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Modification of Food Allergy on the Associations between Early Life Exposure to Size-Specific Particulate Matter and Childhood Allergic Rhinitis

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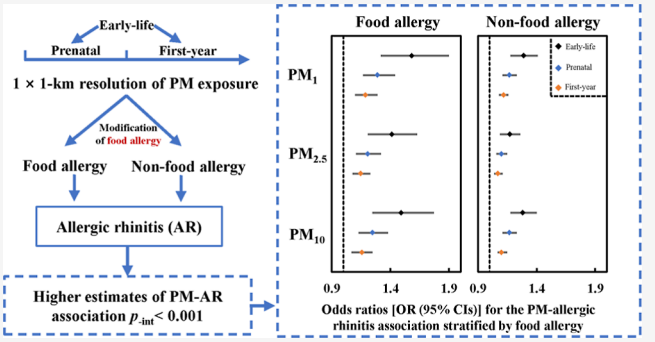
ABSTRACT: Previous studies have reported the association between particulate matter (PM) and childhood allergic rhinitis (AR). However, it is unclear whether food allergy (FA) modifies the PM−AR association. We aimed at evaluating the effect of the modification of FA on PM−AR association in preschool children. We adopted a cross-sectional study and conducted a questionnaire survey among preschool children aged 3−6 years in 7 cities in China from June 2019 to June 2020 to collect information on AR and FA. We used a combination of multilevel logistic regression and restricted cubic spline functions to quantitatively assess whether FA modifies the associations between size-specific PM exposure (1 × 1 km) and the risk of AR. The adjusted odds ratios (ORs) for AR among the children with FA as per a 10 $\mu g/m^3$ increase in early life PM_1, $PM_{2.5}$, and PM_{10} were significantly higher than the corresponding ORs among the children without FA [e.g., OR: 1.58, 95% CI: (1.32, 1.90) vs 1.29, 95% CI: (1.18, 1.41), per 10 $\mu g/m^3$ increase in PM_1]. The interactions between FA and size-specific PM exposure and their effects on AR were statistically significant (all p-int < 0.001). FA, as an important part of the allergic disease progression, may modify the PM−AR association in preschool children.



KEYWORDS: *PM_1, $PM_{2.5}$, modification, food allergy, allergic rhinitis*

1. INTRODUCTION

Allergic rhinitis (AR) is a type I hypersensitivity disease triggered by environmental allergens such as pollen (mainly outdoor origin) and animal allergens such as cockroaches and dust mites (mainly indoor origin).[1] The symptoms of AR can be largely identified by sneezing, nasal congestion, and itchy and runny nose.[2] As one of the most common chronic respiratory diseases in the world, AR usually persists throughout the entire life process. Epidemiological studies have shown that as many as 17−28.5% of adults in Western countries have been diagnosed with AR, and the prevalence of AR has increased worldwide.[3] A rising trend of AR in both adults and children in China has been observed in the past two decades.[4,5] The reason for the increased incidence of AR in the Chinese may be the rapid economic development and urbanization of developing Asian countries as well as the expanding tendency toward Western-style dietary patterns and lifestyles.[6]

As an ambient air pollutant that is harmful to human health and that causes a great global disease burden, particulate matter (PM) has attracted extensive attention from researchers all over the world.[7−9] Previous studies have shown that about 1.4 million deaths were associated with PM exposure in China in 2019.[10] Li et al. conducted a meta-analysis involving 35 studies carried out in 12 countries that showed significant associations of $PM_{2.5}$ (PM with an aerodynamic equivalent diameter ≤ 2.5 μm) and PM_{10} (PM with an aerodynamic equivalent diameter ≤ 10 μm) exposure with the increased risk of AR, which were more pronounced among children.[11] Monitoring and modeling data indicated that submicrometer PM (with an aerodynamic equivalent diameter ≤ 1 μm, PM_1) is a primary contributor to $PM_{2.5}$ concentration in China; the proportion of PM_1 even comes up to more than 80% in some cities.[12] To the best of our knowledge, only one epidemiological study investigated the risk of childhood AR in relation to long-term PM_1 exposure. Liu and colleagues observed a significant association between PM_1 exposure (4 years before

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follow-up) and increased risk of AR in children.[13] Exploration of the relationship between size-specific PM and childhood AR as well as possible prevention and treatment strategies are of great significance in reducing the burden of allergic respiratory diseases in children.

Previous epidemiological studies have confirmed that allergic diseases interact with each other. Hill et al. established a large population-based cohort study and reported that within 333,200 children and adolescents aged 0−17 years in the United States, food allergy (FA) was associated with development of asthma and rhinitis.[14] A family-based cohort study from Chicago showed that children with FA were at higher risk of allergic asthma compared with children without FA.[15] Furthermore, cross-sectional and longitudinal studies have suggested that allergic diseases occur following a time-based order: from atopic dermatitis and FA in infancy to gradual development into allergic asthma and AR in childhood, which is defined as "Atopic march".[16−18] Therefore, FA, as an important allergic disease that happens earlier, may make a critical difference in the progression of allergic diseases. The association between PM and AR may be influenced by FAs from the perspective of susceptibility to allergic diseases. Recent studies indicated that FA may modify the association between PM exposure and childhood AR through mechanisms such as skin barrier dysfunction.[19] Exposure to food and air allergens through impaired skin barrier may result in increased sensitivity to allergens and elevated cytokine levels, therefore potentially leading to a higher risk of AR.[20,21] As far as we know, no studies have examined the impact of FA on PM−AR associations in children.

In this study, we hypothesized that FA is a potential modifier for the association between PM exposure and risk of childhood AR. We aimed to evaluate the association between exposure to size-specific particles and the risk of AR in children with FAs and children without FA. We tested our hypothesis by comparing the difference in the strength of the association between the FA group and the non-FA group.

2. MATERIALS AND METHODS

2.1. Study Design and Population. As the second phase of the China, Children, Homes, Health (CCHH) study, we adopted a cross-sectional study and conducted a questionnaire survey among preschool children aged 3−6 years in seven cities (Wuhan, Changsha, Taiyuan, Nanjing, Shanghai, Chongqing, and Urumqi) in China from June 2019 to June 2020.[22] The reliability and validity of the standardized questionnaire we used have been validated in a previous pilot study.[23] Written informed consent was obtained from parents or legal guardians of children, and our study was approved by the Ethics Committee of the School of Public Health, Fudan University.

As for the selection of participants, we applied a multistage cluster sampling method, which has been detailed previously.[24,25] The caregivers of preschool children in Wuhan, Changsha, Taiyuan, Nanjing, and Shanghai filled out electronic questionnaires for data collection, while those in Chongqing and Urumqi used paper questionnaires. In this cross-sectional study, a total of 38,911 children participated in the survey, of whom 37,858 (response rate, 97.3%) caregivers successfully completed questions for childhood AR. We further restricted our study subjects by the following procedures. First, we ruled out 1971 (5.2%) children whose mothers conceived before January 1, 2013, and 412 (1.1%) children born at less than 28 weeks of gestation. Then, we excluded 2603 (5.4%) children for whom basic covariates were missing from the questionnaire. Finally, 4405 (11.8%) children whose residential addresses were outside the surveyed cities were excluded, leaving 28,467 (76.4%) children for formal data analysis.

2.2. Exposure Assessment for Size-Specific PM. We applied a mature machine-learning-based method—enhanced space-time extremely randomized tree model—to estimate the daily mean concentrations of atmospheric PM_1, $PM_{2.5}$, and PM_{10} in seven cities from January 2013 to December 2018 with a spatial resolution of 1 km. The importance of a 1 × 1 km resolution is shown as follows: (1) the spatial resolution of 1 km is more precise in exposure assessment, especially for pregnant women and children under 1 year old whose movement is relatively limited and the radius of movement is comparatively smaller than that of normal adults. Therefore, 1 km should be more suitable for the exposure assessment of our study population than a higher resolution. (2) Considering that our study cities are seven provincial capital cities with a high population density, a resolution of 1 km is very necessary. Especially in the densely populated main urban areas, the spatial resolution of 1 km can better distinguish the exposure level and reduce the possibility of exposure misclassification. The space-time extremely randomized trees model has been described in our previous studies in detail.[22] Cross-validation of our exposure data showed that the coefficient of determination (CV-R^2, for daily predicted estimates) was 0.83 for PM_1,[26] 0.92 for $PM_{2.5}$,[27] and 0.90 for PM_{10},[28] and the corresponding root-mean-square errors (RMSE) of ground measurements were 4.8, 5.1, and 11.1 $\mu g/m^3$, respectively. In situ determination of daily PM_1 from the China Atmosphere Watch Network and ground-based monitoring data of daily $PM_{2.5}$ and PM_{10} from the China Urban Air Quality Real-Time Publishing Platform from 2013 to 2018 were collected. The method of model development in this study has been described in detail in our previous studies.[26−29]

First, we extracted the daily mean concentrations of size-specific particles for each participant from 2013 to 2018 from the 1 × 1 km resolution gridded estimates based on the residential address of the participants. Then, daily estimated concentrations were used to calculate the average exposure in early life (from conception to the first year of life), prenatal (from conception to delivery), and the first year of life (from the first day after birth to the first-year birthday) by further utilizing information on children birth dates and their mothers' last menstrual date. In order to reduce exposure misclassification, we assigned prenatal and first-year exposure of PM based on the corresponding address information in each different period.

2.3. Respiratory Health Outcomes, FA, and Covariates. Information on lifetime-ever doctor-diagnosed AR and FA were obtained by using a standard questionnaire modified from the questionnaire of the International Study of Asthma and Allergies in Childhood. By asking "Has your child ever been diagnosed with allergic rhinitis by a doctor?" and "Has your child ever had allergic symptoms such as eczema, hives, diarrhea, swollen lips, or eyes caused by foods", a positive outcome variable is defined as a positive answer given to the above question.

Based on previous studies published by the CCHH study and some other relevant studies,[30,31] the following covariates were selected: (1) children characteristics, including child's sex (male or female), child's age at the time of visit, delivery mode

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Table 1. Demographic and Characteristics of Study Participants Stratified by FA[a]

characteristics	total (N = 28,467)	never FA (N = 24,708)	FA (N = 3759)	P-value
	Outcome			
AR	3586 (12.6%)	2691 (10.9%)	895 (23.8%)	<0.001
diagnosis age of AR, mean (SD), years	2.9 (1.0)	3.0 (1.0)	2.7 (1.1)	<0.001
Child's Sex				
boys	14,831 (52.1%)	12,744 (51.6%)	2087 (55.5%)	<0.001
girls	13,636 (47.9%)	11,864 (48.4%)	1672 (44.5%)	
child's age at the time of visit, mean (SD), years	4.9 (0.9)	4.9 (0.9)	4.8 (0.9)	<0.001
vaginal delivery	14,694 (51.6%)	12,685 (51.3%)	2009 (53.5%)	0.016
breastfeeding duration > 6 months	17,868 (62.8%)	15,516 (62.8%)	2336 (62.6%)	0.788
low birth weight	987 (3.5%)	880 (3.6%)	107 (2.9%)	0.018
ever usage of antibiotics	7514 (26.4%)	6799 (27.5%)	715 (19.0%)	<0.001
maternal educational level of university or above	21,592 (75.9%)	18,473 (74.8%)	3119 (83.0%)	<0.001
parental history of atopy	768 (2.7%)	596 (2.4%)	172 (4.6%)	<0.001
keeping pets	12,458 (43.8%)	10,736 (43.5%)	1722 (45.8%)	0.007
air pollution from solid fuel	263 (0.9%)	229 (0.9%)	34 (0.9%)	0.894
passive cigarette smoke exposure in early life[b]	7355 (29.6%)	6218 (29.6%)	1137 (33.9%)	<0.001
household dampness in early life[c]	4459 (13.4%)	3604 (18.1%)	855 (27.2%)	<0.001

[a]P-value for difference between participants with FA and without FA using χ^2 test. [b]Urumqi (n = 4139) did not collect information for this variable. [c]Urumqi (n = 4139) and Chongqing (n = 2200) did not collect information for this variable.

(Cesarean section or vaginal delivery), breastfeeding duration (less than 1 month, 1−6 months, 6−12 months, more than 12 months), low birth weight (yes or no), ever usage of antibiotics (yes or no), (2) characteristics of parents, including maternal education level (high school or less, college, post graduate and above), and parental history of atopy (yes or no), (3) household environmental characteristics, including keeping pets (yes or no), air pollution from solid fuels (yes or no), passive cigarette smoke exposure (yes or no), and household dampness (yes or no). In early life, prenatal, and first-year models, passive cigarette smoke exposure and household dampness corresponded to the situation of these variables in the corresponding period.

2.4. Statistical Analysis. Pearson's correlation was used to calculate the correlation of size-specific particle concentrations in different periods. First, multilevel (city and child) logistic regression analyses were conducted to assess the prevalence of AR by study population characteristics and the associations between size-specific particle exposure and childhood FA (effect modifier). As the results in Table S1 indicate, nonsignificant associations were observed between PM_1 and PM_{10} exposure and childhood FA. Therefore, the present study addressed the role of FA as an effect modifier rather than as a mediator since mediation analysis requires that the mediator should be associated with both exposure and outcome. In the process of formal data analyses, we applied a multilevel (city and child) logistic regression model in all populations to estimate the associations of early life (prenatal and first-year), prenatal, and first-year exposure to size-specific particles with the risk of childhood AR. Early life exposure to size-specific particles was regarded as the primary exposure, while prenatal and first-year exposure was considered as further stratification analyses. The interaction effect between FA and PM exposure was evaluated by inserting an interaction term, FA × PM concentration, into the models, and we further examined the associations between PM exposure and childhood AR stratified by FA. The crude model (seven cities included) was applied first, and the adjusted model (five cities included due to the missing information on passive cigarette smoke exposure and household dampness) with covariates (characteristics of children, parents, and household environment) was established subsequently. In both models, the study city was included as a random intercept. We further used the restricted cubic spline functions (five cities model) to analyze the exposure−response relationships between size-specific particles and childhood AR in early life, during pregnancy, and in the first year of life stratified by FA. Visual inspection and a likelihood ratio test were conducted to determine the linearity of the exposure−response curves of size-specific particles in each period. Epidemiological studies have shown that sex difference appeared in the association between PM exposure and the risk of AR in children.[32] We further conducted a sex-stratified analysis to assess the effect of sex differences on the association. Associations were reported as odds ratios (ORs) with 95% confidence intervals (CIs) as per 10 $\mu g/m^3$ increase in concentrations of size-specific particle.

All statistical analyses were performed using R software (version 4.2.2, R Project for Statistical Computing). Two-sided tests were conducted and a p value < 0.05 was considered statistically significant.

2.5. Sensitivity Analysis. Although pollen FA syndrome has similar symptoms to what is commonly thought of as FA, it is caused by prior sensitization to inhaled allergens (such as pollen) and cross-reactivity (Class II food allergens) and often manifests as allergy to vegetables and fruits (components in some vegetables and fruits that are structurally similar to pollen).[33] Thus, pollen FA syndrome is not the same as FA caused by Class I food allergens, in which the sensitization occurs through the gastrointestinal tract from a protein resistant to digestion.[33] Therefore, we first performed sensitivity analyses excluding children with vegetable and fruit allergy (n = 726) from all children with FA (n = 3759). In addition, in order to exclude the influence of other allergic diseases on the results of our study, we further added asthma and eczema as covariates for the adjustment in the models. Finally, we further removed passive cigarette smoke exposure and household dampness from the model and included data from seven cities for the sensitivity analysis.

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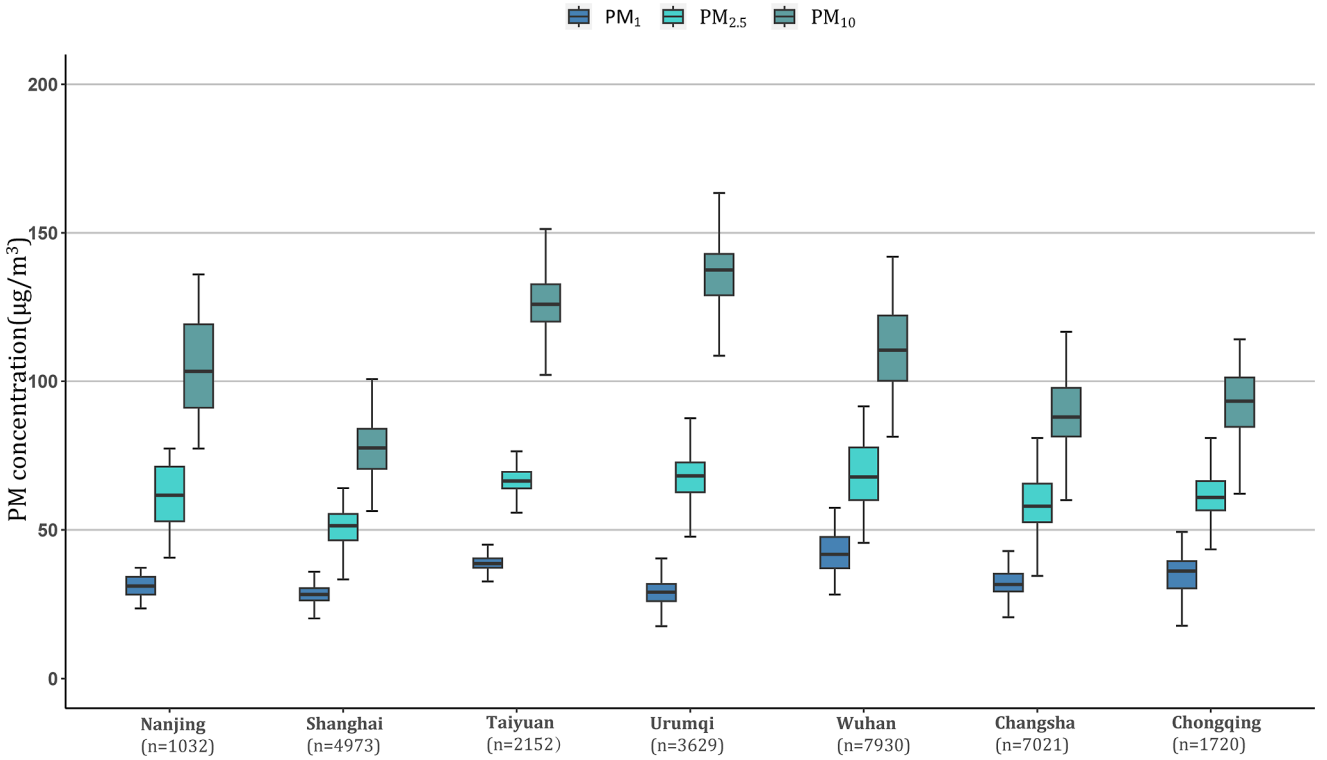

Figure 1. Early life exposure to size-specific PM by city. The horizontal line inside the boxes indicates the median PM concentration, the lower and upper ends of the boxes the lower and upper quartiles of PM concentration, and the whiskers the minimum and maximum PM concentration; subscripted numerals denote the maximum aerodynamic equivalent diameter of PM in micrometers.

3. RESULTS

3.1. Characteristics of Participants and Prevalence of AR by Study Population Characteristics. Table 1 shows the distribution of the basic characteristics and outcomes of the study population stratified by FA. Of the 28,467 children [mean (SD) age at the time of visit, 4.9 (0.9) years] included, 14,831 (52.9%) were boys and 3586 (12.6%) were diagnosed with AR, with the average diagnosis age being 2.9 (1.0) years. Among all children, 14,694 (51.6%) were delivered vaginally, 17,868 (62.8%) were breastfed for over 6 months, 987 (3.5%) had low birth weight, and 7514 (26.4%) had used antibiotics. The majority of children (21,592, 75.9%) had a mother with an educational level of university or above, while only 768 (2.7%) children had parents with a history of atopy. As for household environment, 12,458 (43.8%) families had pets, 263 (0.9%) children had exposure to air pollution from solid fuel, 7355 (29.6%) children had passive cigarette smoke exposure in early life, and 4459 (13.4%) children's houses had visible mold or dampness in early life. In the total population, 3759 (13.2%) children had FA, and the prevalence of AR in children with FA (23.8%) was significantly higher than in children without FA (10.9%) ($p < 0.001$). The prevalence of AR by study population characteristics is presented in Table S2. Older subjects and males showed a higher rate of childhood AR. The prevalence of childhood AR was also higher in subjects with shorter breastfeeding duration, ever usage of antibiotics, higher maternal education level, parental history of atopy, passive smoking exposure, and exposure to household dampness.

3.2. Concentrations and Correlations of PM in Different Periods. As shown in Table S3, the mean concentrations (SD) of PM_1, $PM_{2.5}$, and PM_{10} in early life were 33.6 (7.2) $\mu g/m^3$, 62.4 (10.2) $\mu g/m^3$, and 104.1 (22.1) $\mu g/m^3$, respectively. Average exposure levels of PM_1, $PM_{2.5}$, and PM_{10} during pregnancy and in the first year of life were generally consistent with the exposure in early life. The concentrations of size-specific particles during pregnancy were slightly higher than those in the first year of life. The concentrations of size-specific particles in the same period were significantly correlated, such as PM_1 and $PM_{2.5}$, as well as $PM_{2.5}$ and PM_{10} were highly correlated (Pearson's correlation coefficient ranging from 0.77 to 0.86). Moreover, the concentrations of particles of the same size in the different periods (early life, prenatal, and first-year) were also highly corelated (Pearson's correlation coefficient ranging from 0.64 to 0.97).

3.3. Early Life PM_1, $PM_{2.5}$, and PM_{10} Exposure in Different Cities. Figure 1 and Table S4 present the concentrations of PM_1, $PM_{2.5}$, and PM_{10} in early life in seven cities. Wuhan had the highest mean concentrations (SD) of PM_1 [42.3 (6.0) $\mu g/m^3$] and $PM_{2.5}$ [68.8 (9.8) $\mu g/m^3$]. However, the mean concentrations (SD) of $PM_{2.5}$ [50.8 (5.2) $\mu g/m^3$] and PM_{10} [77.5 (7.6) $\mu g/m^3$] in Shanghai were the lowest, also with a relatively lower mean concentration (SD) of 28.8 (4.3) $\mu g/m^3$ for PM_1. Urumqi had the highest mean PM_{10} concentration (SD) of 135.0 (12.2) $\mu g/m^3$, whereas it had the lowest mean PM_1 concentration (SD) of 28.0 (3.3) $\mu g/m^3$.

3.4. Exposure to Size-Specific Particles in Relation to Childhood AR Stratified by FA. In the whole population, early life exposure to PM_1, $PM_{2.5}$, and PM_{10} was significantly associated with increased risk of childhood AR (OR = 1.38, 95% CI: 1.27, 1.49; OR = 1.21, 95% CI: 1.15, 1.26; and OR = 1.14, 95% CI: 1.11, 1.18, per 10 $\mu g/m^3$ increase in PM_1, $PM_{2.5}$, and PM_{10}, respectively). Similar results were observed for the prenatal and first-year size-specific PM exposures (Table S5).

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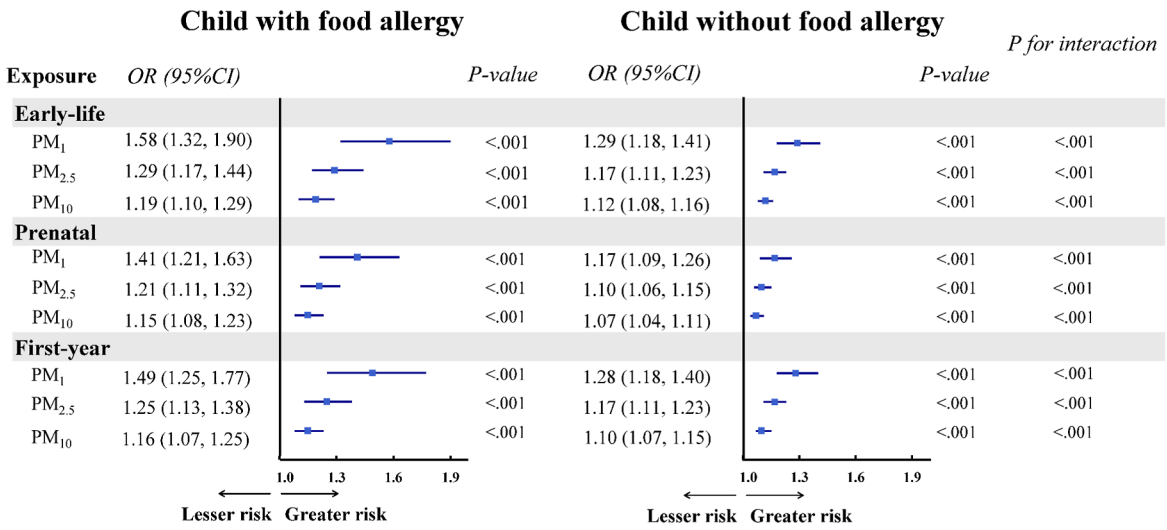

Figure 2. Associations between size-specific PM with childhood AR in early life, during pregnancy, and in first year of life stratified by FA (five cities model). Abbreviations: CI, confidence interval OR, odds ratio. Odds Ratios (95% CI) were estimated for each 10 $\mu g/m^3$ increase in size-specific PM exposure. Models were adjusted for child's sex, child's age at the time of visit, delivery mode, low birth weight, breastfeeding duration, ever usage of antibiotics, maternal education level, parental history of atopy, keeping pets, air pollution from solid fuel, passive cigarette smoke exposure, and household dampness.

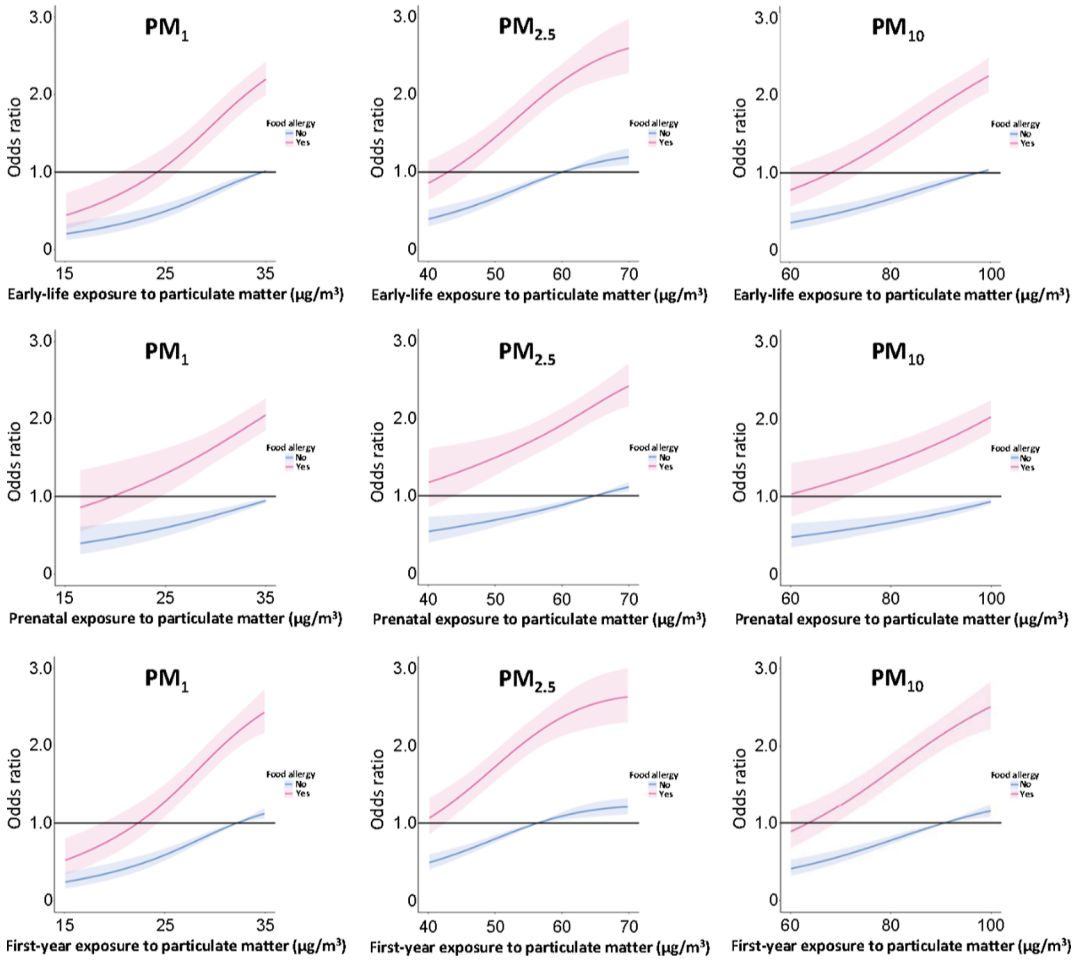

Figure 3. Exposure−response relationships of size-specific PM with childhood AR in early life, during pregnancy, and in the first year of life stratified by FA (five cities model). Models were adjusted for child's sex, child's age at the time of visit, delivery mode, low birth weight, breastfeeding duration, ever usage of antibiotics, maternal education level, parental history of atopy, keeping pets, air pollution from solid fuel, passive cigarette smoke exposure, and household dampness.

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In the adjusted model, the ORs for size-specific PM and childhood AR among the children with FA were significantly higher than the corresponding ORs among the children without FA [e.g., OR: 1.58, 95% CI: (1.32, 1.90) vs 1.29, 95% CI: (1.18, 1.41), for per 10 $\mu g/m^3$ increase in PM_1]. Similar patterns were also observed for both prenatal and first-year size-specific PM exposure (Figure 2). The interactions between FA and size-specific PM exposure and the effect on childhood AR were statistically significant (all p-int < 0.001). The statistically significant interaction suggested that FA may be a potential modifier for the association between size-specific PM exposure and childhood AR.

3.5. Exposure−Response Relationships between Size-specific Particle Exposure and Childhood AR Stratified by FA. Figure 3 shows the exposure−response relationships of exposure to size-specific particles in different periods (early life, prenatal, and first year) with childhood AR, stratified by FA. Consistent with the results of the logistic regression model (Figure 2), the risk of childhood AR shows a significant upward trend with size-specific PM exposure. Moreover, the risk of AR in children with FA is higher than in children without FA.

3.6. Exposure to Size-Specific Particles in Relation to Childhood AR Stratified by Sex and FA. Table S6 shows the association between PM exposure and the risk of AR in children after stratification by sex and FA. Adjusted OR values for associations between size-specific particles and childhood AR in boys ranged from 1.08 (95% CI: 1.03, 1.13, per 10 $\mu g/m^3$ increase in PM_{10}) to 1.72 (95% CI: 1.36, 2.18, per 10 $\mu g/m^3$ increase in PM_1). However, the distribution of adjusted OR for girls ranged from 1.07 (95% CI: 1.02, 1.12, per 10 $\mu g/m^3$ increase for PM_{10}) to 1.41 (95% CI: 1.08, 1.85, per 10 $\mu g/m^3$ increase in PM_1), which indicated that the OR values of boys are generally higher than those of girls. Moreover, the difference value in OR between the FA group and the non-FA group was larger in boys than in girls. Similar results were observed during pregnancy and the first year of life.

3.7. Sensitivity Analyses. Similar results were observed after excluding children with vegetable and fruit allergy (n = 726) from all children with FA (n = 3759) in all above-mentioned associations (Table S7). In all models, the results were comparable to the original results when other allergic diseases [asthma (n = 1021) and eczema (n = 5639)] were added to the model as covariates (Table S8). The results in the seven cities model, which exclude passive cigarette smoke exposure and household dampness were unchanged (Table S9). The results in Table S9 indicate that the PM−AR association stratified by FA would not be influenced by the inclusion of passive cigarette smoke exposure and household dampness.

4. DISCUSSIONS

To our knowledge, this study is the first to explore the potential modification effect of FA on the associations of size-specific particle exposure with childhood AR. Among all children, size-specific PM exposure was associated with an increased risk of childhood AR. Moreover, the associations were stronger in children with a history of FA than in children without a history of FA, which demonstrated that FA, as an important part of the allergic disease progression, may enhance the associations between ambient PM exposure and the risk of childhood AR.

Our study found that the prevalence of AR was different among subjects with different population characteristics. For example, maternal education level and parental history of atopy were positively associated with the risk of childhood AR, which are similar to the results of a large sample size cross-sectional study in Taiwan, China, conducted by Lee et al.[34] We observed that the child's age at the time of visit and the ever usage of antibiotics were potential predictive factors for childhood AR, with older subjects and subjects who had ever usage of antibiotics in relation to the higher risk of childhood AR. Chung et al. established a cohort study in preschool children in Taiwan, China, and suggested that the incidence of AR increased with age, which is comparable to the findings in the present study.[35] A cohort study that included 792,130 children indicated that the use of antibiotics is associated with subsequent development of allergic disease.[36] As for household environment, similar to the results of the present study, Wang et al. and Kim et al. found that being exposed to dampness or mold and passive smoke at home was associated with higher risk of childhood AR.[37,38]

With the increasing level of urbanization and industrialization, the concentration of PM in China is at a relatively high level in the world. The annual average concentration of $PM_{2.5}$ in cities at the prefecture level and above in China was 33 $\mu g/m^3$ in 2020, still far from the annual average target of 5 $\mu g/m^3$ set by the new global air quality guidelines issued by the World Health Organization in 2021.[39] The PM concentrations in our seven study cities are very typical and representative, so our findings may be generalized to cities and regions with similar PM exposure concentrations in China and around the world.

Our results suggested that early life $PM_{2.5}$ and PM_{10} exposures were associated with increased risk of childhood AR. Similarly, a recent meta-analysis involving 35 studies and indicated that the risk of childhood AR increased by 12% for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ (OR = 1.12, 95% CI: 1.05, 1.20) exposure and by 13% for each 10 $\mu g/m^3$ increase in PM_{10} (OR = 1.13, 95% CI: 1.04, 1.22) exposure.[11] In addition, a meta-analysis of 21 observational studies from 8 countries showed that higher levels of $PM_{2.5}$ and PM_{10} exposure were associated with increased risk of childhood AR.[40] In addition, Lin et al. found that the estimated odds ratio of $PM_{2.5}$ exposure (OR = 1.09, 95% CI: 1.01, 1.17, per 10 $\mu g/m^3$ increase) to the risk of childhood AR was also close to that of PM_{10} (OR = 1.06, 95% CI: 1.02, 1.11, per 10 $\mu g/m^3$ increase). We found that estimates of the associations between smaller-size particle (such as $PM_{2.5}$, OR = 1.21, 95% CI: 1.15, 1.26, per 10 $\mu g/m^3$ increase in early life) and childhood AR were stronger than for larger particles (such as PM_{10}, OR = 1.14, 95% CI: 1.11, 1.18, per 10 $\mu g/m^3$ increase in early life). As for PM_1, we also observed that higher levels of PM_1 exposure were associated with an elevated risk of childhood AR in all children. To date, only one epidemiological study has reported the association between PM_1 exposure and the risk of childhood AR,[13] which may be due to the fact that PM_1 is not routinely monitored globally. Liu et al. concluded that PM_1 exposure during four years before follow-up was positively associated with the risk of AR in children and adolescents aged from 2 to 17 years, and the estimate of OR is higher in smaller-size particles (such as PM_1), which is consistent with our findings in the present study.[13] Emerging evidence indicated that the smaller the particle size of PM, the greater its respiratory toxicity.[41] The underlying mechanism may indicate that PM_1 has a larger active surface area compared to the larger-size PM (such as

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$PM_{2.5}$ and PM_{10}) and can attach more toxic substances,[42] which may cause greater damage to respiratory health.

As an allergic disease, FA plays a key role in the progression course of allergic diseases.[43] Compared with the first wave of allergy epidemics (including asthma, AR, and eczema) which increased notably since the 1980s, FA is described as the "second wave" of allergic disease.[44,45] Studies have shown that allergic diseases occur in a chronological order, usually with allergic dermatitis or FA in infancy as the first stage and then gradually developing into AR or allergic asthma in childhood, which is known as the "Atopic march".[16−18] A large number of cohort studies supported the standpoint that children who develop FA or allergic dermatitis in infancy are more likely to develop other allergic diseases such as AR or asthma later in life or earlier than children who do not.[46−49] Our findings suggested that FA may enhance the association between size-specific PM exposure and the risk of childhood AR. The results of the present study suggested that the changes in the immune system of children after suffering from FA or other allergic diseases may lead to increased susceptibility to exogenous pollutants and thus make them more susceptible to other allergic diseases, leading to further development of the progression of allergic diseases.

The biological mechanisms by which FA modifies the associations between size-specific PM exposure and childhood AR are still unclear, with skin barrier dysfunction, microbiome changes, and epigenetic factors as possible underlying causes.[19,50] Among the above-mentioned mechanisms, skin barrier dysfunction is the most extensively studied, which assumes that when allergens, including food and air allergens, enter the skin through the impaired skin barrier, skin epithelial cells were then stimulated to release thymic stromal lymphopoietin (TSLP), interleukin 25 (IL-25), and interleukin 33 (IL-33), which activated the secretion of cytokines by immune cells in the dermis (e.g., eosinophils, basophils, type 2 innate lymphocyte, and mast cells).[20,21] Subsequently, Th2 cells were generated and IgE were produced in the local lymph nodes.[20,21] Th2 cells and IgE can further act on type 2 innate lymphocytes and eosinophils as well as mast cells and basophils, respectively, and this positive feedback leads to the development of allergic dermatitis.[20,21] When re-exposed to allergens, IgE, TLSP, IL-25, and other cytokines may enter the digestive and respiratory tracts through blood circulation, thus further promoting the occurrence of FA, AR, and other allergic diseases.[20,21] Therefore, when children suffered from allergic diseases such as FA or allergic dermatitis in infancy, the levels of cytokines such as IL and TSLP in the body were elevated; the sensitivity to external allergens were then increased, which may lead to the greater risk of AR under the same PM exposure level. We also explain the possible mechanism of FA modifying the association of prenatal PM exposure with AR. In utero exposure to food allergens and environmental/inhaled allergens (e.g., PM) may affect offspring development through epigenetic mechanisms, such as changes in DNA methylation levels in umbilical cord blood. Studies have found that these methylation sites in cord blood can still exist in midchildhood children and may play a vital role in the occurrence and development of allergic diseases.[51]

Our results suggested that the effect of FA as a modifier on the association between PM exposure and the risk of AR in children is more pronounced in boys than in girls; that is, boys with FA are at greater risk of AR at the same level of PM exposure. The biological mechanism to explain this sex difference is still not settled, probably because the average size of the airway of boys is smaller than that of girls in infancy,[52,53] which makes boys more susceptible to allergic inflammation.[54] As a result, boys may be more sensitive to PM exposure, which is more likely to lead to the occurrence and progression of allergic diseases.

The present study has the following advantages. First, this is the first study to use a combination of multilevel logistic regression and restricted cubic spline functions to quantitatively assess whether FA modifies the associations between size-specific PM exposure and the risk of childhood AR. Second, a mature machine-learning-based method—enhanced space-time extremely randomized tree model—was applied for the estimation of size-specific PM exposure at a high-resolution (1×1 km), while the exposure levels were assigned according to the participants' corresponding addresses at different time periods, all of which improved the accuracy of our exposure assessment. Moreover, we included approximately 30,000 children from seven cities located in coastal to inland China, and three categories of covariates including characteristics of children, parents, and household environment were added to the adjusted models. Finally, with important public health significance, we considered a preoccurring allergic disease (FA) as an effect-modifying factor to evaluate the impact of early life PM exposure on a subsequent allergic disease (AR), which may identify susceptible people earlier and provide better strategies for disease prevention.

Our study has some limitations. First, we established a cross-sectional study and were unable to determine a causal relationship between size-specific PM exposure and the risk of a childhood allergic disease. Moreover, although we asked whether children had doctor-diagnosed AR and obtained the age at which doctor-diagnosed AR was found in our questionnaire, the diagnosis of the AR was obtained according to the questionnaire completed by the caregivers of children, which was not verified by doctors through professional diagnosis, so the outcome variable of our study may be affected by recall bias. Besides, we asked about typical symptoms of FAs, including eczema, hives, diarrhea, and swollen lips or eyes caused by foods. However, since food intolerance shares symptoms with FA, such as diarrhea, we were unable to distinguish between FA and food intolerance entirely based on our questionnaire, which may potentially bias the results. Finally, although we adjusted for the maternal education level in our models, we were unable to include household income, a highly representative socioeconomic indicator of the population, as a confounder in the model for analyses.

The findings of our study may provide a scientific basis for the prevention of AR and contribute to the reduction of the disease burden of AR. Children are known to be susceptible to exposure to air pollutants. By further refining the identification of the more susceptible ones, those with FAs, in children, it may be possible to protect their respiratory health through earlier adoption of protective measures. For children already with FAs, PM exposure can be reduced by using personal protection devices (particulate respirator), minimizing outdoor activities during times of high air pollution, and maintaining a clean indoor environment (avoiding passive smoking and preventing indoor dampness and mold growth). By following the above-mentioned potential solutions, children who are already with FAs may be protected from further progression of allergic diseases caused by higher levels of PM exposure. From

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the perspective of government policy, as the concentration of air pollutants in China remains relatively high compared to that in developed countries, it is imperative for government authorities to take further steps in energy conservation and emission reduction. These actions will strengthen the achievements in air quality management and help us meet the air quality guidelines set by the World Health Organization as soon as possible, which can be applied to other countries and regions with PM exposure levels similar to those in China. Our all-out endeavor will not only protect the respiratory health of Chinese children but also have important implications for the improvement of global air quality.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.3c05532.

Odds ratios [OR (95% CIs)] for the associations of early life, prenatal, and first-year exposure to size-specific particles with FA in the whole population; prevalence of AR by study population characteristics; distributions of PM concentrations in early life, during pregnancy, and in the first year of life; distributions of PM concentrations in early life, during pregnancy, and in the first year of life by city; odds ratio for associations of size-specific particle exposure with AR in the whole population; associations between size-specific PM and childhood AR in early life, during pregnancy, and in first year of life stratified by sex and FA; adjusted odds ratios [OR (95% CIs)] for the associations of early life, prenatal, and first-year exposure to size-specific particles with AR stratified by FA after excluding children with vegetable and fruit allergy (n = 726) from all children with FA (n = 3759); adjusted odds ratios [OR (95% CIs)] for the associations of early life, prenatal, and first-year exposure to size-specific particles with AR stratified by FA after additionally being adjusted for other allergic diseases [asthma (n = 1021) and eczema (n = 5639)]; adjusted odds ratios [OR (95% CIs)] for the associations of early life, prenatal, and first-year exposure to size-specific particles with AR stratified by FA in seven cities; and Pearson's correlation coefficients between pairs of size-specific PM in different time periods (PDF)

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Chuansha Wu and Haoran Tang contributed equally to this work. Chuansha Wu performed the conceptualization, writing—original draft, and writing—review and editing; Haoran Tang carried out the formal analysis, visualization, validation, writing—original draft, and writing—review and editing; Wei Jing and Hao Chen achieved the methodology; Zhuohui Zhao executed the supervision, data curation, and investigation; Dan Norbäck performed the supervision; Xin Zhang, Chan Lu, Wei Yu, Tingting Wang, and Xiaohong Zheng carried out the data curation and investigation; Rui Li performed the data curation; Yunquan Zhang accomplished the methodology and data curation; Ling Zhang participated in the funding acquisition, project administration, resource procurement, supervision, data curation, and investigation.

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Notes

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