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Association of multiple environmental exposures with rhinitis and asthma symptoms in preschool children: Identifying critical risk factor

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ABSTRACT

Background: The concept "one airway, one disease" for childhood rhinitis and asthma has been challenged in recent years. This study aimed to evaluate associations of environmental exposures with alone and co-morbid symptoms of rhinitis and asthma and identify critical risk factor.
Methods: 5828 children aged 3–6 years in Shanghai were surveyed in 2019. Rhinitis and wheezing symptoms in the past 12 months were collected using questionnaire. 11 outdoor environment exposure factors were assessed by high-resolution spatial-temporal model based on residences. Logistic regression and random forest were applied to evaluate and rank the association of environmental exposure with rhinitis and wheezing symptoms.
Results: The proportions of children with rhinitis alone, wheezing & rhinitis, and wheezing alone were 37.2 %, 4.6 %, and 2.6 %, respectively. Regression modeling of two exposure factors adjusted for each other showed that PM_1, $PM_{2.5}$ and nighttime light(NTL) remained the robust significant associations with rhinitis alone, whereas NO_2 had the robust significant association with wheezing & rhinitis and wheezing alone. Random forest ranking analysis further corroborated the most significant environmental exposure for rhinitis alone was PM_1, and for wheezing symptoms (both wheezing & rhinitis and wheezing alone) was NO_2. Significant additive and multiplicative interactions were examined between indoor dampness and PM_1 exposure on rhinitis alone.
Conclusion: Children's current rhinitis alone was more susceptible to ambient PM_1 and $PM_{2.5}$, while asthmatic wheezing symptom, either with or without rhinitis, was more susceptible to NO_2. Co-exposure to indoor dampness and PM_1 exposure had synergistic effects on rhinitis alone.

1. Introduction

Asthma and allergic rhinitis (AR) are two most common respiratory diseases in children (Papi et al., 2018). In clinics, they may appear as rhinitis alone, asthma alone or concomitant diseases. In recent years, the viewpoint of considering rhinitis and asthma as "one airway, one disease" has been challenged in clinical observations, treatment response, mechanistic studies and epidemiology, (Bousquet et al., 2023). Regarding the exploration of mechanisms, a comprehensive transcriptome analysis of whole blood in children with rhinitis/asthma/eczema demonstrated that 27 genes were differentially expressed in rhinitis alone, and 13 genes were involved in either rhinitis or asthma or eczema co-morbidities (none of these multimorbidity genes were repeated in rhinitis alone), but none was significant for asthma alone (Lemonnier et al., 2020). In environmental epidemiology, the same air pollutant in the same study presented different relationship

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with asthma or AR. A birth cohort of Toronto children revealed that exposure to nitrogen dioxide (NO_2) at birth and the first 3 years was significantly associated with the incidence of asthma, but not with the incidence of AR (To et al., 2020).Hence, it becomes imperative to consider these diseases separately, examining their potentially associated factors individually.

The associations between environmental exposures and rhinitis and asthma have been widely documented (Eguiluz-Gracia et al., 2020; Nordeide Kuiper et al., 2021). Firstly, air pollutants, which include atmospheric particulate matter (PM) and gaseous pollutants, are classical pollutants. The association between PM and asthma/rhinitis (Chen et al., 2022) has received considerable interest and there has been a recent rise in research on ultrafine particulate matter (UFP), which can reach the alveoli directly due to its small particle size (Wright et al., 2021); the association of NO_2 as a traffic-related pollutant with asthma has been reported. Secondly, nighttime light (NTL) (Tang et al., 2022) and noise (Lee et al., 2023), physical environments in urban life, were significantly associated with the prevalence of allergic diseases. Thirdly, the relationship of climate change to allergic respiratory diseases is receiving increasing attention, as demonstrated by the association between temperature (TEM) and asthma (Han et al., 2023). Finally, green space exposure may have a potential protective effect on rhinitis-related symptoms (Chen et al., 2024). Many existing studies on allergic diseases have focused on single exposure each time. The multi-factor co-exposure pattern in real world, however, warrants investigation to differentiate and identify the most influencing factors for each specific health outcome, so as to refine our understanding on environmental influence on children's asthma and rhinitis and to make evidence-based suggestions for precise prevention and intervention.

Based on these theoretical hypothesis and previous results, we propose the following hypothesis: The outdoor environmental factors associated with rhinitis alone, wheezing alone, and wheezing -rhinitis comorbidity may differ, and key exposure factors need to be identified. In this study, considering the diversity and comprehensiveness of environmental exposures, we evaluated 11 outdoor environmental exposure factors, including four particle sizes of PM (UFP, PM_1, $PM_{2.5}$, PM_{10}), gaseous pollutants (NO_2 and O_3), meteorology (temperature and relative humidity), physical environmental factors (NTL and noise), and green space, as well as residential indoor environment. Next, the association of environmental exposure factors with rhinitis alone, wheezing alone and wheezing with concomitant rhinitis symptom (wheezing & rhinitis) was estimated, respectively. We employed both traditional regression models and machine learning methods (Oskar and Stingone, 2020; Ohanyan et al., 2022) to evaluate and rank the importance of each factor on its association with target health outcomes.

2. Methods

2.1. Study subjects and questionnaire

In December of 2019, a multi-stage randomized cluster sampling method was applied to 25 kindergartens in 6 administrative districts (Jing'an, Hongkou, Xuhui, Minhang, Jiading, Chongming) in Shanghai, China. In each district, at least 3 kindergartens were randomly selected. The investigators and teachers received professional training to manage the distribution and recovery of questionnaires. A total of 6191 children were recruited and 5894 valid questionnaires were returned, resulting in a recruitment rate of 95.2%. Of these, 5828 children aged 3-6 years were recruited as participating subjects in this study. Fig. 1A displayed the geographic distribution of residential addresses of participating children. Their parents or guardians were invited to answer the questionnaire, as described in previous publications (Chen et al., 2023). The core questions on asthma and AR were derived from the International Study for Asthma and Allergy in Children (ISAAC). On wheezing symptom in the last 12 months, typical symptoms of asthma, it was asked "Has your child ever had wheezing or whistling in the chest over the past 12 months?". On AR symptom, "Has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she did NOT have the cold or flu over the past 12 months?". The sensitivity and specificity of wheezing reached 86.3% and 84.1%, respectively, as previously validated in children aged 1-6 year olds (Hederos et al., 2007). The question on AR symptom had a sensitivity and specificity of 68% and 62%, respectively (Kim et al., 2012), in a validation compared with clinician-physician-diagnosed AR in children aged 1-4 and 7 years.

Four health outcomes on rhinitis or wheeze symptoms were categorized into: 1) Rhinitis alone: children with rhinitis symptom but no wheezing or whistling in the past 12 months; 2) Wheezing alone: children with wheezing or whistling but no rhinitis symptom in the past 12

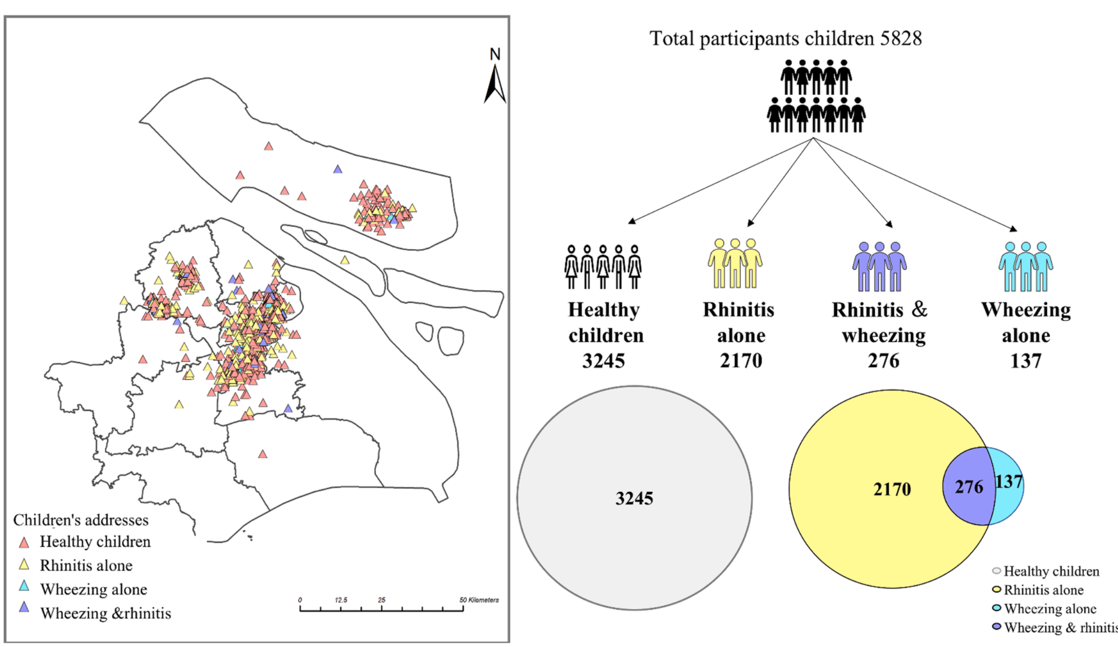

Fig. 1. Distribution of children's residences and number of subjects in each subgroup with and without symptoms. Note: A. Distribution of children's home addresses; B. The number of children in each subgroup with and without symptoms.

months; 3) Wheezing & rhinitis: children with both rhinitis and wheezing or whistling in the past 12 months; 4) Healthy children: children with neither rhinitis nor wheezing or whistling in the past 12 months. Fig. 1B displays the number of each health outcome in this study.

The survey was approved by the Ethics Committee of the School of Public Health, Fudan University (approval numbers IRB00002408 & FWA00002399, IRB#2019-09-0778). All parents/legal guardians of the children participating in the study were informed of the purpose and content of the study and signed the informed consent.

2.2. Exposure assessment

Exposure to a variety of ambient environmental factors in the past 12 months was assessed in each participant surrounding their home addresses, including 4 sizes of PM (ultrafine particulate matter (UFP), PM_1, $PM_{2.5}$ and PM_{10}), 2 gaseous pollutants (NO_2 and O_3), 2 physical environment factors (NTL and noise), 2 meteorological factors (TEM and relative humidity(RH)), and 1 greenspace exposure factor (normalized difference vegetation index in 500 m buffer, NDVI-500m). NDVI is a simple but most commonly used objective measure of vegetation density which is often used in measuring greenness exposure for environmental health studies. NDVI is calculated using the difference between near-infrared (NIR) and red-light reflectance values from satellite imagery. NDVI values range from -1 to 1, where higher values (closer to 1) indicate healthier, denser vegetation, and lower values (closer to 0 or negative) correspond to sparse or no vegetation (Martinez and Labib, 2023). NDVI -500m refers to the calculation of the average vegetation index within a 500-meter radius around a child's home address,

Daily averages of PM_1, $PM_{2.5}$, PM_{10}, and annual averages of NTL were obtained from the ChinaHightAirPollutants (CHAP) dataset at a spatial resolution of 1 km×1 km scale in the last 12 months. For NO_2, the daily averages were obtained at a spatial resolution of 10 km×10 km. The accuracy (i.e., cross-validation coefficient of determination, CV-R (Bousquet et al., 2023)) was 0.77, 0.86-0.90, 0.86, and 0.93 for PM_1, $PM_{2.5}$, PM_{10} and NO_2, respectively (Wei et al., 2019, 2022, 2021a, 2021b). These datasets were elaborated on the website (https://weijing-rs.github.io/product.html). O_3 concentration were assessed as daily maximum 8-hour averages by satellite prediction modelling with a spatial resolution of 1 km×1 km and an accuracy of 0.80 (Chen et al., 2023; Meng et al., 2022). UFP and noise assessment utilized a high spatial resolution land use regression model, and the 10-fold cross-validation R (Bousquet et al., 2023) reached 0.68 and 0.75, respectively (Xu et al., 2022; Ge et al., 2022). NDVI was extracted from the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) (Chen et al., 2024). TEM and RH were assessed using average values calculated from daily values for the past 12 months at the time each study participant completed the questionnaire (daily values derived from the Shanghai Municipality of China National Meteorological Science Data Centre).

2.3. Covariates

The covariates in our study considered gender, family history of AR/asthma (yes/no), self-reported annual household income level, living near a main road (yes/no), passive smoking (yes/no, in the past 12 months), indoor dampness (yes/no, dampness and/or mold in the past 12 months), and air purifiers use(yes/no). Family history of AR/asthma consisted of 3 types. Family history of rhinitis alone indicated either parent had rhinitis only. Family history of asthma & rhinitis indicated either parent had rhinitis and/or asthma, and family history of asthma alone indicated either parent had asthma only. We consulted widely used questionnaires, performed data quality control, and validated with pre-study to improve the accuracy of covariate assessment and reduce information bias (Zhang et al., 2013).

2.4. Statistical analysis

2.4.1. Data descriptions

Descriptions on the demographics, family history of rhinitis/asthma, residential indoor environment and ambient exposure were summarized. For continuous variables with normal distribution, mean ± standard deviation (SD) was calculated. For those with non-normal distribution, medians and interquartile range (IQR) were presented. For categorical data, proportions were described.

2.4.2. Comparisons between subgroups and correlation analysis

The one-way ANOVA test were used to compare continuous outdoor environmental exposures among subgroups, and chi-square tests were used to compare categorical variables between subgroups with rhinitis alone, wheezing alone, wheezing & rhinitis and healthy group, respectively. Pearson correlation analysis was performed between any two outdoor environmental factors.

2.4.3. Logistic regression models

Single-exposure and two-exposure logistic regression models were applied to analyze the associations between exposure factors and health outcomes. The single-exposure model was performed in the crude model and adjusted model, with and without adjusting for covariates, respectively. The two-exposure models were applied with one additional co-exposed environmental factor adjusted, in addition to the same covariates adjusted in the above single-exposure model. Such two-exposure models were run for any two co-exposure environmental factors, to identify the strongest exposure factor associated with health outcome. In the two-exposure model, the variance inflation factor (VIF) between the two exposure factors were calculated and required to be less than 5 to avoid collinearity. To better compare the association coefficients between exposure variables with different dimensions or units for the same health outcome, all continuous variables on environmental exposure were standardized into folds of SD to eliminate the dimensional differences. The adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated per SD increase of each environmental exposure factor. The SD level for each exposure factor in each model is presented in Table S1.

2.4.4. Random forest regression models and feature importance ranking

We constructed random forest models by applying the significant environmental factors involved in the single-exposure regression models (both crude and adjusted) and covariates. The model could solve complicated classification and regression problems, especially in handling high-dimensional data and highly correlated factors by creating multiple decision trees (Breiman, 2001). Mean decrease accuracy (MDA) was calculated as an indicator of feature importance which was used to rank the importance of each exposure factor (Nicodemus, 2011).

2.4.5. Additive and multiplicative interactions

Both the additive and multiplicative interaction effects were analyzed between the strongest outdoor exposure factors associated with each health outcome and demographic and residential categorical characteristics significant in the univariate comparions (Lu et al., 2022). For the additive interaction effects, we assessed whether the associations of concomitant exposure to outdoor exposure factor and demographic/residential characteristic were greater than the sum of two variables, indicated by the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index(SI) (Jang et al., 2021) (null hypothesis: RERI =0, AP=0, SI = 1, respectively) (Li and Chambless, 2007). For the multiplicative interaction effects, we assessed whether the associations of concomitant exposure were larger than the product of two variables with the null hypothesis of multiplicative interaction effect equals to 1.

2.5. Sensitivity analysis

The sensitivity analyses were performed to examine the robustness of main findings. First, we utilized ridge regression to reassess the association between exposure and outcomes by addressing multicollinearity among exposure factors (Segerstedt, 1992) in addition to adjustment of covariates. Second, we applied a more strict definition to redefine the healthy children as those who never had any rhinitis or wheezing/asthma since birth, not only no symptoms in the last 12months, and re-analyzed the associations in the same regression models.

All analyses were performed with R software (version 4.3.2), using *randomForest* and *interactionR* package. P values<0.05 were considered statistically significant. False discovery rate (FDR) was used in the correlations analysis among environmental exposure, accounting for a variety of factors.

3. Results

3.1. Characterization of study population

A total of 2170(37.2%), 267(4.7%), 137(2.4%), and 3245(55.7%) children reported rhinitis alone, wheezing & rhinitis, wheezing alone and being healthy (with neither rhinitis nor wheezing symptom over the last 12 months), respectively (Fig. 1B). Compared to the healthy children, children with rhinitis alone were at larger ages, had more boys, more with family history of diseases, indoor dampness and used air purifiers more frequently and more living near a main road (P<0.05). Besides, children with wheezing & rhinitis and wheezing alone had higher proportions of passive smoking. However, no significant change in indoor humidity and air purifiers was found in the group of children with wheezing alone. We did not observe statistically significant differences in self-reported household income levels between subgroups (Table 1).

3.2. Univariate comparisons of 11 outdoor exposure factors

Based on the average of 11 environmental factors in past 12 month, NO_2 and noise mean values exceeded national standards (Table S2). All PM, gaseous pollutants, physical environment, and greenspace exposures differed significantly between subgroups. No statistical differences were found for meteorological factors (Table S3).

There was a strong correlation for PM_1 and/or $PM_{2.5}$ with O_3, NO_2, NTL and noise (correlation coefficient >0.6), and between O_3 and PM_{10}, TEM and RH. NDVI-500m was negatively correlated with all other exposure factors (Fig. S1).

3.3. Single-exposure regression analyses

Rhinitis alone was significantly associated with all 11 exposure factors in the single-exposure regression models adjusting for demographic and residential environment (Fig. 2). The larger association were with PM_1 (OR=1.19, 95%CI: 1.12-1.27) and $PM_{2.5}$ (OR=1.18, 95%CI: 1.11-1.26), respectively, followed by NTL (OR=1.18, 95%CI:1.11-1.25). Wheezing symptoms, both wheezing & rhinitis and wheezing alone, had robustly positive associations with NO_2 by OR of 1.22 (95%CI:1.04-1.44) and 1.48 (95%CI;1.14-1.92), respectively. The association between NTL and wheezing & rhinitis was significant in crude models (OR=1.17,95% CI:1.02-1.33), whereas a significant association was not found with wheezing alone (OR=1.13,95% CI:0.93-1.36).

3.4. Two-exposure regression analyses

By a round of mutual regression analyses with any two pollutants adjusted for each other, it showed that PM_1 (with ORs ranging from 1.10~1.19), $PM_{2.5}$ (with ORs ranging from 1.09~1.20) and NTL (with ORs ranging from 1.10~1.20) remained the most consistently significant associations with rhinitis alone (Fig. S2, Fig. 3). NO_2 had the most consistently significant association with wheezing symptoms, both wheezing & rhinitis and wheezing alone (Fig. S2, S3, S4, Fig. 3).

3.5. Importance ranking of environmental factors using random forest

According to the calculated MDA values in the random forest analysis, the 3 most important environmental factors for rhinitis alone were PM_1, $PM_{2.5}$ and PM_{10}. For wheezing &rhinitis, they were ranked as NO_2, PM_1 and $PM_{2.5}$, and for wheezing alone, the ranking was NO_2, UFP and $PM_{2.5}$ (Fig. 4).

3.6. Interaction between exposure and demographic/residential factors

For the most significant exposure factors $PM_{1.0,}$ $PM_{2.5}$ and NO_2 as observed above, their interactions with demographic and residential environment were further analyzed (Table S4). A consistently significant interaction between indoor dampness and PM_1 for rhinitis alone was observed. The multiplicative interaction term had an OR of 1.57 (95% CI:1.17, 2.11) and the additive interaction had indices of 0.69 (95% CI:0.27, 1.12), 0.37 (95%CI:0.19, 0.55), and 4.64 (95%CI:1.01, 21.26) corresponding to RERI, AP, and SI, respectively (Table 2).

3.7. Sensitivity analyses

First, the results of the ridge regression constructed for all exposure

Table 1
Demographic characteristics and residential environment in the healthy children compared to 3 subgroups of symptom children.

Characteristics, n (%)		Healthy children	Rhinitis alone		Wheezing & rhinitis		Wheezing alone	
		n=3245	n=2170		n=276	*P*	n=137	*P*
Age, mean(SD)		4.69 (0.98)	4.81 (0.95)		4.75(0.96)		4.57(0.96)	
Boys		1590 (49.0)	**1219 (56.2)**	**<0.001**	**176 (63.8)**	**<0.001**	**81 (59.1)**	**0.025**
Family history of diseases [#]		875 (27.0), 58 (1.8), 43 (1.3)	**1020 (47.0)**	**<0.001**	**31 (11.2)**	**<0.001**	**12 (8.8)**	**<0.001**
Living near a main road		2977 (91.7)	**2052 (94.6)**	**<0.001**	**264 (95.7)**	**0.029**	**128 (93.4)**	**0.024**
Passive smoking		2508 (77.3)	1638 (75.5)	0.133	**188 (68.1)**	**0.001**	**94 (68.6)**	**0.024**
Indoor dampness		487 (15.1)	**456 (21.1)**	**<0.001**	**56 (20.4)**	**0.025**	29 (21.5)	0.058
Use of air purifiers		1853 (57.1)	**1401 (64.6)**	**<0.001**	**185 (67.0)**	**0.002**	80 (58.4)	0.833
Exclusive breastfeeding <6 months		1304 (40.2)	923 (42.5)	0.090	126 (45.7)	0.087	58 (42.3)	0.679
Self-reported	low	463 (14.3)	298 (13.7)	0.838	41 (14.9)	0.445	25 (18.2)	0.164
household income level	medium	2583 (79.6)	1735 (80.0)		213 (77.2)		100 (73.0)	
	high	199 (6.1)	137 (6.3)		22 (8.0)		12 (8.8)	

For age, a continuous variable, ANOVA analysis was performed and the *P*-value was <0.001; *P*-value was the statistical significance on comparisons between healthy subjects and 3 subgroups with rhinitis alone, wheezing & rhinitis and wheezing alone, respectively. [#]Family history of diseases referred to either parent had a history of rhinitis alone, or asthma & rhinitis or asthma alone, corresponding to each symptom. In healthy children, such proportions accounted for 875 (27.0), 58 (1.8%) and 43 (1.3%) for rhinitis alone, asthma & rhinitis and asthma alone, respectively.

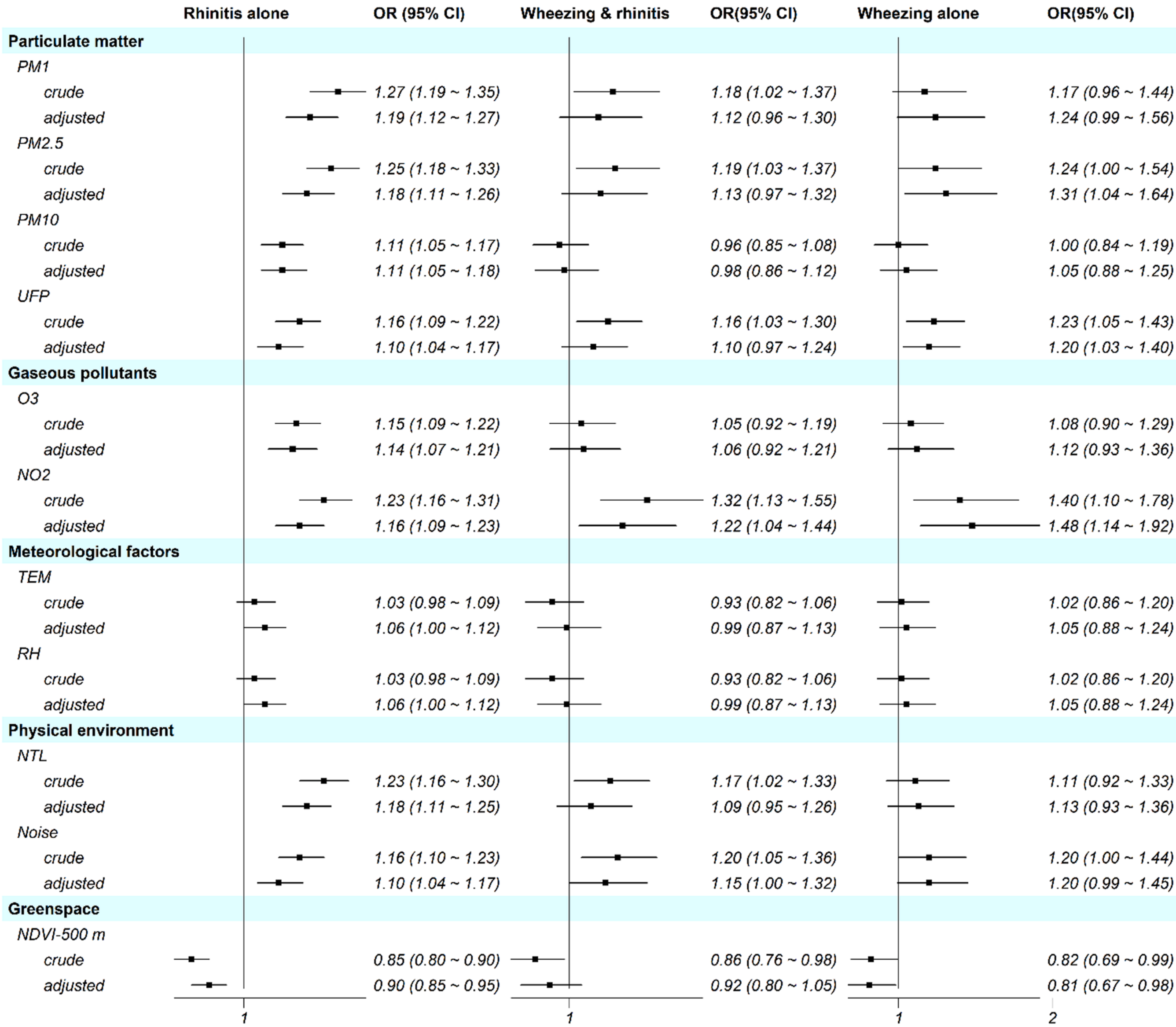

Fig. 2. The single-exposure regression analysis in crude and adjusted models for rhinitis alone, wheezing & rhinitis and wheezing alone, respectively. Note: UFP, ultrafine particles; RH: relative humidity; TEM, temperature; NTL, nighttime light. The adjusted covariates were age, gender, family history of diseases, living near a main road, passive smoking, indoor dampness and use of air purifiers. The associations were calculated as ORs per SD increase of each exposure factor.

factors remained mostly consistent with the results of single-exposure (Fig. S5). It demonstrated the robustness of the association of multiple exposure factors with 3 symptoms. Second, the associations between exposure factors and the 3 symptoms were consistent with the current findings when the healthy children who had never had rhinitis/asthma/wheezing were applied as a new reference group, both in single-exposure and two-exposure regression analyses (Fig. S6 and S7).

4. Discussions

In this study, we assessed 11 co-exposed outdoor environmental factors surrounding children's residences and their associations with 3 airway symptoms (rhinitis only, wheezing & rhinitis, rhinitis only) in preschool children in Shanghai. We aimed to find out the most significant exposure for the aimed symptoms out of multi-dimensional co-exposed pollutants in real life. We found rhinitis only was most susceptible to PM_1 followed by $PM_{2.5}$ exposure while wheezing symptom, either with concomitant rhinitis or wheezing alone, was more sensitive to NO_2. These associations were robust and corroborated by single-exposure logistic regression analyses, two-exposure logistic regression analyses with mutual adjustment for each of the other co-exposed outdoor pollutants, and the random forest ranking method. Additionally, we found a specific association between NTL and rhinitis alone, even if it ranked low in random forests. The above findings remained robust in sensitivity analyses.

By questionnaire survey, we found close to half children (44.3%) had wheezing and/or rhinitis symptoms in the last 12 months. Rhinitis alone accounted for the largest positive reports of symptoms (37.2%), followed by wheezing & rhinitis (4.7%) and wheezing alone (2.4%). Among those with rhinitis, 89% had rhinitis alone and 11% had concomitant wheezing symptom. Among those with wheezing symptoms, 33% reported wheezing alone, while 67% had concurrent rhinitis symptom. These proportions consistently mirrored previous population-based studies. A multi-national cross-sectional study in adults found that 50%-70% of asthma patients had coexisting rhinitis (Leynaert et al., 2004). A meta-analysis on the prevalence of AR and asthma in China across all ages reported that the proportion of AR patients with comorbid asthma ranged from 6.69% to 14.35%, while the proportion of

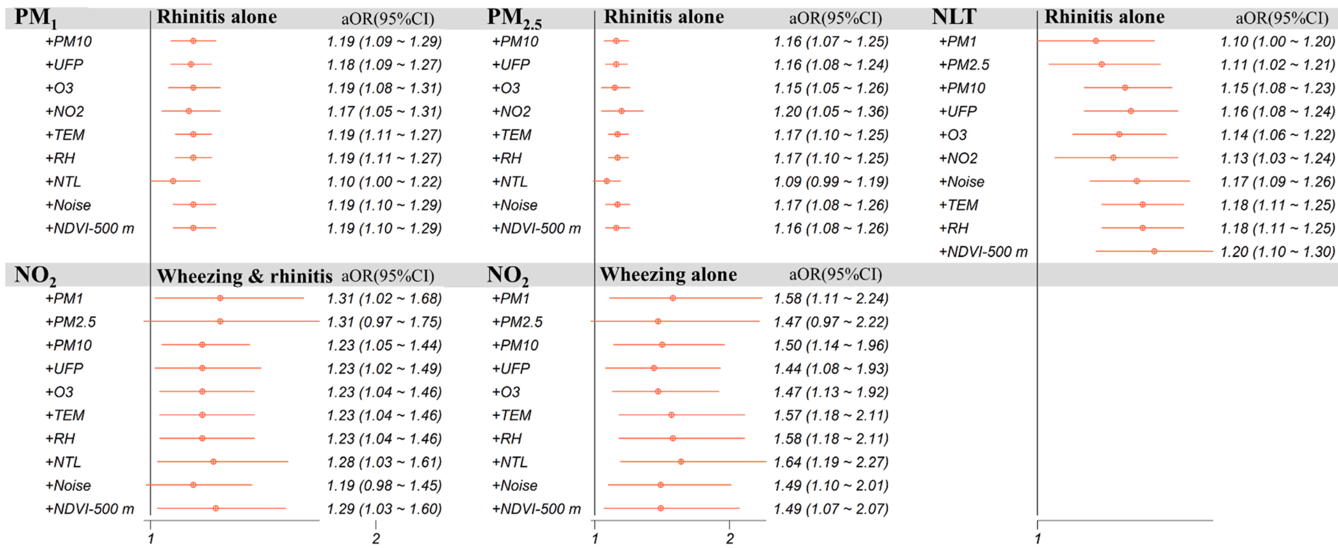

Fig. 3. The two-exposure regression analysis for $PM_{1.0}$ and $PM_{2.5}$ with rhinitis alone, NO_2 with wheezing alone and wheezing & rhinitis, respectively. Note: UFP, ultrafine particles; RH: relative humidity; TEM, temperature; NTL, nighttime light. Each model was adjusted for age, gender, family history of diseases, living near a main road, passive smoking, indoor dampness, and use of air purifiers use. The associations were ORs per SD increase of each exposure factor. $PM_{1.0}$ and $PM_{2.5}$ are the two strongest outdoor exposure factors associated with rhinitis alone, while NO_2 was the strongest outdoor factor associated with wheezing & rhinitis and wheezing alone.

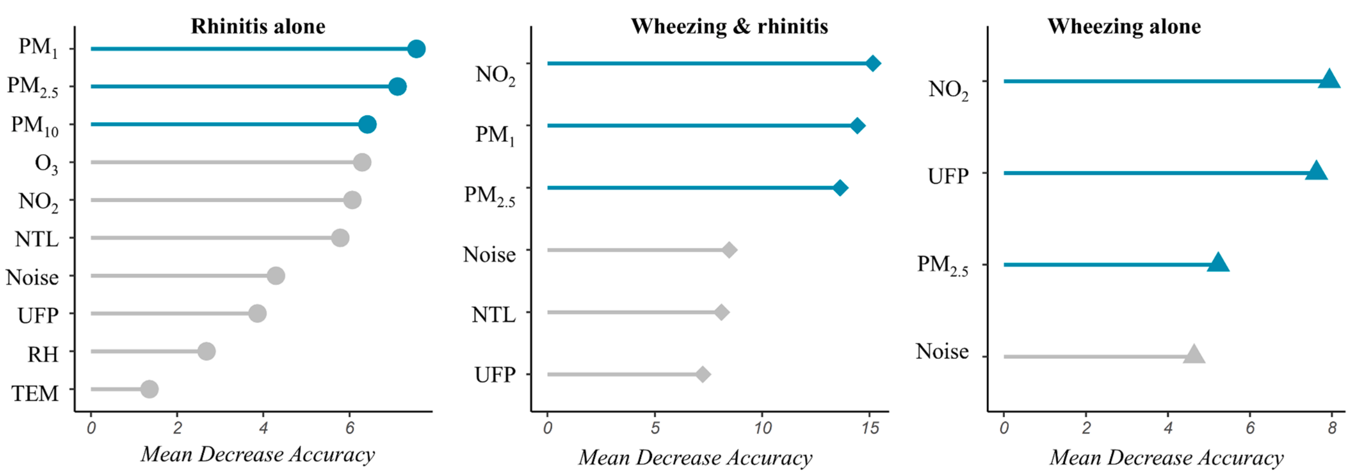

Fig. 4. Rankings of outdoor exposure factors according to their importance on each symptom in random forest analyses. Note: UFP, ultrafine particles; RH: relative humidity; TEM, temperature; NTL, nighttime light. The random forest exposure factors that were significant in single-exposure regressions and demographic characteristics.

asthma patients with comorbid AR ranged from 26.67% to 54.00% (Shen et al., 2019). Wheezing is a classical symptom for asthma. Our survey in preschool children reflected the similar characteristics of co-morbidity between rhinitis and wheezing symptoms.

In our study, children's rhinitis alone was significantly associated with most outdoor environmental exposure factors, whereas wheezing symptoms (wheezing & rhinitis and wheezing alone) was associated with much less factors. Recent studies reported that rhinitis and asthma could not be simply considered as a uniform airway disease (Bousquet et al., 2023). Previous studies comparing whole blood comprehensive transcriptome analysis in children with rhinitis and asthma reported that, participants with rhinitis alone did not express genes associated with co-morbidities, and functional analysis of these genes found that IL-17 was involved, whereas co-morbidities were associated with T2 signaling genes (IL-33) (Aguilar et al., 2023). Epidemiologic studies have provided similar evidence. In a survey of over 200,000 French adults using standardized questionnaires, it revealed the significant differences between individuals with rhinitis alone and those with rhinitis and concomitant asthma in perspectives of age of onset, number of symptoms and severity and blood eosinophil counts. In particular, AR with concomitant asthma had an earlier age of onset, more comedication and higher blood eosinophil counts than those with allergic rhinitis alone (Savouré et al., 2023).

PM_1 and $PM_{2.5}$ had robust associations with rhinitis alone, while NO_2 was predominantly associated with wheezing symptoms (both wheezing & rhinitis and wheezing alone). Similar different associations have been reported in Toronto children in a birth cohort examining early life exposure on air pollution and asthma and AR. they found childhood asthma was associated with O_3 and NO_2 at birth, while AR was associated only with O_3 at birth (To et al., 2020). Evidence from a prospective cohort of South African school children demonstrated that annual NO_2 concentration was strongly associated with new reports of wheezing symptoms at 12-months follow-up, but not significantly with rhinitis, either in the single- or two-pollutant model (Olaniyan et al., 2020).

The identification of distinct outdoor environmental exposure factors separately associated with rhinitis alone and wheezing symptoms

Table 2
Additive and multiplicative interaction effects between ambient PM_1 and indoor dampness on rhinitis alone.

Items	In crude model		In adjusted model	
	Lower PM_1	Higher PM_1	Lower PM_1	Higher PM_1
Associations (OR, 95%CI)				
Without indoor dampness	1.00 (Reference)	1.15 (0.94, 1.40)	1.00 (Reference)	1.14 (0.92, 1.40)
With indoor dampness	1.12(0.99, 1.26)	2.19 (1.79, 2.69)	1.06 (0.93, 1.20)	1.88 (1.53, 2.32)
Interaction effects				
Additive interaction*				
RERI	0.93 (0.46, 1.39)		0.69 (0.27, 1.12)	
AP	0.42 (0.27, 0.58)		0.37 (0.19, 0.55)	
SI	4.50 (1.50, 13.44)		4.64 (1.01, 21.26)	
Multiplicative interaction*	1.71 (1.28, 2.28)		1.57 (1.17, 2.11)	

Note: PM_1 levels were stratified into lower and higher levels by its median level in the last 12 months (20.3 μg/m^3).
* Null hypothesis for each additive interaction was AP = 0, RERI = 0, SI = 1 and multiplicative interaction=1, respectively.

suggested, children with upper airway or lower airway symptoms were susceptible to different air pollutants. This could be due to pollutant physio-chemical and toxic characteristics and pathology mechanisms. On the one hand, on the exposure characteristics, the upper airway is directly exposed to outdoor environmental factors. So rhinitis alone was indeed significantly related with most outdoor environmental exposure factors or factors highly related with outdoor environmental exposure factors in our study. Moreover, by impaction or sedimentation in the nasal cavity, $PM_{1.0}$ and $PM_{2.5}$ may damage the nasal epithelial barrier, causing damage to the nasal mucosa and triggering symptoms such as nasal congestion and runny nose (Gu et al., 2023). PM_1 and $PM_{2.5}$ can be attached with substantial quantities of airborne microorganisms (Zhai et al., 2018), and harmful microorganisms may impact on rhinitis and symptoms. On the other hand, wheezing is a typical symptom of lower airway in asthmatic patients (Mims, 2015). NO_2, a traffic-related pollutant with potent oxidizer, can easily penetrate deeply into the distal airways and alveoli, aggravating airway hyperresponsiveness (Poynter et al., 2006). Most of the children in our study had exposures to NO_2 that exceeded the Chinese air quality standards. Furthermore, it generated reactive oxygen species, causing oxidative stress and damage to the lower airways as evidenced in mouse models (Lu et al., 2023). Additive and multiplicative interactions between ambient PM_1 and indoor dampness was observed on rhinitis alone, enabling their mutual reinforcement in increasing the risk of rhinitis. This suggested that the synergistic effects of outdoor air and indoor residential environment could have more serious health effects than a single exposure factor. This may also partly be attributed to the synergistic effect of PM exacerbating outdoor allergens such as pollen, as well as mold allergens caused by indoor dampness (Singh and Hays, 2016) which warrants for further examination.

Furthermore, we also observed a robust association between NTL and rhinitis symptoms in two-exposure regression analysis, rather than wheezing. A study of college students from 2013-2018 illustrated a significant association between NTL exposure at the county/district level and self-reported physician diagnoses of asthma and atopic rhinitis. Specifically, NTL exposure was associated with an increased risk of asthma (prevalence ratio PR=1.80, 95% CI: 1.48-2.19) and atopic rhinitis (PR=1.42, 95% CI: 1.33-1.51) (Tang et al., 2022). These findings are consistent with the association we observed between NTL exposure and rhinitis symptoms in our study, and we analyzed more exposure factors. Rapid urbanization disrupts the nocturnal environment and light pollution is a concern. The current focus on the regulatory role of NTL and human health is mainly on circadian rhythms (Zielinska-Dabkowska et al., 2023), with studies also reporting that disruption of circadian rhythms exacerbates the immune response in allergic airway inflammation (Cheng et al., 2022), and further studies are needed to provide scientific evidence of the health effects of NTL.

The study has several strengths. First, we assessed 11 outdoor exposure factors, including PM, gaseous pollutants, physical environment, meteorological factors, and greenspaces, which provided a comprehensive understanding on the multiple exposure close to the exposure patterns in real life. Second, we distinguished three symptom phenotypes, rhinitis alone, wheezing & rhinitis and wheezing alone, and investigated their associated factors separately, which enabled us to identify the distinct pollutants more precisely corresponding to each type of symptoms. Third, our study combined traditional logistic regression, as well as machine learning method to assess the association between exposure and outcome. The consistent findings on the most significant outdoor exposure factors contributing most to aimed symptoms underscored the credibility and robustness of our findings.

There are also some limitations in this study. First, self-reported symptoms of rhinitis and wheezing might introduce inaccuracies. However, the long-erm application and validation results of the standardized questionnaire for the investigation of both rhinitis and asthma symptoms in large sample studies make it still credible. Combined with the multiple statistical methods used in our study and the underlying pathological rationale, we believe that these findings on rhinitis and asthma are reasonable and provide epidemiological clues for subsequent mechanistic studies and interventions. Second, exposure assessment for NTL and UFP exposure was based on the annual average for 2019, not daily averages, However the exposure evaluation was for the past 12 months which could match the exposure time window. Third, this was a study in Shanghai preschool children, which limited the generalization to the whole country or other cities with different environmental context. Finally, cross-sectional studies could not indicate causal relationship, despite the associations observed hinted for valuable insights for future investigations.

5. Conclusions

Our study comprehensively assessed multiple outdoor environmental exposures in preschool children and their association with rhinitis and asthma symptoms. Rhinitis only was most susceptible to PM_1 followed by $PM_{2.5}$ exposure, while wheezing symptom, either with concomitant rhinitis or wheezing alone, was more sensitive to NO_2. Indoor dampness and atmospheric PM_1 had synergistic effects for rhinitis alone.

CRediT authorship contribution statement

Shuang Du: Writing – original draft, Visualization, Software, Methodology, Data curation, Conceptualization. **Hao Tang:** Writing – original draft, Visualization, Software, Methodology, Data curation, Conceptualization. **Han Chen:** Software, Resources, Methodology. **Yang Shen:** Resources, Methodology. **Zhiping Niu:** Software, Resources. **Tianyi Chen:** Software, Investigation. **JingWei:** Resources. **Xia Meng:** Resources. **Wen Su:** Supervision. **Qun Wu:** Supervision. **Yongqiang Tan:** Supervision. **Jing Cai:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Zhuohui Zhao:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.117490.

Data availability

Data will be made available on request.

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