size-segregated particles during different exposure windows. Potential spatial clustering for childhood AR was considered and a random effect for the intercept on the city was included in the models. In our main analysis, four models were evaluated via sequentially adjusting for (a) cities as random intercept (Model 1); (b) plus children's characteristics (Model 2); (c) plus parental characteristics (Model 3); (d) plus household environmental characteristics (Model 4). Size-segregated PMs (PM_1, $PM_{1–2.5}$, $PM_{2.5}$, $PM_{2.5–10}$, and PM_{10}) were included as terms of continuous variables in the models separately, and effect estimates were reported as odds ratios (ORs) for per 10-μg/m^3 increase in the exposure. Also, trimester-specific associations were assessed to identify potential vulnerable exposure window (trimester 1, trimester 2, and trimester 3). Given the high correlation between trimester-specific PM exposure, exposure levels for each trimester were included in separate models, echoing with prior CCHH investigations (Wu et al., 2022; Zhang et al., 2021, 2022).

We investigated the exposure-response relationships between PM exposures and childhood AR, via smoothing restricted cubic spline terms with 3 knots placed at 10th, 50th, and 90th percentiles (Desquilbet and Mariotti, 2010). Extreme lower (<1%) and upper (>99%) exposure values were excluded when generating the curves due to their poor constraint in the spline curve (Qiu et al., 2023). Likelihood ratio tests were used to examine nonlinearity in the exposure-response relationships (Beelen et al., 2014). In addition, we performed stratified analyses to evaluate effect modification by sex (boy *vs.* girl), age (<5 years *vs.* ≥5 years), and birth season (spring *vs.* summer *vs.* autumn *vs.* winter) in associations between PMs and childhood AR risk. Two-sample *z*-test or meta-regression approach was used to test effect heterogeneity between subgroups. To illustrate potential between-city heterogeneity in PM-AR associations, we assessed city-specific associations and derived the pooled estimate using a random effects meta-analysis. Effect

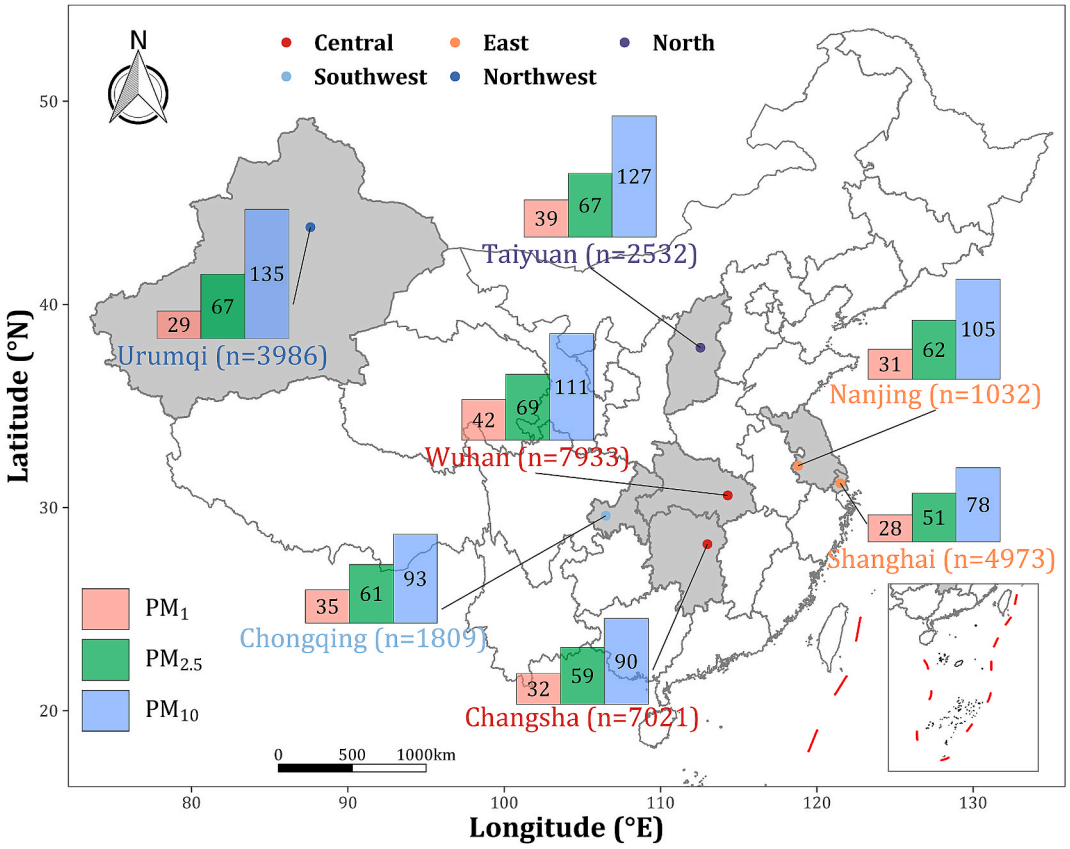

Fig. 1. Geographical distributions and sample sizes of the seven cities in CCHH Phase-II survey, and concentrations of early-life exposures to particulate matter (μg/m^3). Abbreviations: CCHH, China, Children, Homes, Health; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

heterogeneity was checked via I^2 statistic.

Multiple sensitivity analyses were performed to check the robustness of our results. First, we restricted the analyses to full-term (gestational age ≥37 weeks) children only and compared associations between models with and without adjustment for preterm birth to assess the impact of premature delivery. Second, we performed sensitivity analyses by fitting two-pollutant models additionally adjusted for residential NO_2, SO_2, O_3, or CO estimated by CHAP at 0.1° × 0.1° (approximately 10 × 10-km) resolution (Wei et al., 2022, 2023b), so as to eliminate the potential confounding effects of co-exposure to gaseous pollutants.

R software (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria) was used for all analysis, with the "lme4" package (version 1.1–33) for fitting the mixed-effects models. All tests were two-sided and *P*-value <0.05 indicated statistical significance.

3. Results

Table 1 summarizes the basic characteristics of included children. A total of 29286 (mean ± standard deviation [SD], 4.9 ± 0.9 years) children were enrolled, including 15258 (52.1%) boys. Among all children, 3652 (12.5%) were identified by their caregivers as ever having AR. Winter-born children were 7234 (24.7%) and 18436 (63.0%) were breastfed for more than 6 months. Over half of the mothers had a university or higher degree, and 571 (2.3%) of the children's mothers were either smokers or former smokers during pregnancy. Children who had passive smoking exposure or experienced household renovations accounted for 29.6% and 23.5%, respectively.

Table 2 gives the summary distribution of ambient air pollutants during pregnancy and the first year of life. Across all cities, concentrations of size-segregated particles exhibited consistent declines in the first year of life compared to in utero period, with average exposures of 33.1 (SD: 6.9) μg/m^3 *vs.* 36.3 (8.6) μg/m^3 for PM_1, 59.7 (10.7) μg/m^3 *vs.* 65.8 (12.2) μg/m^3 for $PM_{2.5}$, and 99.6 (22.8) μg/m^3 *vs.* 108.7 (23.1) μg/m^3 for PM_{10}, respectively. Prenatal and early postnatal PM estimates were moderate-to-highly correlated, with Spearman correlation coefficients ranging from 0.69 to 0.94 (Fig. S1). Descriptive statistics of trimester-specific PM concentrations were summarized in Table S1.

Table 1
Basic characteristics of the children, parents and domestic environment in the study.

Characteristic	No. (%)
Total mother-child pairs	29286 (100)
Children diagnosed with allergic rhinitis	3652 (12.5)
Child	
Age, mean ± SD, years	4.9 ± 0.9
Boy sex	15258 (52.1)
Han ethnicity	27754 (94.8)
Vaginal delivery	15140 (51.7)
Birth season	
Spring	7521 (25.7)
Summer	8035 (27.4)
Autumn	6496 (22.2)
Winter	7234 (24.7)
Preterm birth	1543 (5.3)
Low birth weight	1017 (3.5)
>6 months' breastfeeding	18436 (63.0)
Parental	
Parental atopy	782 (2.7)
Maternal smoking [a]	571 (2.3)
High maternal education	22176 (75.7)
Household environment	
Passive smoke exposure [a]	7478 (29.6)
Soid cooking fuel	265 (0.9)
Renovation [b]	5532 (23.5)
Visible mold or damp [b]	4439 (18.9)

Notes: SD, standard deviation. [a] The variable information was not collected in Urumqi (n = 3993); [b] The variable information was not collected in Urumqi (n = 3993) and Chongqing (n = 1853).

Table 2
Summary distributions of particulate matter concentrations during pregnancy and in the first year of life.

Exposure	Mean ± SD	Percentiles				
		P_5	P_{25}	P_{50}	P_{75}	P_{95}
In utero, μg/m^3						
PM_1	36.3 ± 8.6	24.0	30.0	35.0	41.8	53.3
$PM_{1–2.5}$	29.5 ± 6.5	21.2	24.7	28.2	33.6	41.7
$PM_{2.5}$	65.8 ± 12.2	48.7	56.3	65.5	73.2	89.0
$PM_{2.5–10}$	42.9 ± 15.7	25.0	31.0	40.1	48.9	74.9
PM_{10}	108.7 ± 23.1	75.0	89.4	107.4	124.9	148.5
First-year, μg/m^3						
PM_1	33.1 ± 6.9	23.3	28.3	31.9	37.5	44.8
$PM_{1–2.5}$	26.6 ± 6.7	18.6	22.1	25.1	29.4	40.2
$PM_{2.5}$	59.7 ± 10.7	43.2	51.8	58.7	67.8	77.3
$PM_{2.5–10}$	39.9 ± 14.8	23.1	28.6	37.5	44.9	70.7
PM_{10}	99.6 ± 22.8	68.4	81.1	96.0	115.0	141.1

Abbreviations: SD, standard deviation; P_5 = 5th percentile; P_{25} = 25th percentile; P_{50} = 50th percentile; P_{75} = 75th percentile; P_{95} = 95th percentile; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{1–2.5}$, particulate matter with aerodynamic diameter between 1 and 2.5 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; $PM_{2.5–10}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

Fig. 2 illustrates the associations between childhood AR and exposures to size-segregated PMs during pregnancy and the first year of life, estimated by sequentially adjusted models. Generally comparable risk estimates were seen as estimated by models 1–4, indicating that PM-AR associations were robust to the adjustment of multiple covariates. In the fully adjusted analysis (model 4), PM_1 and $PM_{2.5}$ exposures in both pregnancy and the first year of life were found to be associated with increased risks of AR in children, while we did not observe AR associations with $PM_{1–2.5}$ and $PM_{2.5–10}$ exposures. For instance, per 10-μg/m^3 increase of in utero and first-year exposures to PM_1 was associated with an odds ratio for childhood AR of 1.132 (95% CI: 1.022–1.254) and 1.151 (95% CI: 1.014–1.306), respectively. Similar results were found in children born at term in associations of early-life exposure to size-segregated particles with childhood AR (Table S2). In two-pollutant models, we found that the results were broadly stable after adjusting for gaseous pollutants (Table S3). In trimester-stratified analyses, compared with $PM_{2.5}$ and PM_{10}, PM_1 was more strongly associated with childhood AR during the third trimesters, with significant increases in AR risk (OR = 1.077, 95% CI: 1.027–1.128) (Fig. 3).

Fig. 4 depicts the exposure-response relationships between childhood AR and exposure to size-segregated particles. Consistent evidence for non-threshold effects on AR was identified, exhibiting no departures from linear associations with in utero $PM_{2.5}$ exposure (P = 0.60 for nonlinearity), and first-year exposures to $PM_{2.5}$ (P = 0.39) and PM_1 (P = 0.43). We observed nonlinear risk patterns for PM_{10} exposure in both prenatal and postnatal periods (P <0.05 for nonlinearity), showing a steeper rise in AR risk under low exposure ranges (<100 μg/m^3).

Fig. 5 provides subgroup analyses of PM-AR associations stratified by child's sex, age, and birth season. Generally comparable PM-associated risks were identified between boys and girls (P >0.40 for heterogeneity, Table S4). PM-AR associations varied across age groups in both periods, and children under 5 years-of-age suffered higher risks from PM exposures. In particularly, significant age modifications were found in associations of childhood AR with exposures to PM_1 (P = 0.017), $PM_{2.5}$ (P = 0.015), and PM_{10} (P = 0.028) during the first year of life (Table S5). We identified a consistent seasonal pattern in PM-AR associations, showing notably greater risks in children born in winter only. For instance, per 10-μg/m^3 increase in PM_1 during pregnancy and the first year of life was associated with a 37.4% (95% CI: 11.6–69.2%) and 43.4% (95% CI: 12.7–82.5%) rise in AR risk among winter-born children, respectively (Table S6). We observed great between-city heterogeneity (I^2 >50%) in PM-AR associations (Fig. S2), with odds ranging from 0.940 (95% CI: 0.722–1.224) in Urumqi to 1.853 (95% CI: 1.401–2.451) in Changsha

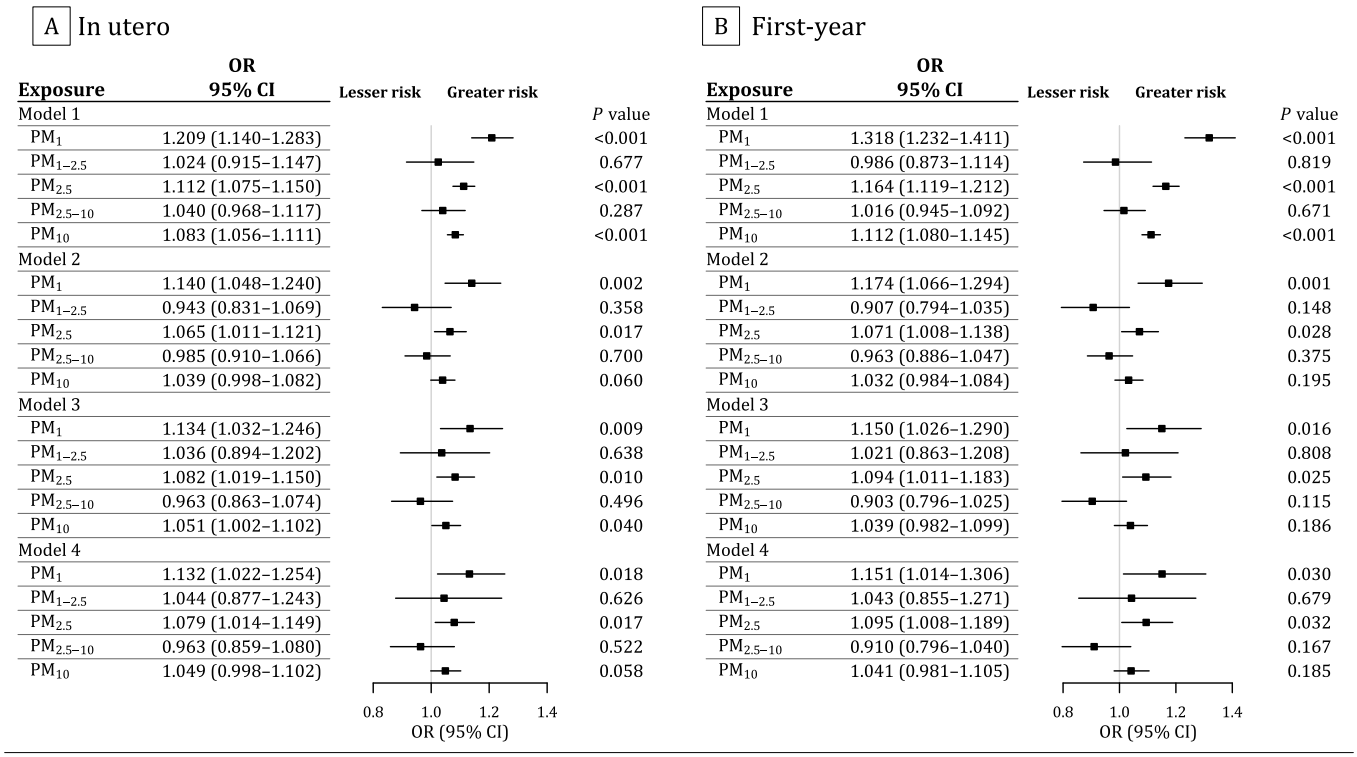

Fig. 2. Risks of childhood allergic rhinitis associated with per 10-μg/m^3 increase of in utero and first year exposures to size-segregated particles. Abbreviations: OR, odds ratio; CI, confidence interval; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{1–2.5}$, particulate matter with aerodynamic diameter between 1 and 2.5 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; $PM_{2.5–10}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm. Notes: Model 1 was adjusted for random effects of city; Model 2 was adjusted for random effects of city and the characteristics of child (child's sex, child's age, ethnicity, mode of delivery, birth season, and breastfeeding duration); Model 3 was adjusted for covariates in Model 2 plus characteristics of parents (maternal education level, maternal smoking status, and parental history of atopy); Model 4 was additionally adjusted for covariates in Model 3 plus characteristics of household environment (passive smoke exposure, air pollution from solid fuel, renovation, and visible mold/damp in early life).

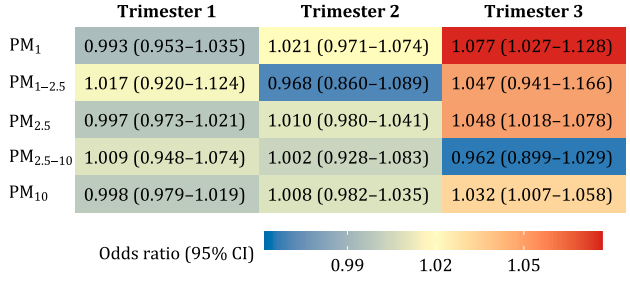

Fig. 3. Odds ratios (with 95% CIs) of childhood allergic rhinitis associated with a 10-μg/m^3 increase in trimester-specific exposures to size-segregated particles. Abbreviations: CI, confidence interval; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{1–2.5}$, particulate matter with aerodynamic diameter between 1 and 2.5 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; $PM_{2.5–10}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm. Notes: The model was adjusted for random effects of city, child's sex, child's age, ethnicity, mode of delivery, birth season, breastfeeding duration, maternal education level, maternal smoking status, parental history of atopy, passive smoke exposure, air pollution from solid fuel, house renovation, and visible mold/damp in early life.

for each 10-μg/m^3 rise in prenatal PM_1 exposure.

4. Discussion

To the best of our knowledge, this is the first study to evaluate the association between early-life exposure to ambient PM_1 and childhood AR. The analyses provided consistent evidence that prenatal and first-year exposures to ambient PM_1 and $PM_{2.5}$ increased the risk of childhood AR. These associations were found to be stronger among the younger (<5 years old) and winter-born children. Our findings may contribute to improved understanding of the nexus between childhood AR and early-life exposure to size-segregated particles, and the development of evidence-based rhinitis prevention strategies in highly polluted areas.

Consistent with prior cross-sectional (Liu et al., 2020) and birth cohort (Lin et al., 2021b) studies in China, this research linked an odds ratio of 1.079 (95% CI: 1.014–1.149) for childhood AR to per 10-μg/m^3 increase in prenatal $PM_{2.5}$ exposure, which was slightly lower than the pooled estimate from a meta-analysis of 13 international studies (OR = 1.172; 95% CI: 1.095–1.254) (Zou et al., 2018). Possible reasons are variations in $PM_{2.5}$ concentrations and constituents across geographic areas and time periods, as well as differences in exposure assessment and study populations (Wang et al., 2015; Zou et al., 2018). Review evidences revealed that smaller particles may exhibit greater risk effects on children's allergic respiratory syndrome (Johnson et al., 2021; Luong et al., 2019). Our recent CCHH analysis indicated that for a 1% rise in

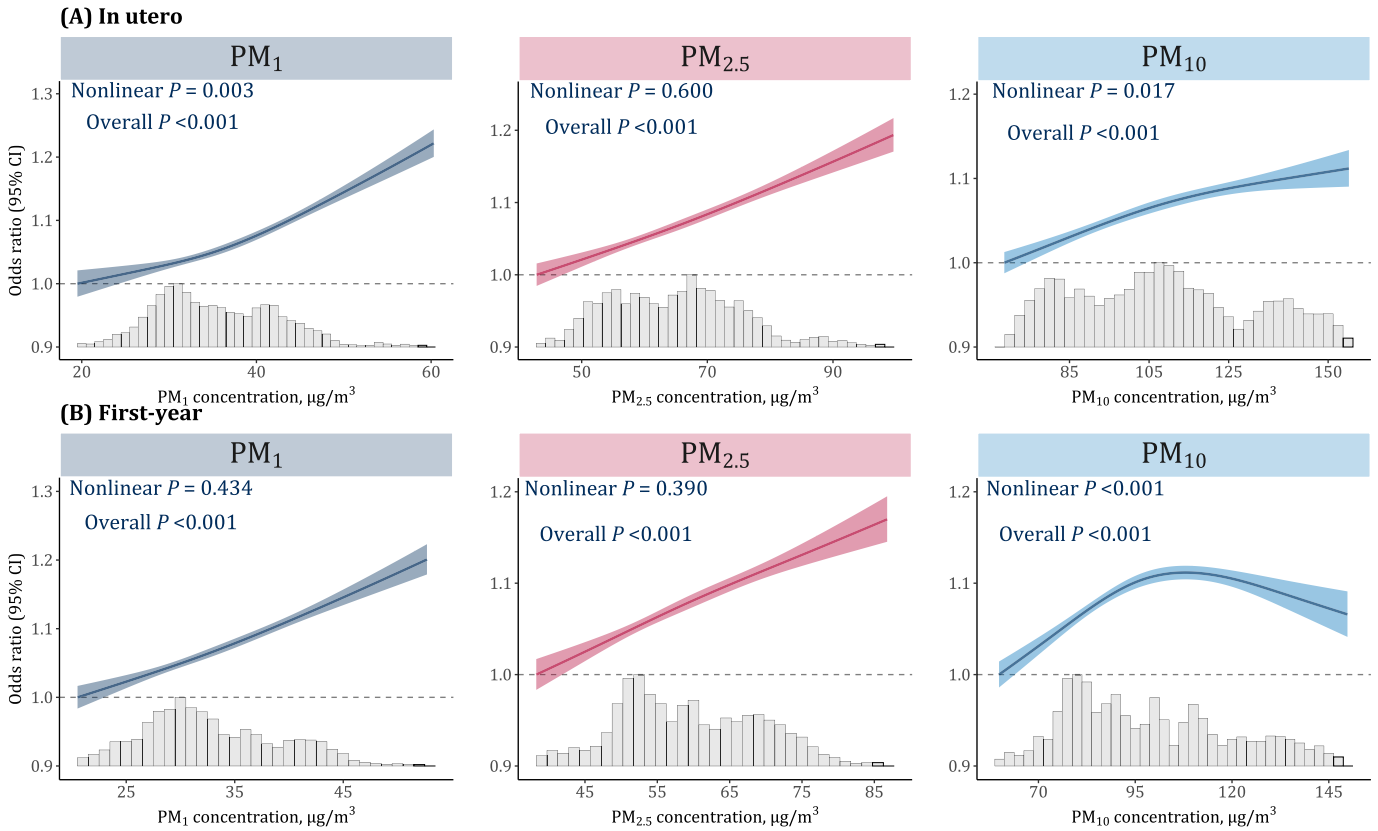

Fig. 4. Exposure-response relationships of in utero and first-year exposures to size-segregated particles with childhood allergic rhinitis. Abbreviations: CI, confidence interval; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm. Notes: The model was adjusted for random effects of city, child's sex, child's age, ethnicity, mode of delivery, birth season, breastfeeding duration, maternal education level, maternal smoking status, parental history of atopy, passive smoke exposure, air pollution from solid fuel, house renovation, and visible mold/damp in early life.

the exposure ratio of early-life PM_1 to $PM_{2.5}$, the odds of childhood asthma increased by 4.0% (95% CI: 2.0–5.0%) (Wu et al., 2022). The current analysis provided novel insights into the effects of PM_1 by performing comparative risk assessments linking AR with size-segregated PMs, and the heightened impacts of PM_1 were in accordance with some preceding studies on respiratory hospitalizations (Wang et al., 2021), cardiovascular (Wu et al., 2020) and mental (Chen et al., 2018) diseases. These results strengthened the notion that submicron particulate exposure could induce more deleterious health effects compared with larger fractions. The potential biological mechanism may be that smaller particles have higher surface area-to-volume ratio, which makes them more likely to adsorb more toxins and to deposit deeper into the respiratory tract (Manigrasso et al., 2020). Moreover, smaller size-segregated PMs are easier to penetrate the alveolar and somatic circulations, leading to greater damage to the lungs and genes and epigenetic alterations through oxidative stress and inflammatory mechanisms (Fang et al., 2022; Zou et al., 2017). Given the great achievement in reducing $PM_{2.5}$ pollution in China over the past decade, it is of critical importance and urgency to develop air quality standards for smaller particles such as PM_1, so as to further mitigate the health risks from PAP.

Previous publications reported less consistent findings on sensitive windows in associations between prenatal air pollution exposure and childhood respiratory infection and diseases (Hsu et al., 2015; Huang et al., 2015). In two Canadian cohorts (Lavigne et al., 2018, 2019), only second-trimester exposures to air pollutants (e.g., $PM_{2.5}$ and NO_2) were associated with increased risks of developing asthma in children up to 6 years of age, while the risk of eczema in infants during the first 12–18 months of age was linked with maternal NO_2 exposure during the 2nd and 3rd trimesters in Spain (Aguilera et al., 2013). Our analyses noted that the third trimester emerged as the susceptibility window for maternal exposure to PMs in associations with childhood AR among Chinese preschool children. Apart from trimester-stratified analyses, advanced statistical methods (e.g., distributed lag models [DLM]) may allow us to investigate sensitive exposure windows at the finer scale of gestational weeks. In DLM-based analyses of two large birth cohorts (n >140 thousands) in Chinese Taiwan, for instance, pediatric AR onset was related to $PM_{2.5}$ exposure at 30 weeks of gestation (Lin et al., 2021b), whereas asthma development was associated with prenatal $PM_{2.5}$ exposure at 6–22 weeks' gestation (Jung et al., 2019). Such inconsistency in sensitivity throughout the gestation weeks was also shown in some studies exploring the relationship between prenatal air pollution exposure and birth outcomes (Niu et al., 2022; Sheridan et al., 2019; Wang et al., 2018a). Notably, exposure assessment in aforementioned studies failed to take into account mothers' daily activities and mobility during pregnancy, and more sophisticated methods are needed in future research to better capture individual-level exposure dose and characterize vulnerable exposure windows, which may helpfully guide maternal air pollution prevention actions and provide novel insights into potential mechanisms.

In the stratified analysis, we observed a notably elevated risk of AR among children born in winter only. Although underlying mechanisms for the interplay between air pollution and winter birth remain intricate to elucidate, several plausible pathways could possibly favor the finding in this study. First of all, the prenatal period was critical for respiratory development, and the fetal respiratory tract develops rapidly during the mid- and late-gestation period (Shi et al., 2007). While our analysis identified the third trimester as a vulnerable period for the link between

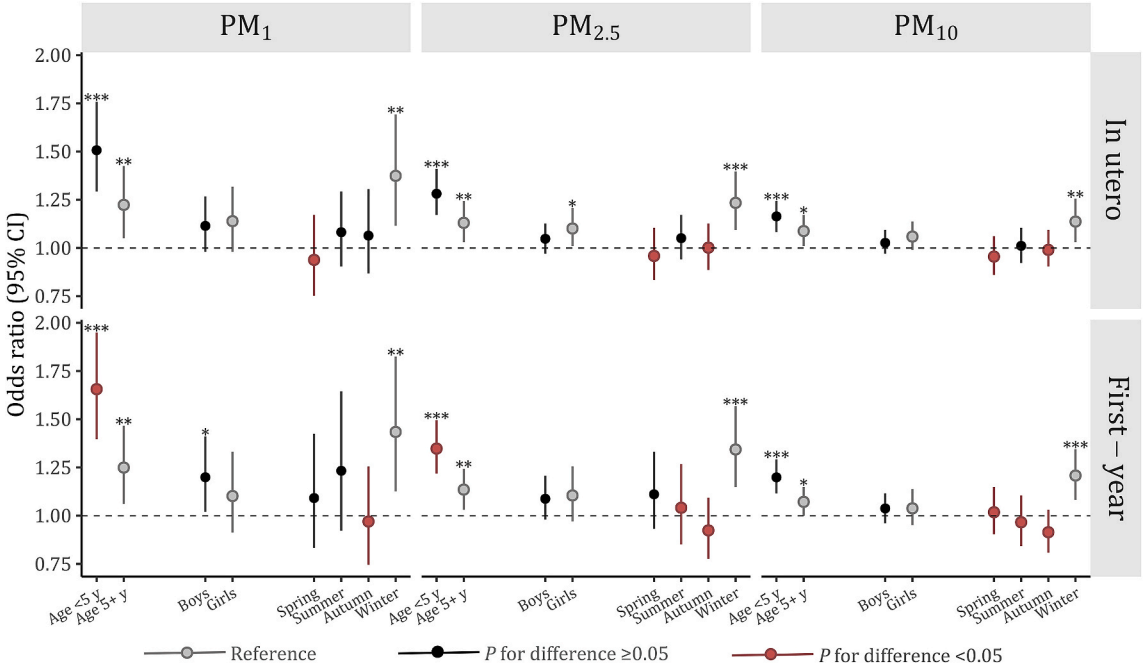

Fig. 5. Odds ratios (with 95% CIs) of childhood allergic rhinitis associated with per 10-μg/m^3 increase of in utero and first year exposures to size-segregated particles, stratified by sex, age, and birth season. Abbreviations: CI, confidence interval; PM_1, particulate matter with aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm. Notes: The model was adjusted for random effects of city, child's sex, child's age, ethnicity, mode of delivery, birth season, breastfeeding duration, maternal education level, maternal smoking status, parental history of atopy, passive smoke exposure, air pollution from solid fuel, house renovation, and visible mold/damp in early life. *P <0.05, **P <0.01, and ***P <0.001 for the estimated associations.

maternal PM exposure and childhood AR (Fig. 3), winter-born children being exposed to higher levels of PMs during later gestation may consequently be at heightened risks of AR. In addition, both PAP and vitamin D deficiency adversely affect respiratory health, and evidence suggested that adequate vitamin D levels may counteract PM-induced inflammation (Mann et al., 2017) and attenuate asthma development following traffic-related PM exposure (Bolcas et al., 2019). For winter births, late-gestation mothers may experience the trough with evidently lower vitamin D levels (Vinkhuyzen et al., 2016), which should be possibly insufficient to counteract the AR risks associated to seasonal peak PAP. Population-based experiments from multiple countries are warranted in the coming decade, so as to unveil the in-depth mechanisms for seasonal susceptibility to PM-associated childhood allergies.

Evidence showed mixed findings for effect modification by sex and age in PM-AR analyses (Bowatte et al., 2015; Pang et al., 2022). Our results revealed comparable effect sizes of AR risk associated with size-segregated PMs exposure between boys and girls, indicating no clear sex differences, and similar findings were seen in CCHH PHASE-I surveys in six cities in Chinese mainland (Chen et al., 2018a) and large birth cohorts in Chinese Taiwan (Lin et al., 2021b). We observed evidently greater AR susceptibility associated with early postnatal PM exposure in younger children (<5 years old), broadly aligning with CCHH single-city analyses on allergies or asthma (Deng et al., 2016; Lu et al., 2022; Zhang et al., 2021). The observed higher risk of AR in younger children could be possibly related to the delayed and cumulative effects (e.g., inflammatory responses and autoimmune damage) of early-life PAP exposure on infants' respiratory system (Wang et al., 2019; Wu et al., 2023), owing to their immature immunity and limited immune memory (Kollmann et al., 2017). This finding could also be partially supported by birth cohort evidence in developed locations. In Stockholm, Sweden (Codispoti et al., 2015) and mid-USA (Gruzieva et al., 2012), PAP exposure during infancy was associated with 40–83% increased risks of aeroallergen sensitization at children's 4 years-old of age. As also highlighted in a meta-analysis of birth cohort studies, early childhood exposure to traffic-related $PM_{2.5}$ may have sustained effects on new onset of asthma with about 3-year lag time (Bowatte et al., 2015). The age-specific associations merits further in-depth analysis, in order to identify vulnerable subgroups and clarify the intrinsic relationships, thereby facilitating the implementation of targeted measures.

Several limitations of this research should be acknowledged. First, due to the cross-sectional nature of CCHH study, recall bias was present and no causal inference could be provided. Second, there may introduce information bias on the outcome of childhood AR, since it was ascertained by questionnaire survey completed by children's caregivers instead of by physician-diagnosed records. Third, considering the lack of the AR onset timing in CCHH questionnaire surveys, it is infeasible to accurately determine whether exposures occurred before the occurrence of AR, which may potentially lead to reverse temporal relationships between first-year exposure and childhood AR. Fourth, despite the robust PM-AR associations through multiple analyses, the findings of our study may be potentially influenced by unmeasured confounders. Due to data unavailability, we failed to consider risk factors of parental behavior (e.g., alcohol consumption and physical activity), metabolic status (e.g., body composition and nutrition), and pregnancy-related characteristics (e.g., fetal parity, gravidity and maternity diseases) in our study. Despite this, sequentially adjusted models produced approximative risk estimates, suggesting minimal impacts from unmeasured confounders. Fifth, since only 7 provincial capitals in China were selected for our investigation, generalizations to other locations should be made with caution due to great between-city heterogeneities in air pollution and climate conditions.

5. Conclusions

In summary, this largescale cross-sectional investigation provided multicity evidence that prenatal and postnatal exposures to PM_1 and $PM_{2.5}$ were associated with increased AR risks in Chinese preschool

children. Comparative analyses highlighted stronger associations of ambient PM_1 than of larger particles with childhood AR. The window of vulnerability may be later trimesters of gestation, and young and winter-born children were at greater AR risks due to early-life PM exposures. These results emphasize the great public health significance to minimize ambient exposure to PAP for pregnant women and early infants in China. Given the accumulating evidence for more dramatic health effects of smaller particles, PM_1-targeted air quality guidelines are urgently needed globally for the sake of safeguarding mother-to-infant and the whole life-cycle health from air pollution threats.

CRediT authorship contribution statement

Yachen Li: Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Lifeng Zhu:** Software, Visualization, Writing – review & editing. **Jing Wei:** Data curation, Writing – review & editing. **Chuansha Wu:** Data curation, Writing – review & editing. **Zhuohui Zhao:** Conceptualization, Data curation, Funding acquisition, Investigation. **Dan Norbäck:** Conceptualization, Data curation, Funding acquisition, Investigation. **Xin Zhang:** Data curation, Investigation. **Chan Lu:** Data curation, Investigation. **Wei Yu:** Data curation, Investigation. **Tingting Wang:** Data curation, Investigation. **Xiaohong Zheng:** Data curation, Investigation. **Ling Zhang:** Data curation, Funding acquisition, Investigation, Supervision, Writing – review & editing. **Yunquan Zhang:** Conceptualization, Data curation, Funding acquisition, Methodology, Software, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118165.

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