Early-life exposure to submicron particulate air pollution in relation to asthma development in Chinese preschool children

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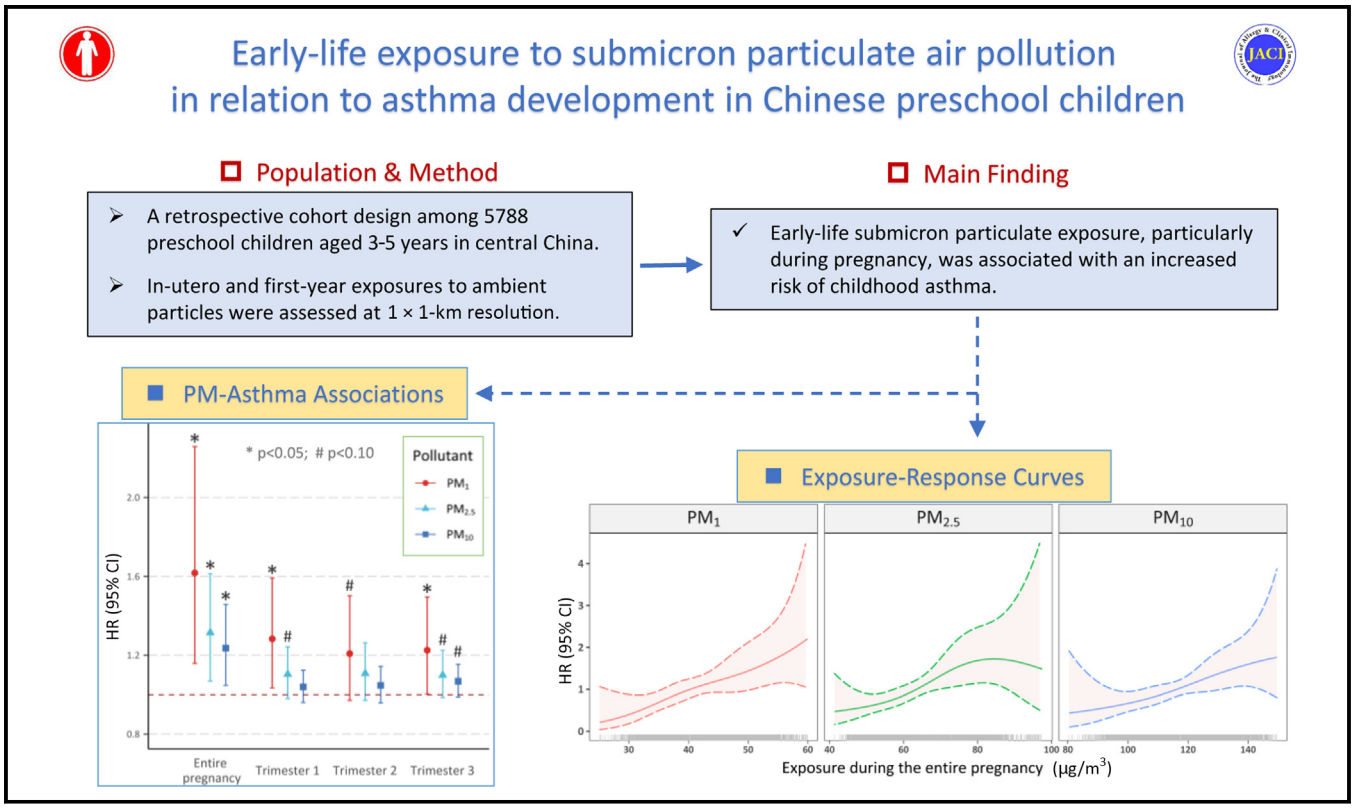
GRAPHICAL ABSTRACT



Background: Emerging research suggested an association of early-life particulate air pollution exposure with development of asthma in childhood. However, the potentially differential effects of submicron particulate matter (PM; PM with aerodynamic diameter ≤1 μm [PM_1]) remain largely unknown.

Objective: This study primarily aimed to investigate associations of childhood asthma and wheezing with *in utero* and first-year exposures to size-specific particles.

Methods: We conducted a large cross-sectional survey among 5788 preschool children aged 3 to 5 years in central China.

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In utero **and first-year exposures to ambient PM_1, PM with aerodynamic diameter less than or equal to 2.5 μm, and PM with aerodynamic diameter less than or equal to 10 μm at 1 × 1-km resolution were assessed using machine learning–based spatiotemporal models. A time-to-event analysis was performed to examine associations between residential PM exposures and childhood onset of asthma and wheezing.**

Results: Early-life size-specific PM exposures, particularly during pregnancy, were significantly associated with increased risk of asthma, whereas no evident PM-wheezing associations were observed. Each 10-μg/m^3 increase in *in utero* and first-year PM_1 exposure was accordingly associated with an asthma's hazard ratio in childhood of 1.618 (95% CI, 1.159-2.258; P = .005) and 1.543 (0.822-2.896; P = .177). Subgroup analyses suggest that short breast-feeding duration may aggravate PM-associated risk of childhood asthma. Each 10-μg/m^3 increase in *in utero* exposure to PM_1, for instance, was associated with a hazard ratio of 2.260 (1.393-3.666) among children with 0 to 5 months' breast-feeding and 1.156 (0.721-1.853) among those longer breast-fed.

Conclusions: Our study added comparative evidence for increased risk of childhood asthma in relation to early-life PM exposures, highlighting stronger associations with ambient PM_1 than with PM with aerodynamic diameter less than or equal to 2.5 μm and PM with aerodynamic diameter less than or equal to 10 μm. (J Allergy Clin Immunol 2021;148:771-82.)

Key words: *Fine particulate matter, PM_1, early-life exposure, asthma, wheezing, preschool children*

Childhood asthma gives rise to great health burden from chronic respiratory diseases and substantially affects quality of life among children across the globe.[1,2] It was widely acceptable that development of childhood asthmatic symptoms could largely result from gene-environment interaction.[3-5] Ambient air pollution, particulate matter (PM) in particular, has been identified as an important environmental determinant of asthma onset and exacerbation in recent systematic reviews.[6-8] However, findings regarding PM-asthma association in children exhibited great heterogeneity and inconsistency across studies.

Targeting critical exposure windows of particulate air pollution could largely help develop effective measures of prevention and intervention for childhood asthma. Emerging research[9,10] has linked particulate air pollution exposure (eg, inhalable and fine particles, namely PM with aerodynamic diameter ≤10 μm [PM_{10}] and PM with aerodynamic diameter ≤2.5 μm [$PM_{2.5}$]) during early-life time with later asthma and allergies in children, whereas most of these studies were conducted in developed areas with low pollution levels such as North America and Europe.[6,7] Related evidence was largely sparse in developing countries such as China, where most locations have been experiencing serious particulate air pollution and rapid increase in childhood asthma during recent decades.[1,11,12]

Size-fractional particles may have differential toxic effects on respiratory health in children. As suggested in existing epidemiologic investigations, smaller particles (eg, submicron and ultrafine PM) generally exhibited more adverse health effects in both short- and long-term exposures.[13-16] Monitoring and modeling data estimated that PM_1 (PM with aerodynamic diameter ≤1.0 μm) may contribute a large proportion of ambient $PM_{2.5}$ and PM_{10}.[17-20] Owing to a wide lack of ground PM_1 measurements worldwide, however, PM_1-health investigations have been sparsely conducted.[21-23] Such research gap has largely hampered in-depth understanding of PM-associated impacts on human circulatory and respiratory systems, especially in early childhood.

We hypothesized that early-life exposures to submicron particulate air pollution may relate to the development of childhood asthma. In this study, we thus performed a retrospective investigation among preschool children in Wuhan, China, playing as a part of the phase II CCHH (the China, Children, Homes, Health) study, and conceived a time-to-event analysis to examine the associations of *in utero* and first-year exposures to size-specific PMs (ie, PM_1, $PM_{2.5}$, and PM_{10}) with childhood asthma and wheezing. Individual residential exposure assessments at 1 × 1-km resolution were assigned by taking advantage of satellite-based space-time models using machine learning methods. Trimester-specific associations were assessed to identify potential vulnerable window, and stratified analyses were performed by child sex, breast-feeding duration, as well as age of first-ever incidence.

Abbreviations used
CCHH: China, Children, Homes, Health
HR: Hazard ratio
NDVI: Normalized difference vegetation index
PM: Particulate matter
PM_1: PM with aerodynamic diameter less than or equal to 1 μm
$PM_{2.5}$: PM with aerodynamic diameter less than or equal to 2.5 μm
PM_{10}: PM with aerodynamic diameter less than or equal to 10 μm

METHODS

Study design and participants

We conducted a cross-sectional questionnaire survey in Wuhan between November and December 2019, which belongs to a part of phase II of the CCHH study during the period 2019 to 2020. On the basis of a standard questionnaire validated by a previous pilot study,[24] the CCHH survey is mainly designed to assess the impacts of household environmental exposures on childhood asthma and rhinitis among Chinese preschool children. More details for the CCHH study can be found in several previous publications.[24,25] The questionnaire and proposal for this study were approved by the Medical Research Ethical Committee of School of Public Health, Fudan University.

In line with investigations of the phase I CCHH study through 2010 to 2012,[25,26] we adopted a multistage sampling method to select participants. Briefly, we investigated 14 kindergartens randomly selected from 7 urban districts, which was chosen by lottery from 13 districts in Wuhan city. All preschool children in these kindergartens were included as the study subjects by surveying their caregivers (eg, parents or grandparents) through a standard questionnaire. These questionnaires were posted online through WeChat quick response code and distributed to each survey participant by the child's teacher. The caregivers (eg, parents or grandparents) were asked to fulfill the survey questionnaire under the online guidance. By taking full advantage of online questionnaire platform, we could perform good quality control on data collection.

Of 12,031 valid survey questionnaires originally returned, we picked out 8,387 preschool children aged 3 to 5 years. In line with the research purpose of this study, we further excluded 87 questionnaires by completeness and logic checking with information of interest such as pregnancy week, birth date, and residence address. Given that individual exposure assignments of ambient particulate air pollution were available for Wuhan city only during the period 2014 to 2018, we additionally excluded 1999 children who were conceived

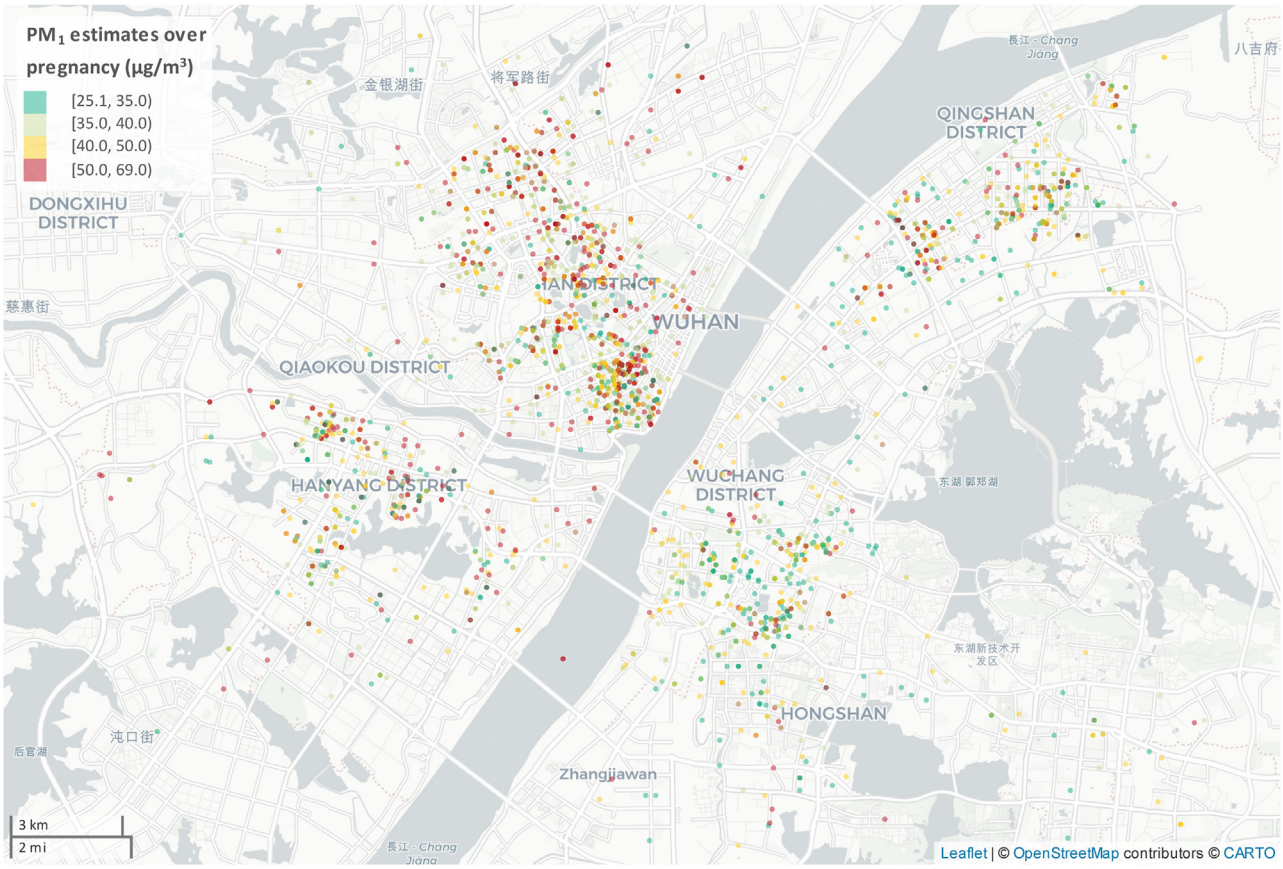

FIG 1. Geographical locations of participants' residence address and estimated PM_1 concentrations over the pregnancy.

before January 2014 and 513 resided outside Wuhan during the prenatal period and the first year of life time. Finally, we included 5788 children for the analysis in this study. Fig 1 shows geographical locations of residence address for surveyed children in Wuhan city.

Ascertainment of asthma and wheezing incidence

Incidence of wheezing was defined as "has ever had the symptoms of wheezing or whistling in the chest in the past," and asthma was ascertained as "has ever had doctor-diagnosed asthma from birth to the survey." We also collected time information on onset of wheezing and asthma diagnosis by asking the following 2 questions: (1) "At what ages has the child had symptoms of wheezing or whistling?"; (2) "How old was the child when first diagnosed as asthma?" These above items regarding childhood wheezing and asthma were modified from the International Study of Asthma and Allergies in Childhood questionnaire.[27,28]

Exposure assessment for ambient air pollutants

Daily average concentrations in Wuhan through the period 2014 to 2018 for ambient PM_1, $PM_{2.5}$, and PM_{10} were estimated at a 1-km spatial resolution using a well-developed machine learning–based method—space-time extremely randomized trees model.[29-33] As one of tree-based ensemble learning approaches, extremely randomized trees model splits nodes by randomly selecting cutoff points and uses all training samples to grow trees instead of the bootstrap approach. In comparison to other tree-based approaches (eg, decision tree and random forest), this model could efficiently solve variance problems. Space-time extremely randomized trees well incorporates spatiotemporal information into extremely randomized trees model through introducing the spatial autocorrelation between PM observations weighted by geographical distance (space) and temporal difference (time).

The space-time extremely randomized trees model showed good predictive performance across mainland China, by well incorporating spatiotemporal information of ground measurements, satellite-retrieved aerosol optical depth (1-km resolution Multi-Angle Implementation of Atmospheric Correction aerosol products), land use, topography, pollution emission, population, and meteorological data. For monthly predicted estimates, validation results showed they have a high correlation coefficient (R^2) of 0.96 for PM_1,[30] 0.94 for $PM_{2.5}$,[32] and 0.94 for PM_{10},[33] and a corresponding root-mean-square error of 4.8 $\mu g/m^3$, 5.1 $\mu g/m^3$, and 11.1 $\mu g/m^3$ with ground measurements, respectively. In-situ measurements for daily PM_1 for the years 2014 to 2018 were gathered from 153 monitoring stations of the China Atmosphere Watch Network (regulated by the China Meteorological Administration). And ground measurements for daily $PM_{2.5}$ and PM_{10} during the same period were collected from 1497 stations of China National Urban Air Quality Real-time Publishing Platform (regulated by the China National Environmental Monitoring Center). More details of the modeling development could be found in our previous publications.[30-33]

For each participant involved in this study, we first derived monthly mean concentrations of size-specific PMs during the period 2014 to 2018 on the basis of residence address for specific periods (eg, prenatal and 0-1-year-old) from aforementioned 1 × 1-km gridded estimates. These monthly estimates were then aggregated into average exposures for the entire pregnancy, trimester-specific periods, and the first year after birth (0-1-year-old), through further taking into account information on birth date and date of conception. Prenatal and first-year PM exposures were assigned on the basis of corresponding address information for specific periods. Such exposure assessments could largely reduce exposure misclassification, through accounting for participants' residential movements. Similar calculating methods

were adopted for exposure assessments of gaseous pollutants (eg, nitrogen dioxide [NO_2] and ozone [O_3]) using city-average monthly measurements from monitoring stations due to unavailability of satellite-derived data sets.

Covariates

In accordance with previous CCHH publications[26,34,35] and related literatures,[7,9,10] we considered several sets of covariates in our analysis. These covariates included (1) child's individual characteristics: the child's sex (boy vs girl), ethnicity (Han vs the minority), vaginal delivery (yes vs no), birth year and season (winter [December to February] vs spring [March to May] vs summer [June to August] vs fall [September to November]), gestational weeks (<37 weeks [preterm birth] vs ≥37 weeks), birth weight (<2500 g [low birth weight] vs ≥2500 g), and breast-feeding duration (0-5 months vs ≥6 months); (2) family or maternal characteristics: family history of atopy (yes vs no), maternal education attainment (high school and below vs university and above), maternal smoking status (never vs former or current), area-based income (low vs medium vs high); (3) residential environment: household renovation during the early lifetime (yes vs no), indoor passive smoke exposure (yes vs no), residence-located area (urban vs suburban/rural district), and early-life residence greenness (measured by normalized difference vegetation index [NDVI]). We derived monthly NDVI estimates at a 1-km spatial resolution for assessment of exposure to green space surrounding the residential address, from the Moderate-Resolution Imaging Spectro-Radiometer in the National Aeronautics and Space Administration's Terra Satellite.

Statistical analysis

Descriptive statistics were summarized as counts (proportions) and means ± SD, as appropriate. Pearson chi-square tests and *t* tests were performed to compare distributions of covariates between groups of asthma/wheezing cases and controls. We conceived a time-to-event study design and used Cox proportional hazards models to assess associations of asthma and wheezing incidence with early-life (prenatal and first-year) PM exposures.[10,36] Follow-up time was measured as each child's age in months from birth until incidence of the outcome of interest (ie, diagnosis of childhood asthma and first onset of wheezing), or end of follow-up (survey time in 2019).[10,37] We tested the proportionality of hazards assumption by evaluating the weighted Schoenfeld residuals[38] in our Cox modeling analysis. Tests of proportional hazards assumptions showed no violations, with all *P* values more than .05. In our main analytic models, we separately included prenatal and first-year size-specific PM exposures in the regression models as terms of continuous variables. Associations were estimated through hazard ratios (HRs) and their 95% CIs, associated with per 10-$\mu g/m^3$ increase in exposures to size-specific PMs. Alternatively, we used a natural cubic spline term with 3 degrees of freedom for PM_1, $PM_{2.5}$, and PM_{10} to model dose-response curves.[23,39] Nonlinearity in PM-asthma/wheezing associations was checked visually and tested using likelihood ratio tests.[40] Collinearity in Cox models was assessed through the statistic of variance inflation factor, and our analyses did not show evident collinearity because variance inflation factors for all covariates were less than 2.

We performed several subgroup analyses stratified by sex, breast-feeding duration, and age at diagnosis to identify potential vulnerability. To ensure sufficient statistical power between subgroups, we used 6 months' breast-feeding as a stratum cutoff, given that about 60% children in our investigation were breast-fed for 6+ months. Sensitivity analyses with various cutoffs were also performed. Two-sample *z* tests[41,42] were used to examine the potential effect modification, based on stratum-specific point estimates (β = lnHR) and their SEs. For instance, effect differences between sex could be tested using the following formula:

$$z = \frac{\beta_{\text{girl}} - \beta_{\text{boy}}}{\sqrt{\text{SE}^2_{\text{girl}} + \text{SE}^2_{\text{boy}}}}$$

We checked the robustness of our main findings through some sensitivity analyses. First, we conducted 2-pollutant models by simultaneously including one of gaseous pollutants (NO_2 and O_3) and size-specific PMs in our models, so as to eliminate the potential confounding effects of exposures to gaseous pollutants on development of childhood asthma. Differences between nested single- and 2-pollutant models were examined through the likelihood ratio test.[40] Second, we adjusted for the potential confounding effects of early-life residential greenness exposure, measured by satellite-derived NDVI at a 1-km spatial resolution. Third, we included both *in utero* and first-year PM exposures for mutual adjustments in our analytic models.[9] Finally, we restricted the analyses to Han-ethnicity and full-term (gestational age ≥37 weeks) children only.

As a secondary analysis of our time-to-event approach, we alternatively adopted modified Poisson regression[43] with robust (sandwich) estimation of variance applied to binary and nonrepeated outcomes. Such a method allows estimation of relative risk when the rare disease assumption is violated, and has been well applied in recent retrospective cohort analysis[44-46] with rare outcomes.

R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses, with "survival" package for the time-to-event modeling, "splines" package for natural cubic spline smoothing, and "car" package for collinearity diagnosis. All tests were conducted 2-sided, and effects with P less than .05 were considered statistically significant.

RESULTS

Data description

Table I summarizes the characteristics of 5788 children involved in this retrospective cohort. Included children were aged from 3 to 5 years (mean age, 4.1 ± 0.6 years), with 3017 (52.1%) being boys. Only 2554 (44.1%) children were born from vaginal delivery. A total of 363 (6.3%) children were preterm births, and 278 (4.8%) were born with low birth weight. A total of 176 children reported asthma diagnosis, and boys accounted for about 70%. Among the 521 children who ever had wheezing, 320 (61.4%) were boys. A total of 3429 (59.2%) children experienced 6+ months' breast-feeding, whereas around half asthma (50.6%) and wheezing (48.2%) cases were from these longer breast-fed. Compared with baseline, a higher proportion of cases were observed among children with the family history of atopy, house renovation experience, indoor smoke exposure, and household dampness during early life (*in utero* or first year).

Table II depicts the summary distributions of *in utero* and first-year exposures to ambient air pollutants. During the entire pregnancy, particulate air pollutants estimated by spatiotemporal models were averaged at 42.5 $\mu g/m^3$ (range, 25.1-68.6) for PM_1 (Fig 1), 64.9 $\mu g/m^3$ (41.4-109.3) for $PM_{2.5}$, and 117.4 $\mu g/m^3$ (80.4-173.4) for PM_{10}, respectively. Accordingly, station-based measurements showed an *in utero* exposure (mean ± SD) of 49.4 ± 2.6 $\mu g/m^3$ for NO_2 and 95.2 ± 2.6 $\mu g/m^3$ for ozone. Particulate pollutants were highly correlated with NO_2 (Spearman correlation coefficient [r] ranging from 0.67 to 0.82), but had a weak correlation with O_3 during the pregnancy and child's first year of lifetime (see Fig E1 in this article's Online Repository at www.jacionline.org). *In utero* and first-year PM exposures were only lowly or moderately correlated ($0.26 \le r \le 0.53$). The first year of children's lifetime saw a consistent reduction in both particulate and gaseous air pollution levels. For instance, PM_1 showed a decline of 5.1 $\mu g/m^3$ and O_3 decreased by 2.4 $\mu g/m^3$. Distributions of trimester-specific PM concentrations are summarized in Table E1 in this article's Online Repository at www.jacionline.org.

Associations by exposure window

Table III outlines associations of *in utero* and first-year PM exposures with childhood asthma and wheezing. PM exposures, particularly during pregnancy, were strongly associated with

TABLE I. Characteristics of children included in study

Characteristic	All children (n = 5788)	Diagnosed with asthma			Ever had wheezing		
		Yes (n = 176)	No (n = 5612)	*P* value	Yes (n = 521)	No (n = 5267)	*P* value
Child							
Boys, n (%)	3017 (52.1)	123 (69.9)	2894 (51.6)	<.001	320 (61.4)	2697 (51.2)	<.001
Age (y), mean ± SD	4.1 ± 0.6	4.2 ± 0.6	4.1 ± 0.6	.156	4.2 ± 0.6	4.1 ± 0.6	.088
Vaginal delivery, n (%)	2554 (44.1)	75 (42.6)	2479 (44.2)	.739	202 (38.8)	2352 (44.7)	.011
Born in year 2014 and 2015, n (%)	3421 (59.1)	111 (63.1)	3310 (59.0)	.313	323 (62.0)	3098 (58.8)	.174
Born in warm season, n (%)	2966 (51.2)	82 (46.6)	2884 (51.4)	.239	272 (52.2)	2694 (51.1)	.678
Preterm birth, n (%)	363 (6.3)	16 (9.1)	347 (6.2)	.159	44 (8.4)	319 (6.1)	.040
Low birth weight, n (%)	278 (4.8)	8 (4.5)	270 (4.8)	1.000	41 (7.9)	237 (4.5)	<.001
Han ethnicity, n (%)	5563 (96.1)	170 (96.6)	5393 (96.1)	.892	496 (95.2)	5067 (96.2)	.313
Breast-feeding duration ≥6 mo, n (%)	3429 (59.2)	89 (50.6)	3340 (59.5)	.021	251 (48.2)	3178 (60.3)	<.001
Family or maternal characteristics							
Maternal smoking status (current and former), n (%)	170 (2.9)	8 (4.5)	162 (2.9)	.291	23 (4.4)	147 (2.8)	.050
Maternal education with university and above, n (%)	4408 (76.2)	145 (82.4)	4263 (76.0)	.060	424 (81.4)	3984 (75.6)	.004
Middle and high household income, n (%)	4672 (80.7)	143 (81.2)	4529 (80.7)	.933	413 (79.3)	4259 (80.9)	.412
Family history of atopy, n (%)	1150 (19.9)	50 (28.4)	1100 (19.6)	.005	165 (31.7)	985 (18.7)	<.001
Residential environment							
Living in urban area, n (%)	5590 (96.6)	171 (97.2)	5419 (96.6)	.826	498 (95.6)	5092 (96.7)	.237
House renovation during pregnancy or age 0-1 y, n (%)	1356 (23.5)	55 (31.2)	1301 (23.3)	.027	142 (27.3)	1214 (23.2)	.056
Residence NDVI during pregnancy and age 0-1 y, mean ± SD	0.261 ± 0.055	0.255 ± 0.056	0.261 ± 0.055	.161	0.262 ± 0.052	0.261 ± 0.055	.830
Passive smoke exposure, n (%)	1725 (29.8)	65 (36.9)	1660 (29.6)	.044	190 (36.5)	1535 (29.1)	<.001
Household visible mold or damp, n (%)	1051 (18.2)	48 (27.3)	1003 (17.9)	.002	139 (26.7)	912 (17.3)	<.001

Warm season, April to September.

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

Air pollution concentration	Mean ± SD	Min	Percentiles			Max
			P_{25}	P_{50}	P_{75}	
During entire pregnancy ($\mu g/m^3$)						
PM_1*	42.5 ± 7.7	25.1	35.7	40.5	49.7	68.6
$PM_{2.5}$*	64.9 ± 12.2	41.4	54.8	61.8	75.8	109.3
PM_{10}*	117.4 ± 14.7	80.4	104.9	115.1	130.4	173.4
NO_2†	49.4 ± 2.6	42.2	47.5	49.3	51.7	62.8
O_3†	95.2 ± 6.8	56.0	89.2	94.3	100.7	120.5
During age 0-1 y ($\mu g/m^3$)						
PM_1*	37.4 ± 3.1	23.3	35.5	37.1	38.9	61.2
$PM_{2.5}$*	56.5 ± 4.5	41.1	53.4	55.9	58.7	91.6
PM_{10}*	105.7 ± 6.7	82.1	101.8	104.8	108.9	145.1
NO_2†	47.7 ± 1.5	45.5	46.8	47.6	47.8	51.8
O_3†	92.8 ± 4.3	82.9	89.3	92.0	97.0	100.5

*Spatiotemporal estimates based on machine learning method.
†Station-average concentration.

increased risk of asthma, whereas no evident associations were observed between wheezing and exposures to size-specific PMs. Each 10-$\mu g/m^3$ increase in *in utero* and first-year PM_1 exposure was accordingly associated with an asthma HR of 1.618 (95% CI, 1.159-2.258; $P = .005$) and 1.543 (0.822-2.896; $P = .177$). Lower $PM_{2.5}$- and PM_{10}-related risks were consistently found, with corresponding HRs of 1.314 (1.070-1.614) and 1.236 (1.047-1.458) associated with $PM_{2.5}$ and PM_{10} exposures during pregnancy. Significant effect of first-year exposure on asthma was identified only in PM_{10}, with an HR of 1.409 (1.037-1.915; $P = .028$).

Fig 2 demonstrates risks of childhood asthma and wheezing associated with trimester-specific PM exposures. Compared with $PM_{2.5}$ and PM_{10}, PM_1 was more strongly associated with childhood asthma, with significant increases in risk during the first (HR, 1.283; $P = .024$) and third (HR, 1.225; $P = .046$) trimesters. Marginally significant ($.05 < P < .1$) PM-asthma associations were also observed for exposures of $PM_{2.5}$ during the early trimester, PM_1 during the second trimester, and PM_{10} during the late trimester. In terms of wheezing, we observed a marginally significant association ($P = .056$) with PM_1 only during the first trimester. Detailed HR estimates associated with trimester-specific PM exposures are presented in Table E2 in this article's Online Repository at www.jacionline.org.

Fig 3 illustrates concentration-response curves between PM exposures during pregnancy and risks of childhood asthma and wheezing. Visual checking and nonlinearity tests (see Table E3 in this article's Online Repository at www.jacionline.org; all

TABLE III. Estimates of HRs (with 95% CIs) for childhood asthma and wheezing, associated with per 10-μg/m^3 increase in *in utero* and first-year exposures to PM_1, $PM_{2.5}$, and PM_{10}

	Asthma		Wheezing	
Exposures	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Entire pregnancy				
PM_1	1.618 (1.159-2.258)	.005	1.020 (0.834-1.246)	.850
$PM_{2.5}$	1.314 (1.070-1.614)	.009	0.992 (0.876-1.124)	.904
PM_{10}	1.236 (1.047-1.458)	.012	0.962 (0.872-1.063)	.447
First year (0-1 y)				
PM_1	1.543 (0.822-2.896)	.177	1.214 (0.831-1.771)	.316
$PM_{2.5}$	1.358 (0.876-2.104)	.171	1.148 (0.880-1.499)	.309
PM_{10}	1.409 (1.037-1.915)	.028	1.119 (0.935-1.338)	.219

All Cox models adjusted for a list of covariates including (1) child's individual characteristics: the child's sex, ethnicity, vaginal delivery, birth year and season, gestational weeks, birth weight, and breast-feeding duration; (2) family or maternal characteristics: family history of atopy, maternal education attainment, maternal smoking status, area-based income; and (3) residential environment: household renovation during the early life time, indoor passive smoke exposure, and residence-located area.

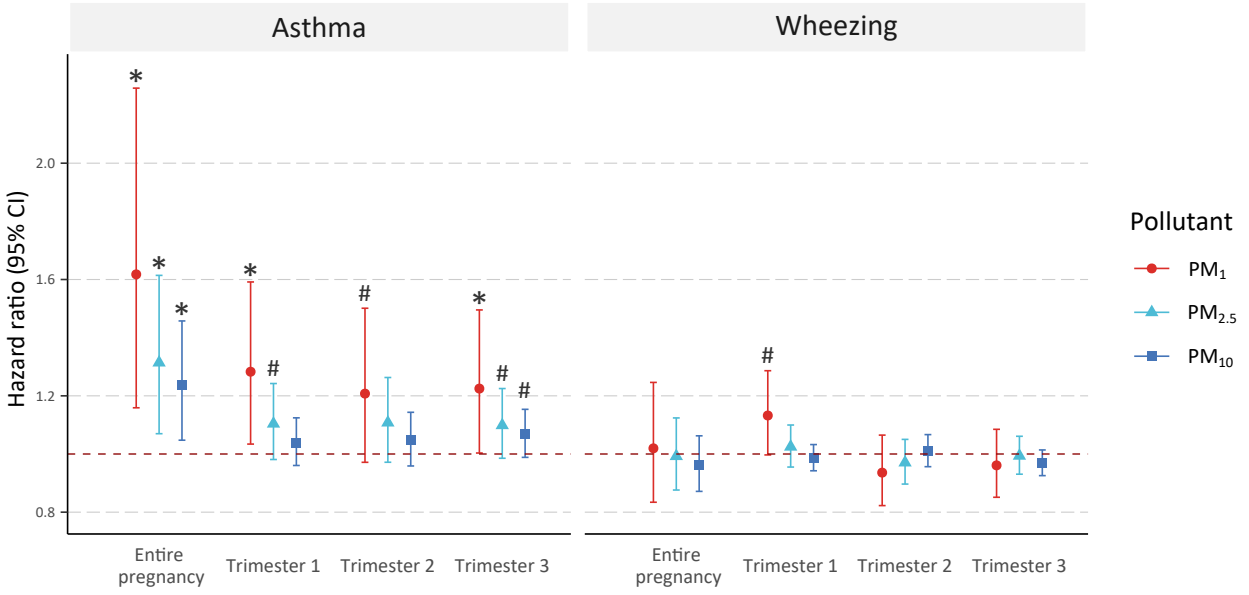

FIG 2. HRs (with 95% CIs) of childhood asthma and wheezing, associated with a 10-μg/m^3 increase in trimester-specific exposures to PM_1, $PM_{2.5}$, and PM_{10}. *$P < .05$, #$P < .10$.

$P > .05$) largely supported the evidence of linear increases in risks associated with *in utero* PM exposures, especially for the outcome of asthma.

Associations by subgroup. Fig 4 gives subgroup-specific HRs of asthma associated with *in utero* PM exposures, stratified by child sex, breast-feeding duration, and age at diagnosis. Exposures to size-specific PMs during pregnancy showed significant effects on boys only, children with 0 to 5 months' breast-feeding, and being first diagnosed before being 3 years old. Despite a higher PM_1-associated risk among boys, we observed comparable $PM_{2.5}$/PM_{10}-asthma associations between sexes. We observed suggestive evidence that short breast-feeding duration may aggravate PM-associated risks of childhood asthma, with *P* value of .052, .049, and .099 for the interaction of breast-feeding duration with PM_1, $PM_{2.5}$, and PM_{10}, respectively. Each 10-μg/m^3 increase in *in utero* exposure to PM_1, for instance, was associated with an HR of 2.260 (1.393-3.666) among children with 0 to 5 months' breast-feeding and 1.156 (0.721-1.853) among children with 6+ months' breast-feeding. Similar results were found when using 3 months' breast-feeding as subgroup cutoff (see Table E4 in this article's Online Repository at www.jacionline.org), and additionally stratifying breast-feeding durations into 3 strata of less than 1, 1 to 6, and more than 6 months (see Table E5 in this article's Online Repository at www.jacionline.org). Early development of asthma in childhood exhibited more robust associations with prenatal PM exposure. Specifically, PM_1-associated HR was 1.785 (1.160-2.747) and 1.400 (0.824-2.379) for children being diagnosed before and after age 3 years. Generally similar findings were also revealed in subgroup analyses for PM-asthma associations based on first-year exposures (see Fig E2 in this article's Online Repository at www.jacionline.org), showing stronger associations among boys, children with shorter breast-feeding, and earlier age at diagnosis. Additional stratified analyses by breast-feeding duration (see Table E6 in this article's Online Repository at www.jacionline.org) showed significantly higher risks of asthma associated with postnatal PM exposures in children breast-fed less than 1 month only.

Fig 5 illustrates subgroup analyses of PM-asthma associations stratified by housing environmental factors (ie, passive smoke exposure, household mold or damp, and house renovation). Interestingly, we observed significantly increased HRs only in

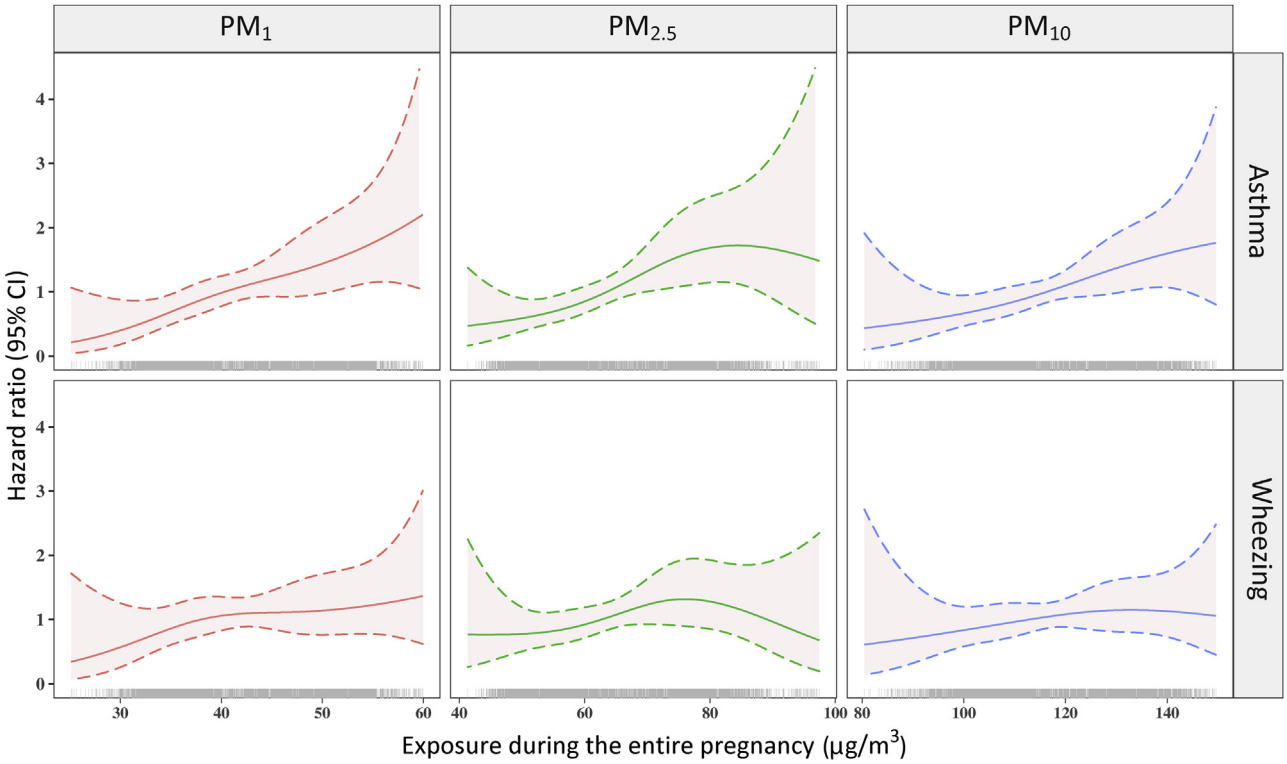

FIG 3. Concentration-response curves (smoothing by natural cubic spline function with df = 3) between exposures to size-specific particles during pregnancy and risks of childhood asthma and wheezing. *df*, Degrees of freedom.

nonexposure subgroups. Each 10-μg/m^3 increase in *in utero* exposure to PM_1, for instance, was associated with childhood asthma risks of 1.898 (1.245-2.894), 1.639 (1.105-2.433), and 1.923 (1.283-2.882) among mothers/children who were not exposed to early-life passive smoke, household dampness, and house renovation, respectively. Despite these disparities in associations between subgroups, we failed to identify any significant modifying effects (all *P* values >.1).

Sensitivity analyses

Sensitivity analysis shows the robustness of our main findings on PM-asthma associations. Estimated risks associated with prenatal PM exposures did not change substantially (all *P* values >.5 for likelihood ratio tests), after separately introducing gaseous pollutants (ie, NO_2 and O_3), NDVI, and first-year PM in the Cox regression model for additional adjustment (see Table E7 in this article's Online Repository at www.jacionline.org). Associations also kept unchanged when restricting the analyses to Han-ethnicity and full-term (gestational age ≥37 weeks) children only (see Table E8 in this article's Online Repository at www.jacionline.org). In compassion to our time-to-event analysis, risk estimates for childhood asthma and wheezing were highly comparable by performing a secondary analysis of modified Poisson regression approach (see Tables E9 and E10 in this article's Online Repository at www.jacionline.org).

DISCUSSION

To our knowledge, this is the first study assessing associations of prenatal and first-year exposure to ambient PM_1 with first-ever incidence of asthma and wheezing in children. We observed strong evidence that early-life particulate air pollution exposures (particularly submicrometric PM) increased the risk of childhood asthma among preschool children. Besides, we identified potential modifying effects by breast-feeding duration, suggesting longer breast-feeding may lower asthma risk in children exposed to particulate air pollutants. Our findings may have significant public health implications in informing environmental and health care policymakers to make greater efforts in clean air actions, particularly in highly polluted Chinese megacities, so as to reduce the burden of childhood asthma associated with ambient particulate air pollution.

We observed increased risks of childhood asthma associated with exposures to $PM_{2.5}$ and PM_{10} during early life (eg, *in utero* and first year since birth). This finding generally echoed with several birth cohort studies conducted in Canada[9,47] and the United States[36,48,49] and Taiwan province of China,[10] while great heterogeneity still existed across studies. Clark et al[9] found significant effects of *in utero* and first-year exposures to PM_{10} (HR, 1.09 [1.05-1.13] and 1.07 [1.03-1.12] for a 1-μg/m^3 increase) on asthma development, but these associations were not identified for $PM_{2.5}$ using both inverse distance weighted method and land use regression for exposure assessment. A cross-sectional investigation in Shanghai[26] showed a significant PM_{10}-asthma relation for first-year exposure rather than prenatal exposure. In addition, some research[34,37] linked no associations of childhood asthma with entire pregnancy's PM exposure, but found evidence for specific trimesters. Underlying reasons for the substantial discrepancy in estimated association of interest were complex, but could be in part attributed to between-study differences

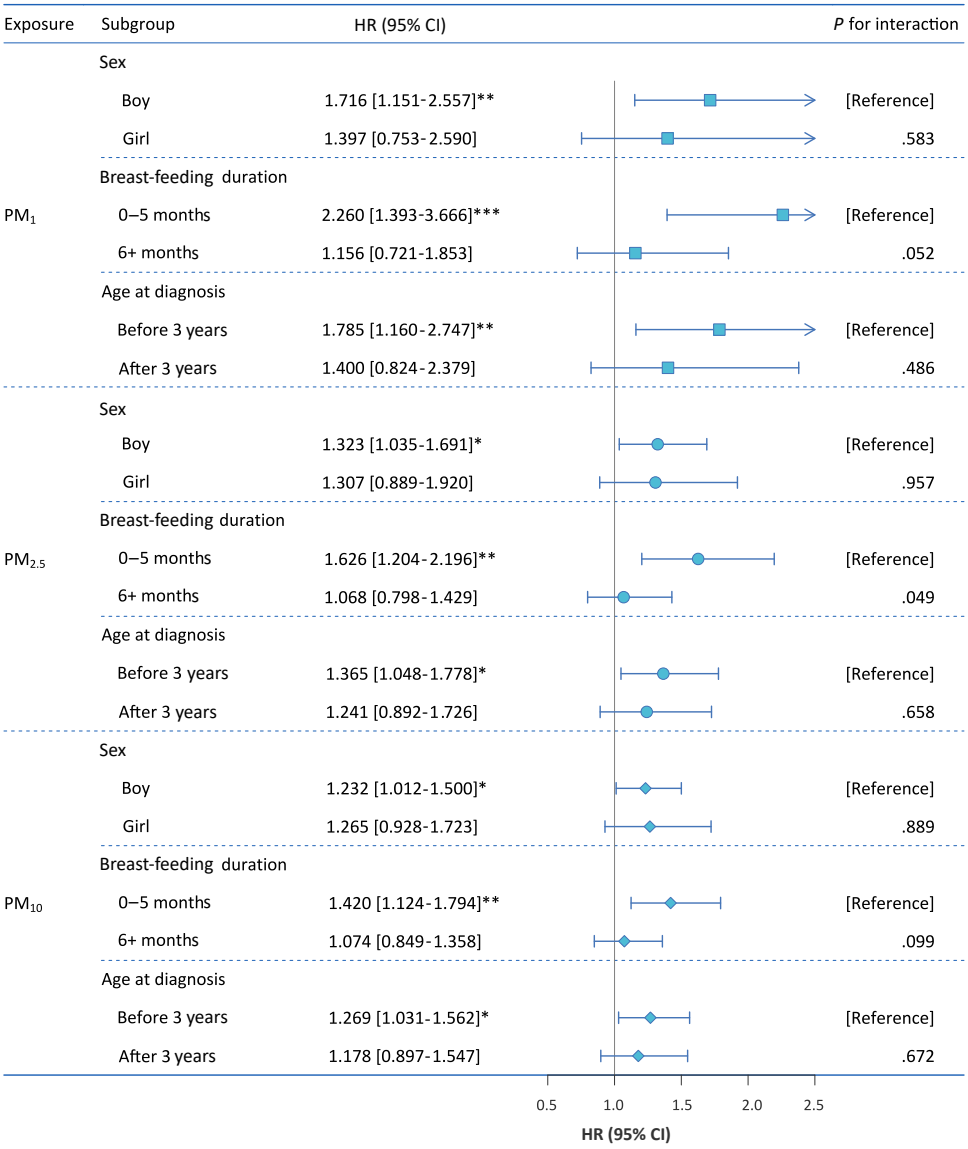

FIG 4. HRs (with 95% CIs) of asthma among subgroups stratified by child sex, breast-feeding duration, and age of incidence, associated with per 10-μg/m^3 increase in *in utero* exposure to PM_1, $PM_{2.5}$, and PM_{10}. **P* < .05; ***P* < .01; ****P* < .001.

including study designs, methods used for exposure assignment, population vulnerability, as well as asthma ascertainment. Environmental differences across study locations such as pollution levels and sources, PM components, urbanity, and greenness within cities may also relate to this discrepancy. Similar mixed findings were also elucidated for gaseous air pollutants such as NO_x and SO_2[26,36,47] when assessing air pollution-asthma associations. In this investigation, we observed a significant association of childhood asthma only with first-year PM_{10} exposure. This result could be possibly related to disparity in exposure concentrations between size-specific PMs. Relatively narrower ranges in PM_1 and $PM_{2.5}$ exposures (Table II) may have hampered the statistical power in detecting their associations with asthma to some extent.

For a 10-μg/m^3 rise in prenatal PM exposure, our time-to-event analysis associated an HR of 1.618 (1.159-2.258), 1.314 (1.070-1.614), and 1.236 (1.047-1.458) for childhood asthma with PM_1, $PM_{2.5}$, and PM_{10}, respectively, suggesting larger effects of smaller particles. Generally consistent results were seen in a large cross-sectional investigation investigating 59,754 Chinese children aged 2 to 17 years in 7 northeast cities.[50] Yang et al assessed the liaison between 4-year average air pollution and doctor-diagnosed asthma, and they found an odds ratio of 1.56 (1.46-1.66) and 1.50 (1.41-1.59) corresponding to a 10-μg/m^3 increase in PM_1 and $PM_{2.5}$. In addition to childhood or adolescent asthma, there are emerging epidemiologic evidence[14,21,51,52] showing more adverse cardiopulmonary effects associated with PM_1 in comparison with $PM_{2.5}$ and PM_{10}. In a case-crossover study,[52] for instance, short-term risks of hospital admission for respiratory diseases increased by 9% (4%-14%) and 6% (2%-10%) associated with per 10-μg/m^3 rise in exposure to PM_1 and $PM_{2.5}$, respectively. In terms of long-term assessment, the 33 Communities Chinese Health Study[14] demonstrated that PM_1 may play a greater role than $PM_{2.5}$ in associations with prevalence of

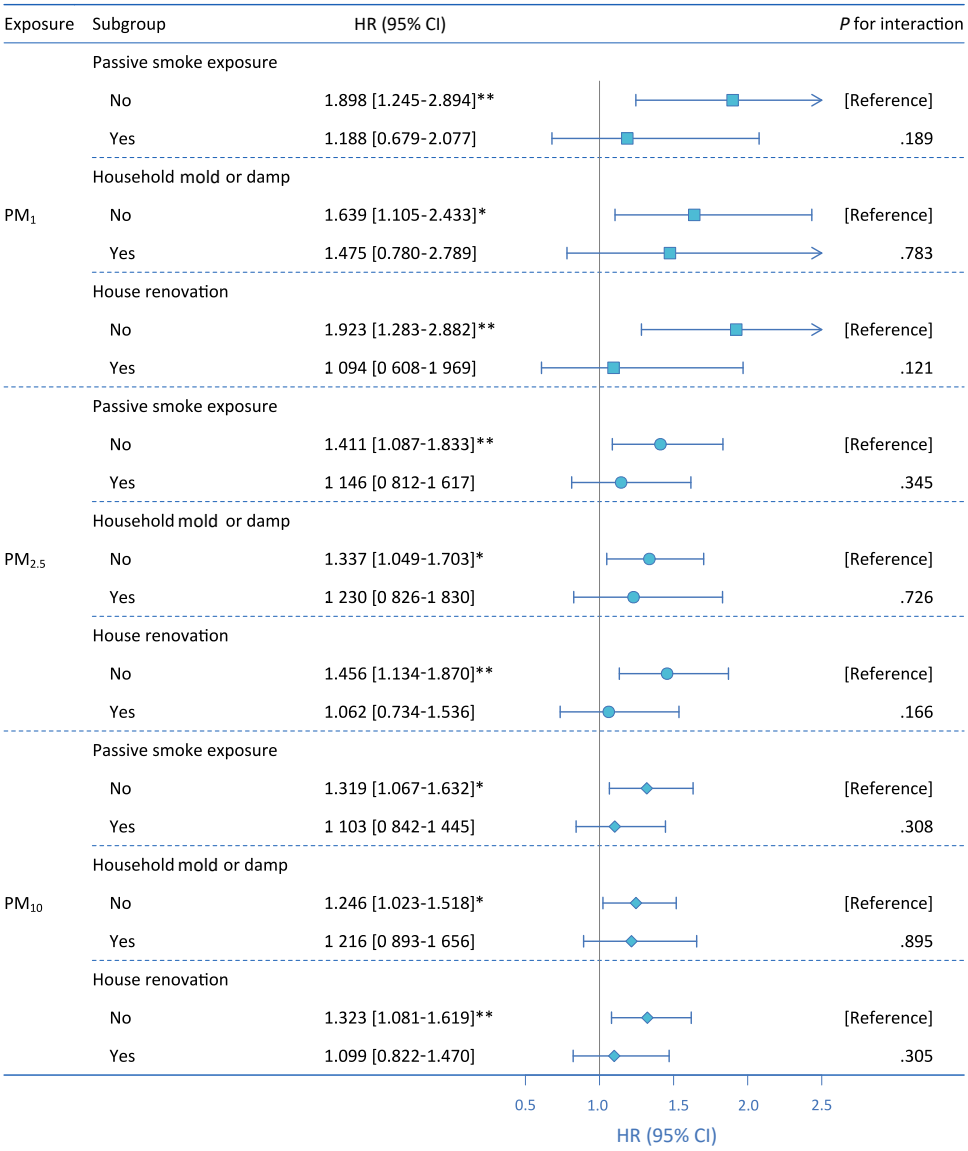

FIG 5. HRs (with 95% CIs) of asthma among subgroups stratified by housing environmental factors (ie, passive smoke exposure, household mold or damp, and house renovation), associated with per 10-μg/m^3 increase in *in utero* exposure to PM_1, $PM_{2.5}$, and PM_{10}. *P < .05; **P < .01; ***P < .001.

cardiovascular diseases, with an estimated risk of 1.12 (1.05-1.20) versus 1.06 (1.01-1.11) per 10-μg/m^3 increase. To date, very limited evidence has focused on health assessments of *in utero* PM_1 exposure as well as its constituents on offspring's early-life organ development.[53-57] Despite the fact that DNA methylation could be possibly one of underlying pathogenic pathways,[58-60] maternal PM_1-induced toxic effects on offspring's heart and lung development still remain largely unknown from the perspective of biological mechanisms. More laboratory and population-based studies are urgently warranted for better understanding of the adverse health effects caused by ambient submicrometric and ultrafine particulate exposure.

Only a few studies[7,34,49] have investigated the sensitive windows of childhood asthmatic symptoms in association with early-life air pollution exposure, while findings differed substantially. A large cohort study[37] investigated 160,641 singleton live births occurring in Toronto, and found significant associations of asthma with air pollutants including ultrafine particles, $PM_{2.5}$, and NO_2 only in the second trimester. A cross-sectional study of 2598 preschool children in China showed mixed results in sensitive trimesters,[34] but a Mexican birth cohort study[61] of 552 mother-child pairs identified an association between childhood wheeze and prenatal $PM_{2.5}$ exposure in the first trimester only. Our trimester-specific analyses showed much smaller effect estimates than the entire pregnancy, and did not identify clear vulnerable periods. By incorporating distributed lag modeling strategy, several researchers performed in-depth analysis of sensitive windows based on gestational weeks.[10,48,49] A Chinese birth cohort study[10] including 184,604 children in Taiwan found $PM_{2.5}$-asthma associations during gestational weeks 6 to 22, with the highest risk occurring at gestational week 12. Another US cohort study[48] in Boston included 736 full-term children and suggested a susceptible window of $PM_{2.5}$ exposure at 16 to 25 weeks' gestation associated with early childhood asthma development. Such

an inconsistency in vulnerability across gestational weeks was also observed in a number of investigations linking prenatal air pollution exposure and birth outcomes.[55,62-65] Future large-scale (eg, multicity and multicountry) investigations covering wider exposure ranges should focus on more sophisticated design and methods (eg, precise exposure assessments considering mother's and child's daily activities) to capture and better characterize the vulnerable exposure windows, which may guide the maternal preventive actions against air pollution and provide novel insights into underlying mechanisms.[48] Also, these efforts may greatly contribute to more comprehensive understandings by including additional large cohorts wherein childhood asthma is more prevalent.

Sex difference in air pollution epidemiology has aroused great research interest during past decades.[66] In this study, we observed more evident associations of prenatal PM exposure with childhood asthma in boys, whereas the risk intervals largely overlapped between sexes. Findings of effect modification by sex varied across studies,[10,36,48] and more investigations suggested stronger associations among boys[37,48,49] together with 2 providing contrary results.[9,36] Our retrospective analysis showed that *in utero* particulate pollution was more strongly associated with early development of asthma in childhood, with significantly increased risk occurring only in the first 3 years of life. This finding was generally consistent with a prospective birth cohort study in Poland[67] and a large Canadian nested case-control study,[68] and could be supported by a recent meta-analysis[7] including 9 studies, which yielded a pool risk of 1.15 (1.00-1.31) and 1.04 (1.00-1.09) for before and after age 3 years, respectively.

Breast-feeding has been identified as an important protective determinant for childhood respiratory health including asthma onset.[69-71] Assessments of combined effects of breast-feeding and environmental exposures have also prompted a growing epidemiological interest.[72] For instance, evidence suggested that breast-feeding may protect children from adverse effect of environmental tobacco exposure on acute respiratory illness,[73] lung function,[74] and respiratory diseases and symptoms.[75,76] Our study provided some suggestive clue of reduced asthma risk among children being ever longer breast-fed when exposed to ambient particulate pollution during the *in utero* period. Consistent findings were also illustrated in several multicity cross-sectional studies in China, indicating breast-feeding was associated with a lower risk of respiratory conditions including wheeze and asthma,[77-79] and lung function impairment[15] induced by particulate and gaseous air pollutants. Also, there is emerging AP-health evidence[72] reporting the potential modifying effects of breast-feeding on outcomes such as hypertension, mental development, and under-5 mortality. Underlying mechanisms for protective effects of breast-feeding on aforementioned adverse health effects induced by air pollution need more investigations, but could be possibly related to multifunctional breast milk nutrients and bioactive factors that may boost the immune system and reduce systemic inflammation and oxidative stress.[72]

Indoor and housing environment has been closely associated with respiratory diseases or symptoms (eg, asthma and wheezing) in children.[3,8] Consistent evidence suggested increased risks of childhood asthma triggered by prenatal exposures to environmental tobacco smoke, housing renovation, and dampness, whereas little was known regarding their complex interactions with ambient particulate exposure.[8,25] Our investigation in central China found significant associations only in children without aforementioned exposures. With respect to passive smoking exposure, for instance, a prospective birth cohort in the Netherlands[80] found increased risks of wheezing associated with traffic-related air pollutants (PM_{10} and NO_2) only among children who were exposed to both fetal and infant tobacco smoke, showing a significant synergistic effect (*P* values for interactions <.05). Nevertheless, a US panel study[81] reported a contrary finding regarding the direction of interaction, suggesting lower PM-associated risks of asthma in children exposed to higher tobacco smoke. Despite opposite interactions, these studies both implied the potential nonlinear dose-response relationship between asthma mediators and particulate exposures.[81] Owing to the complex and mixed exposures to indoor pollutants (eg, induced by housing renovation and passive smoking) and outdoor air pollution,[82] findings on their interplays are difficult to interpret and specific well-designed investigations are needed to reveal the potential mechanisms.

Our study has 2 major strengths over previous investigations. First, exposure assignments were based on high-resolution (1×1 km) space-time modeling estimates using a machine learning technique, which could better represent personal exposures than widely used spatial interpolation methods[26,35] (eg, ordinary Kriging and inverse distance weighted methods) through well incorporating spatiotemporal scales of satellite images, land use, and meteorological factors. Second, we are the first to assess the effects of prenatal exposure to submicron particulate pollution (ie, PM_1) on early childhood asthma and wheezing, and performed a comparative analysis of associations with larger particles ($PM_{2.5}$ and PM_{10}).

Several limitations should also be noted. First, outcomes of asthma and wheezing in this study were self-reported rather than physician-diagnosed or being ascertained by medical hospital records. Recall bias might exist with regard to the first-ever incidence of wheeze and asthma investigated through the International Study of Asthma and Allergies in Childhood questionnaire. Second, our time-to-event analyses for PM-wheeze associations may fail to fully exclude viral-induced transient wheeze, because first-ever wheeze was assessed retrospectively over previous years across all seasons. Third, we failed to include maternal age and body mass index for further modeling adjustments in the analysis due to data unavailability. Fourth, this is a single-city study and its results should be interpreted with caution when directly generalizing our results to other Chinese megacities, because PM pollution levels and its chemical components vary substantially by locations. In addition, findings from this study could not directly be generalized to other low-educated populations, because young mothers included in our survey have an elevated educational attainment.

Conclusions

This retrospective study added novel evidence for increased risk of childhood asthma onset associated with early-life exposures to submicron particulate pollution as well as $PM_{2.5}$ and PM_{10}. Comparative analyses highlighted stronger associations of ambient PM_1 than of larger particles with asthma development. PM-asthma associations could be possibly modified by breast-feeding, which indicated that longer breast-feeding may lower asthma risk in children exposed to particulate air pollutants. Our findings may help guide the prenatal preventive actions

against air pollution and have implications for further research on underlying mechanisms. Continued efforts of air cleaning action are urgently needed in China to reduce health burden of asthma in children associated with particulate air pollution.

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Key messages

- **Early-life submicron particulate exposure, particularly during pregnancy, was associated with an increased risk of childhood asthma.**
- **Longer breast-feeding may lower asthma risk in children exposed to particulate air pollutants.**

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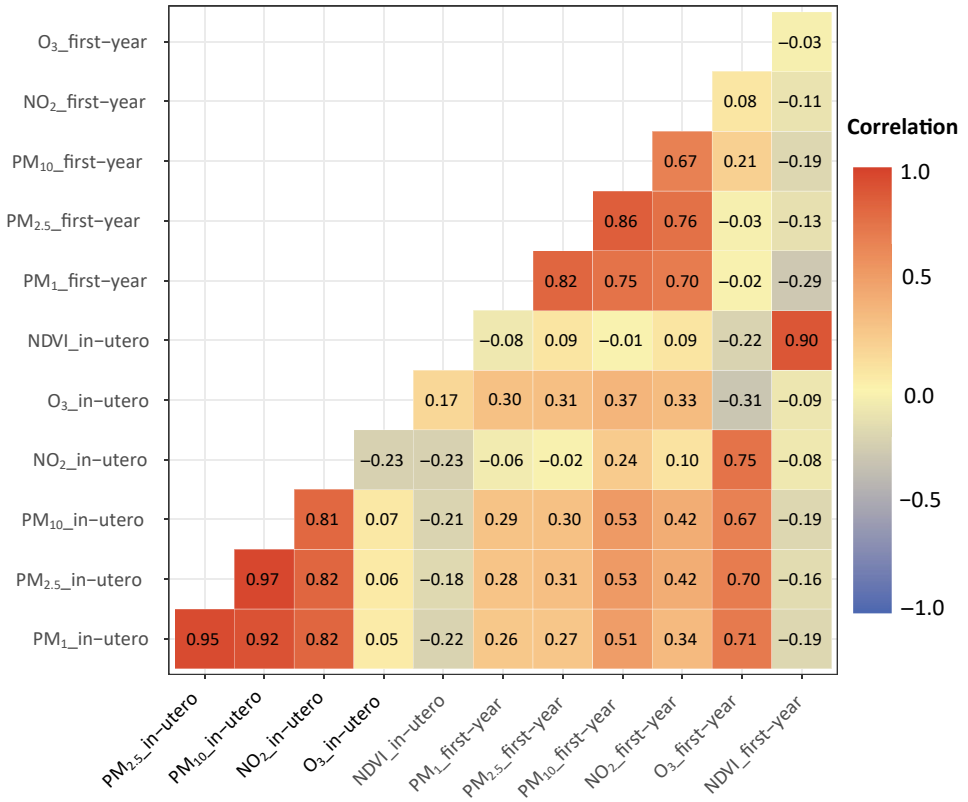

FIG E1. Pairwise Spearman correlation matrix between *in utero* and first-year exposures to ambient air pollutants and greeness.

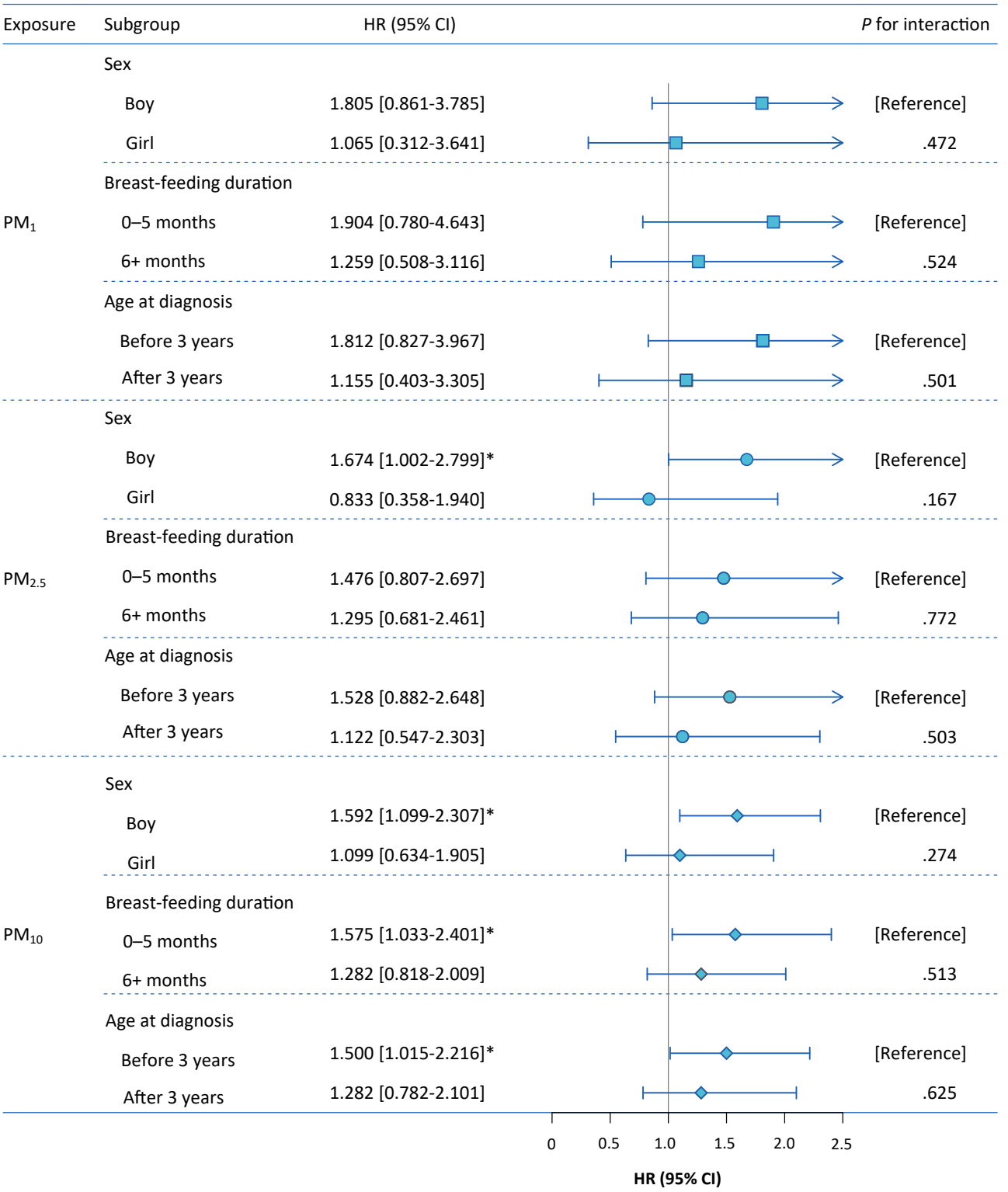

FIG E2. HRs (with 95% CIs) of asthma among subgroups stratified by child sex, breast-feeding duration, and age at diagnosis, associated with per 10-$\mu g/m^3$ increase in first-year exposure to PM_1, $PM_{2.5}$, and PM_{10}. *$P <$ .05.

TABLE E1. Summary distributions of trimester-specific particulate pollution concentrations

Air pollution concentration	Mean ± SD	Min	Percentiles			Max
			P_{25}	P_{50}	P_{75}	
Trimester 1 ($\mu g/m^3$)						
PM_1	43.7 ± 11.9	17.2	35.2	41.5	52.6	85.4
$PM_{2.5}$	67.9 ± 21.8	18.8	57.2	68.9	79.4	148.9
PM_{10}	120.9 ± 30.5	46.0	104.9	121.5	143.7	223.9
Trimester 2 ($\mu g/m^3$)						
PM_1	42.4 ± 9.7	19.0	35.8	41.5	48.9	70.3
$PM_{2.5}$	65.0 ± 15.9	23.2	57.4	65.8	75.5	110.4
PM_{10}	117.0 ± 22.5	54.2	104	119.6	130.9	223.9
Trimester 3 ($\mu g/m^3$)						
PM_1	39.5 ± 12.0	17.8	28.7	38.0	46.9	82.2
$PM_{2.5}$	59.5 ± 20.8	18.8	40.7	61.1	74.6	140.1
PM_{10}	110.6 ± 28.1	42.0	87.4	116.1	130.2	197.7

TABLE E2. Estimated HRs (95% CIs) of asthma and wheezing associated with per 10-$\mu g/m^3$ increase in trimester-specific PM exposures (PM_1, $PM_{2.5}$, and PM_{10})

	Asthma		Wheezing	
Exposures	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Trimester 1				
PM_1	1.283 (1.034-1.592)	.024	1.132 (0.997-1.286)	.056
$PM_{2.5}$	1.104 (0.981-1.242)	.100	1.025 (0.955-1.100)	.495
PM_{10}	1.039 (0.961-1.124)	.338	0.986 (0.942-1.032)	.556
Trimester 2				
PM_1	1.208 (0.971-1.501)	.089	0.936 (0.823-1.065)	.315
$PM_{2.5}$	1.108 (0.972-1.263)	.126	0.970 (0.897-1.050)	.457
PM_{10}	1.047 (0.959-1.143)	.305	1.010 (0.956-1.067)	.719
Trimester 3				
PM_1	1.225 (1.003-1.495)	.046	0.961 (0.851-1.085)	.520
$PM_{2.5}$	1.099 (0.985-1.225)	.090	0.994 (0.931-1.061)	.849
PM_{10}	1.068 (0.988-1.154)	.096	0.969 (0.926-1.014)	.173

TABLE E3. Estimated HRs (95% CIs) and *P* value for nonlinear trend of asthma and wheezing associated with *in utero* and first-year exposures to size-specific particulate pollutants

Particulate pollutants	Outcome	Exposure interval	HR (95% CI)	*P* for nonlinear trend*
In utero exposure				
PM_1	Asthma	10 $\mu g/m^3$	1.618 (1.159-2.258)	.618
$PM_{2.5}$	Asthma	10 $\mu g/m^3$	1.314 (1.070-1.614)	.531
PM_{10}	Asthma	10 $\mu g/m^3$	1.236 (1.047-1.458)	.922
PM_1	Wheezing	10 $\mu g/m^3$	1.020 (0.834-1.246)	.496
$PM_{2.5}$	Wheezing	10 $\mu g/m^3$	0.992 (0.876-1.124)	.784
PM_{10}	Wheezing	10 $\mu g/m^3$	0.962 (0.872-1.063)	.959
First-year exposure				
PM_1	Asthma	10 $\mu g/m^3$	1.543 (0.822-2.896)	.383
$PM_{2.5}$	Asthma	10 $\mu g/m^3$	1.358 (0.876-2.104)	.342
PM_{10}	Asthma	10 $\mu g/m^3$	1.409 (1.037-1.915)	.302
PM_1	Wheezing	10 $\mu g/m^3$	1.214 (0.831-1.771)	.455
$PM_{2.5}$	Wheezing	10 $\mu g/m^3$	1.148 (0.880-1.499)	.143
PM_{10}	Wheezing	10 $\mu g/m^3$	1.119 (0.935-1.338)	.087

*Estimated using likelihood ratio test.

TABLE E4. Sensitive analysis of HRs (95% CIs) for childhood asthma and wheezing stratified by breast-feeding durations of 0-3 and 3+ mo, associated with a 10-$\mu g/m^3$ increase in prenatal exposure to PM_1, $PM_{2.5}$, and PM_{10}

Exposures	Breast-feeding duration (mo)	Asthma			Wheezing		
		HR (95% CI)	*P* for association	*P* for interaction	HR (95% CI)	*P* for association	*P* for interaction
PM_1				.120			.117
	0-3	2.353 (1.318-4.201)	.004		1.250 (0.897-1.740)	.187	
	3+	1.337 (0.881-2.027)	.172		0.894 (0.693-1.155)	.391	
$PM_{2.5}$				.163			.119
	0-3	1.250 (1.011-1.544)	.039		1.106 (0.979-1.250)	.104	
	3+	1.041 (0.901-1.204)	.585		0.982 (0.900-1.071)	.681	
PM_{10}				.077			.002
	0-3	1.175 (1.014-1.362)	.032		1.133 (1.033-1.243)	.008	
	3+	0.995 (0.890-1.111)	.923		0.950 (0.888-1.016)	.136	

TABLE E5. Sensitive analysis of HRs (95% CIs) for childhood asthma and wheezing stratified by breast-feeding durations of 0-1, 1-6, and 6+ mo, associated with a 10-$\mu g/m^3$ increase in prenatal exposure to PM_1, $PM_{2.5}$, and PM_{10}

Prenatal exposures	Breast-feeding duration (mo)	Asthma		Wheezing	
		HR (95% CI)	*P* for association	HR (95% CI)	*P* for association
PM_1					
	<1	4.017 (1.699-9.494)	.002	1.327 (0.885-1.988)	.171
	1-6	1.953 (1.066-3.578)	.030	1.291 (0.868-1.919)	.207
	>6	1.156 (0.721-1.853)	.547	0.784 (0.587-1.046)	.098
$PM_{2.5}$					
	<1	1.446 (1.078-1.939)	.014	1.039 (0.893-1.210)	.617
	1-6	1.171 (0.939-1.460)	.161	1.228 (1.076-1.401)	.002
	>6	0.986 (0.835-1.165)	.872	0.913 (0.826-1.010)	.078
PM_{10}					
	<1	1.279 (1.077-1.519)	.005	1.159 (1.033-1.301)	.012
	1-6	1.062 (0.901-1.251)	.475	0.999 (0.901-1.108)	.991
	>6	0.967 (0.852-1.096)	.599	0.956 (0.885-1.033)	.258

TABLE E6. Sensitive analysis of HRs (95% CIs) for childhood asthma and wheezing stratified by breast-feeding durations of 0-1, 1-6, and 6+ mo, associated with a 10-$\mu g/m^3$ increase in postnatal exposure to PM_1, $PM_{2.5}$, and PM_{10}

		Asthma		Wheezing	
Postnatal exposures	**Breast-feeding duration**	**HR (95% CI)**	***P* for association**	**HR (95% CI)**	***P* for association**
PM_1					
	<1	3.922 (1.125-13.678)	.032	1.156 (0.529-2.527)	.715
	1-6	1.279 (0.374-4.376)	.694	1.800 (0.873-3.711)	.111
	>6	1.259 (0.508-3.116)	.619	0.907 (0.523-1.573)	.727
$PM_{2.5}$					
	<1	2.100 (0.874-5.049)	.097	1.071 (0.620-1.848)	.807
	1-6	1.435 (0.613-3.357)	.405	1.523 (0.932-2.490)	.093
	>6	1.295 (0.681-2.461)	.430	0.967 (0.651-1.435)	.866
PM_{10}					
	<1	2.232 (1.175-4.238)	.014	1.222 (0.852-1.755)	.276
	1-6	1.405 (0.779-2.531)	.258	1.340 (0.952-1.886)	.093
	>6	1.282 (0.818-2.009)	.278	0.937 (0.722-1.215)	.623

TABLE E7. Sensitive analysis of HRs (95% CIs) for childhood asthma associated with a 10-$\mu g/m^3$ increase in *in utero* exposure to PM_1, $PM_{2.5}$, and PM_{10}, by additionally adjusting for gaseous pollutants, NDVI, and first-year PM exposures

Particulate pollutants	Additional adjustment	HR (95% CI)	*P* for association	*P* for LR test
In utero PM_1	Main analysis	1.618 (1.159-2.258)	.005	Reference
	+ NO_2	1.611 (1.065-2.437)	.024	.973
	+ O_3	1.679 (1.164-2.424)	.006	.632
	+ NDVI	1.567 (1.118-2.196)	.009	.295
	+ First-year PM_1	1.598 (1.106-2.309)	.013	.878
In utero $PM_{2.5}$	Main analysis	1.314 (1.070-1.614)	.009	Reference
	+ NO_2	1.317 (0.997-1.739)	.053	.984
	+ O_3	1.350 (1.071-1.702)	.011	.620
	+ NDVI	1.292 (1.051-1.588)	.015	.225
	+ First-year $PM_{2.5}$	1.300 (1.035-1.634)	.024	.835
In utero PM_{10}	Main analysis	1.236 (1.047-1.458)	.012	Reference
	+ NO_2	1.233 (0.981-1.549)	.072	.978
	+ O_3	1.251 (1.043-1.500)	.016	.753
	+ NDVI	1.216 (1.030-1.436)	.021	.249
	+ First-year PM_{10}	1.183 (0.990-1.413)	.065	.174

LR, Likelihood ratio.

TABLE E8. Sensitive analysis of HRs (95% CIs) for childhood asthma associated with a 10-$\mu g/m^3$ increase in *in utero* and first-year exposures to PM_1, $PM_{2.5}$, and PM_{10}, by restricting analyses to Han-ethnicity and full-term (gestational age ≥37 wk) children only

Particulate pollutants	Analytic strategy	HR (95% CI)	*P* for association
In utero PM_1	Main analysis	1.618 (1.159-2.258)	.005
	Han-ethnicity children only	1.604 (1.145-2.246)	.006
	Full-term children only	1.636 (1.150-2.328)	.006
In utero $PM_{2.5}$	Main analysis	1.314 (1.070-1.614)	.009
	Han-ethnicity children only	1.323 (1.074-1.629)	.008
	Full-term children only	1.346 (1.082-1.675)	.008
In utero PM_{10}	Main analysis	1.236 (1.047-1.458)	.012
	Han-ethnicity children only	1.252 (1.058-1.482)	.009
	Full-term children only	1.282 (1.077-1.528)	.005
First-year PM_1	Main analysis	1.543 (0.822-2.896)	.177
	Han-ethnicity children only	1.497 (0.787-2.849)	.219
	Full-term children only	1.490 (0.759-2.923)	.247
First-year $PM_{2.5}$	Main analysis	1.358 (0.876-2.104)	.171
	Han-ethnicity children only	1.366 (0.875-2.131)	.170
	Full-term children only	1.323 (0.822-2.131)	.249
First-year PM_{10}	Main analysis	1.409 (1.037-1.915)	.028
	Han-ethnicity children only	1.404 (1.028-1.918)	.033
	Full-term children only	1.440 (1.036-2.001)	.030

TABLE E9. Secondary analysis of risk estimates (with 95% CIs) for childhood asthma and wheezing, associated with per 10-$\mu g/m^3$ increase in *in utero* and first-year exposures to PM_1, $PM_{2.5}$, and PM_{10}

	Asthma		Wheezing	
Exposures	**RR* (95% CI)**	***P* value**	**RR* (95% CI)**	***P* value**
Entire pregnancy				
PM_1	1.618 (1.164-2.248)	.004	1.159 (0.968-1.389)	.109
$PM_{2.5}$	1.315 (1.082-1.597)	.006	1.087 (0.973-1.215)	.139
PM_{10}	1.236 (1.055-1.447)	.009	1.027 (0.939-1.123)	.557
First year (0-1 y)				
PM_1	1.553 (0.873-2.760)	.134	1.281 (0.905-1.813)	.163
$PM_{2.5}$	1.362 (0.913-2.033)	.130	1.226 (0.966-1.555)	.094
PM_{10}	1.407 (1.087-1.822)	.009	1.170 (0.991-1.381)	.064

*RR (relative risk) was estimated using modified Poisson regression approach. All models adjusted for a list of covariates including (1) child's individual characteristics: the child's sex, ethnicity, vaginal delivery, birth year and season, gestational weeks, birth weight, and breast-feeding duration; (2) family or maternal characteristics: family history of atopy, maternal education attainment, maternal smoking status, and area-based income; and (3) residential environment: household renovation during the early lifetime, indoor passive smoke exposure, and residence-located area.

TABLE E10. Secondary analysis of risk estimates (with 95% CIs) for childhood asthma and wheezing, associated with per 10-$\mu g/m^3$ increase in trimester-specific exposures to PM_1, $PM_{2.5}$, and PM_{10}

	Asthma		Wheezing	
Exposures	**RR* (95% CI)**	***P* value**	**RR* (95% CI)**	***P* value**
Trimester 1				
PM_1	1.282 (1.031-1.594)	.026	1.131 (1.004-1.274)	.043
$PM_{2.5}$	1.105 (0.982-1.243)	.098	1.034 (0.966-1.106)	.338
PM_{10}	1.041 (0.954-1.135)	.368	0.985 (0.941-1.031)	.504
Trimester 2				
PM_1	1.208 (0.991-1.472)	.062	1.016 (0.903-1.144)	.789
$PM_{2.5}$	1.108 (0.991-1.239)	.071	1.014 (0.945-1.089)	.692
PM_{10}	1.046 (0.969-1.129)	.251	1.033 (0.982-1.086)	.206
Trimester 3				
PM_1	1.230 (1.014-1.494)	.036	1.027 (0.918-1.150)	.638
$PM_{2.5}$	1.100 (0.985-1.227)	.090	1.035 (0.971-1.103)	.296
PM_{10}	1.069 (0.992-1.151)	.080	0.998 (0.955-1.043)	.929

*RR (relative risk) was estimated using modified Poisson regression approach. All models adjusted for a list of covariates including (1) child's individual characteristics: the child's sex, ethnicity, vaginal delivery, birth year and season, gestational weeks, birth weight, and breast-feeding duration; (2) family or maternal characteristics: family history of atopy, maternal education attainment, maternal smoking status, and area-based income; and (3) residential environment: household renovation during the early life time, indoor passive smoke exposure, and residence-located area.