

Early-Life Ozone Exposure and Childhood Allergic Rhinitis: Critical Exposure Windows, Exposure-Response Relationships, and Protective Modifiers

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Cite This: *Environ. Health* 2026, 4, 630–640

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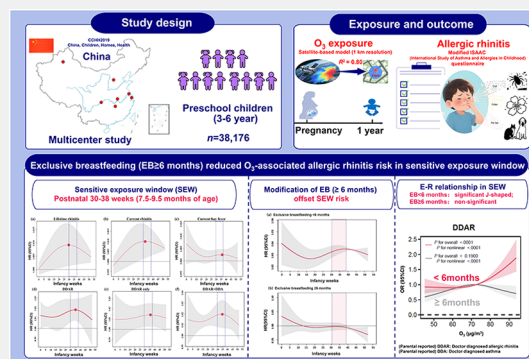
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ABSTRACT: Childhood allergic rhinitis (AR) is associated with ozone (O_3) exposure, yet the sensitive exposure window (SEW) remains unclear. This multicenter survey of 38,176 children aged 3–6 years across 7 Chinese cities (2019–2020) estimated satellite-based individual maximum daily 8 h average O_3 exposure. The SEW and its exposure–response (E – R) relationship were assessed. Doctor-diagnosed AR prevalence was 11.9%. Average O_3 exposure from prenatal to AR onset ranged from 67.5 to 76.7 $\mu\text{g}/\text{m}^3$. The critical SEW was identified as infancy, specifically 30–38 weeks postnatal (7.5–9.5 months). Per interquartile range (IQR) ($10.1 \mu\text{g}/\text{m}^3$) increase in O_3 , the adjusted odds ratio was 1.29 (95% CI: 1.22–1.36), independent of $\text{PM}_{2.5}$. The E – R relationship was nonlinear, J-shaped, and threshold-free. The SEW effect was stronger in southern cities and mitigated by ≥ 6 months of exclusive breastfeeding. In conclusion, O_3 significantly increases AR risk, with 7.5–9.5 months postnatal being a critical SEW, especially in exclusive breastfeeding <6 months and southern regions.

KEYWORDS: allergies, exposure–response curve, ozone exposure, airway diseases



1. INTRODUCTION

Allergic rhinitis (AR) is a prevalent chronic respiratory disorder that often persists throughout an individual's lifetime. In children, the prevalence of AR varies significantly, ranging from 2 to 25% globally.¹ AR demonstrates a high comorbidity rate with asthma, affecting between 2 and 40% of AR patients.² The condition substantially impairs patients' quality of life by disrupting daily activities, emotional well-being, and sleep patterns.³

Environmental exposure increases the risk of developing AR, including outdoor air pollution (ozone (O_3) and fine particulate matter ($\text{PM}_{2.5}$))⁴ and indoor environmental factors (microorganisms).^{5,6} Air pollution, particularly the worsening O_3 levels, is a significant risk factor for AR.⁷ O_3 promoted allergic respiratory diseases through multiple mechanisms, including oxidative stress-mediated lipid peroxidation, protein modification, DNA damage, and disruption of signal transduction pathways.⁸ Cohort studies have demonstrated that O_3 exposure during pregnancy and early childhood significantly increased the risk of allergic respiratory diseases in children.^{9–11}

One year before pregnancy and the first 1000 days of life represent a critical window for the development of allergic diseases. These periods influenced the onset of AR in children

through intergenerational epigenetic mechanisms, oxidative stress, and inflammatory pathways.^{12–15} The first 1000 days of life—spanning from pregnancy to two years old, represent a critical window for epigenetic programming and immune development. This period may profoundly influence long-term susceptibility to AR.^{16,17} However, the most sensitive exposure window (SEW) for the exposure of O_3 in relation to AR onset remains unclear. Identifying the specific SEW for O_3 and the development of AR is crucial for developing targeted prevention strategies and elucidating the underlying pathogenic mechanisms.

Investigating the exposure–response (E – R) relationship between O_3 and AR, in particular, during the SEW, is crucial for understanding how risk characteristics evolve with progressively increasing exposure levels. North American studies have indicated that no safe threshold exists for O_3 exposure regarding allergic respiratory disease risks.^{18,19}

Received: July 19, 2025

Revised: November 9, 2025

Accepted: November 13, 2025

Published: November 25, 2025



However, in China, comprehensive $E-R$ analyses for O_3 and AR remain scarce. Recent multiprovincial studies in China have demonstrated a linear, nonthreshold $E-R$ relationship between four-year average O_3 exposure and pediatric AR incidence.²⁰ Notably, no existing research has examined the $E-R$ characteristics of O_3 and AR from the perspective of critical SEW, significantly limiting the ability to develop targeted prevention strategies.

The risk of AR associated with O_3 exposure can be modified by genetic predisposition and early-life feeding factors.²¹ Previous research has established that the relationship between particulate matter exposure and childhood respiratory allergies could be modified by breastfeeding duration, familial allergy history, and geographic area.^{22–24} The potential modifying effects of these factors—particularly regarding O_3 exposure during the SEW and subsequent AR risk, remain poorly characterized. Clarifying these interactions is critical for identifying vulnerable subpopulations, developing targeted early-life prevention approaches, and elucidating the pathophysiological mechanisms underlying the O_3 -AR relationship.

This study aimed to identify the SEW and characterize the $E-R$ relationship between O_3 exposure in the SEW and childhood AR in preschool children. We conducted a multicenter cross-sectional study (2019–2020) within the China, Children, Homes, Health (CCHH) project, enrolling over 40,000 preschool children across diverse regions of China. O_3 exposure levels were assessed from the prenatal period to the onset of AR diagnosis. To achieve our objectives, we employed a comprehensive analytical approach: multilevel binomial regression (MLBR) combined with distributed lag nonlinear models (DLNM) to identify critical exposure windows and restricted cubic spline (RCS) analysis to evaluate the $E-R$ relationship, with rigorous adjustment for individual, household, and environmental covariates.

2. METHODS

2.1. Study Design and Subjects

This study is the second phase of the China Children's Home Health (CCHH) project. The CCHH is a multicenter repeated health survey focusing on allergic diseases among children in China. Launched in 2011, its first-round investigation, the project employed a multistage sampling approach (city-kindergarten-individual) and was carried out across kindergartens in seven Chinese cities.²⁵ All questionnaires were completed by the children's parents or their legal guardians. In this repeated survey conducted in 2019, it collected information from 40,486 preschool children aged 3–6 years across 351 kindergartens in seven cities. The geographic distribution of the participants' home addresses is shown in Figure S1.

2.2. Ethical Approval

This study received ethical approval from the Institutional Review Board of Fudan University (IRB00002408 and FWA00002399, IRB#2019–09–0778). Prior to the survey, informed consent was obtained from all participating children's parents or guardians.

2.3. Health Outcomes

We assessed AR and asthma using questions adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. These questions have been extensively validated in both Chinese and international populations.^{26–28} All questionnaires were completed by the children's parents or their long-term legal guardians. The primary outcome of this study was doctor-diagnosed allergic rhinitis (DDAR), with five symptoms serving as secondary outcomes. The specific definitions of these outcomes are as follows:

DDAR: Has the child ever been diagnosed with allergic rhinitis by a physician doctor? If "yes", at what age was your child first diagnosed? (The onset age)

Lifetime rhinitis: Has your child ever had a sneezing, runny, or stuffy nose without having a cold or flu? If "yes", at what age did these symptoms first appear?

Current rhinitis: In the past 12 months, has your child had a sneeze, runny nose, or stuffy nose without having a cold or flu?

Current hay fever: In the past 12 months, has your child had any sneezing, runny, or stuffy nose after contact with plants or pollen?

DDAR only: AR diagnosis by a physician without asthma/eczema comorbidity.

DDAR+DDA (doctor-diagnosed asthma): Children with both DDAR and DDA, in which AR diagnosis preceded DDA development. This temporal relationship was established by comparing the ages of the initial diagnosis for DDAR and DDA. We operationally defined this specific phenotype as a clinically relevant subtype that represented a distinct developmental pathway, in which DDAR likely contributed to subsequent DDA manifestation.

In addition, we collected detailed information on demographic characteristics (including age, gender, single child, preterm birth, and birth weight), family history of allergic diseases (FHA), infant feeding practices, and living environment (such as exclusive breastfeeding, residential proximity to major roads [within 200 m], urban or suburban/rural location, home new renovation, dampness, mold, and second-hand smoke exposure (SSE)), as well as socio-economic status indicators like household per capita income. The income data was obtained from the China Statistical Yearbook Database maintained by the National Bureau of Statistics, with city-specific values used for analysis.

2.4. Pollutants and Meteorological Data

Daily concentrations of O_3 were estimated using a high-resolution ($1 \times 1 \text{ km}^2$) random forest prediction model. This model integrated multiple data sources, including monitoring data (2013–2019) on the maximum daily 8 h average of O_3 , Community Multiscale Air Quality simulations, elevation, meteorological variables, road networks, and population density. The model exhibited strong predictive performance, achieving a cross-validated R^2 of 0.80 and a root-mean-square error (RMSE) of $20.93 \mu\text{g}/\text{m}^3$ at the daily level.²⁹ This O_3 prediction approach has been previously validated and applied in large-scale cohort studies³⁰ and multicenter cross-sectional investigations.²³ O_3 exposure was assessed from one year before pregnancy to the year of DDAR onset in three periods: (1) one year before pregnancy, (2) the first 1000 days (encompassing pregnancy through age two), and (3) age two to DDAR onset (92.5% of cases occurred after age two), respectively.

We obtained particulate matter (PM) concentrations (including $\text{PM}_{1.0}$, $\text{PM}_{2.5}$, and PM_{10}) and nitrogen dioxide (NO_2) levels from satellite-based prediction models at $1 \times 1 \text{ km}$ resolution. These models incorporated multiple data sources: aerosol optical depth measurements, meteorological parameters, demographic characteristics, and land use information. The models demonstrated strong predictive performance, with the following validation metrics: $\text{PM}_{1.0}$ ($R^2 = 0.77$, $\text{RMSE} = 14.6 \mu\text{g}/\text{m}^3$),³¹ $\text{PM}_{2.5}$ ($R^2 = 0.89$, $\text{RMSE} = 10.33 \mu\text{g}/\text{m}^3$),³² PM_{10} ($R^2 = 0.86$, $\text{RMSE} = 24.28 \mu\text{g}/\text{m}^3$),³³ and NO_2 ($R^2 = 0.80$, $\text{RMSE} = 7.78 \mu\text{g}/\text{m}^3$).³⁴ Coarse particulate matter ($\text{PM}_{2.5-10}$) was calculated as the difference between the PM_{10} and $\text{PM}_{2.5}$ concentrations. Daily mean temperatures for each city were acquired from the China Meteorological Data Sharing Service System (<http://data.cma.cn/>).

2.5. Statistical Analysis

2.5.1. Demographic Characteristics and Environmental Exposure. We described the demographic characteristics, feeding and living habits, and O_3 exposure levels among all children, comparing the differences between those with and without DDAR children. For continuous variables, the independent samples t -test was used, while the chi-square test was applied for categorical variables. We summarized the mean concentrations and standard deviation of O_3 , PMs, and NO_2 across different time windows in each city. To

Table 1. Comparison of Demographic Characteristics, Growing, Feeding, and Living Environment between Non-DDAR and DDAR Subjects^a

Variables	All subjects (n = 40,486)	Non-DDAR (n = 35,320)	DDAR (n = 4754)	P value
Demographic characteristics				
Age, year, mean (SD)	4.8(1.0)	4.8 (1.0)	4.8(0.9)	<0.001
Boys, n (%)	20973(51.9)	18009(51.1)	2757(58.0)	<0.001
Single child, n (%)	22970(56.8)	19581(55.5)	3208(67.5)	<0.001
FHA, n (%)	15014(38.1)	11694(34.0)	3228(68.7)	<0.001
Preterm birth, n (%)	1653(4.2)	1416(4.1)	211(4.5)	0.235
Birth weight, kg, mean (SD)	3.3(0.5)	3.3(0.5)	3.3(0.5)	0.429
Growing, feeding, and living area				
Exclusive breastfeeding ≥ 6 months, n (%)	25340(62.7)	22410(63.5)	2695(56.8)	<0.001
Main road within 200 meters er, n (%)	17310(43.3)	14912(42.7)	2252(47.8)	<0.001
Living in urban areas, n (%)	31905(79.3)	27646(78.7)	3954(83.5)	<0.001
Living in the southern region at birth, n (%)	29232(72.2)	25054(70.9)	3983(83.8)	<0.001
Home environment and socio-economic status				
Home new decoration, n (%)	2512(6.3)	2132(6.2)	361(7.7)	<0.001
Home dampness, n (%)	4318(10.9)	3590(10.4)	718(15.3)	<0.001
Home mold, n (%)	2893(7.3)	2431(7.0)	442(9.4)	<0.001
SSE, n (%)	9657(24.1)	8467(24.2)	1073(22.7)	0.022
Per capita income,1000 CNY, mean (SD)	27.7(8.7)	27.6(8.7)	28.5(9.3)	<0.001
O₃ concentration (μg/m³), mean (SD)				
One year before pregnancy	67.5(8.1)	67.2(8.2)	69.8(7.5)	<0.001
In pregnancy	67.7(11.8)	67.4(11.8)	70.6(11.3)	<0.001
In infancy	69.2(10.9)	69.0(10.9)	71.9(10.3)	<0.001
Age 1–2	73.1(11.4)	72.9(11.5)	74.8(10.3)	<0.001
The first 1000 days (from pregnancy to age 2)	69.9(10.7)	69.7(10.4)	72.4(9.7)	<0.001
From age 2 to the first onset of DDAR	76.7(11.9)	75.6(13.8)	76.9(11.6)	<0.001

^aDDAR: doctor-diagnosed allergic rhinitis. Non-DDAR: children never diagnosed with AR by a doctor. FHA: family history of allergies (either parent has a doctor-diagnosed asthma, allergic rhinitis, or eczema); Dampness was defined as a binary exposure variable based on a positive response to the following question: “Are there visible signs of dampness, water flooding, leakage, seepage, or water damage on the floor, walls, and/or ceiling?”. SSE: second-hand smoke exposure. P value refers to the statistical significance of comparisons between subgroups with and without DDAR. For home environment and socio-economic status, we collected data in pregnancy and in infancy. The table shows the data on pregnancy.

assess the relationships of O₃, PM, and NO₂ with meteorological variables, we conducted partial correlation analyses.

To identify sensitive exposure windows (SEWs), we combined the MLBR and DLNM models to progressively refine the precise SEWs in MLBR, and accounted for the risk and lag effects of cumulative exposure in DLNM.

2.5.2. MLBR Assessment of O₃-AR Association. To evaluate the association between O₃ exposure in each of the 3 periods and AR onset in children, we employed the MLBR model, with the risks calculated as odds ratios (ORs) per interquartile range (IQR) increase of the level of O₃. The construction of the MLBR model is presented in Table S3. According to our survey framework, we initially constructed a three-level model based on the research design (city-kindergarten-individual), but found that the variance at the kindergarten level was negligible (<0.1). Therefore, we adopted a two-level model, the city-individual model. According to the Directed Acyclic Graph (DAG, Figure S6), the model was adjusted for the following covariates: temperature, age, gender, exclusive breastfeeding, FHA, single child, dampness, SSE, urban residency, and per capita income. The city was considered as a random effect variable. The model formulation is as follows

$$Y_{ij} = \beta_{00} + \beta_{10} \times X_{ij} + \beta_{01} \times W_j + \beta_{11} \times X_{ij} \times W_j + \mu_{0j} + \mu_{1j} \times X_{ij} + e_{ij} \tag{1}$$

Here, Y_{ij} denotes the AR/symptoms of the i individual in the j city; X_{ij} represents predictor variables for the i individual in the j city, including age, gender, exclusive breastfeeding, FHA, single child, dampness during pregnancy, SSE during pregnancy, and O₃ and living area (urban); W_j indicates city-level characteristics for the j city, including temperature and per capita income; μ_{0j} represents the

random intercept error associated with city-level variables; μ_{1j} denotes the random slope error attributable to city-level variables; and e_{ij} refers to the measurement error for the i individual in the j city.

By comparing the association of O₃ and AR onset across 3 periods, the time period exhibiting the strongest OR was considered as the exposure window containing the target SEW. To eliminate potential confounding effects from co-exposure to other pollutants, we developed two-pollutant models that adjusted for PM and gaseous pollutants.

2.5.3. Identification of SEW by DLNM. In the identified exposure time period as mentioned above, we performed a DLNM analysis using weekly lag intervals^{35,36} to capture SEW. The Cox link function was employed in DLNM. A cross-basis function was constructed to generate a two dimensional matrix representing the exposure of O₃ and its lags. Natural cubic splines were applied to both the exposure and lag dimensions, each with 3 degrees of freedom, while the median value served as the reference for risk estimation.³⁷ SEWs were identified by analyzing the lag-response relationship curves. Covariates adjusted in the model were consistent with those in MLBR. The specific model formulation is as follows

$$g(\mu_t) = \alpha + \sum_{j=1}^J f_j(x_{tj}; \beta_j) + \sum_{k=1}^K \gamma_k \mu_{tk} \tag{2}$$

Here, t denotes time, μ_t = E(Y_t), and g is the Cox link function. Y_t represents the dependent variables, namely AR/symptoms. The independent variable x_{tj} corresponds to the value of O₃, while f_j denotes the cross-basis function. The term μ_{tk} indicates the linear effect of covariates, with β_j and γ_k being their respective coefficients.

2.5.4. Modifiable Factors for the O₃-AR Associations. In the identified exposure time period containing target SEW, MLBR analyses were performed in subgroups, stratified by exclusive

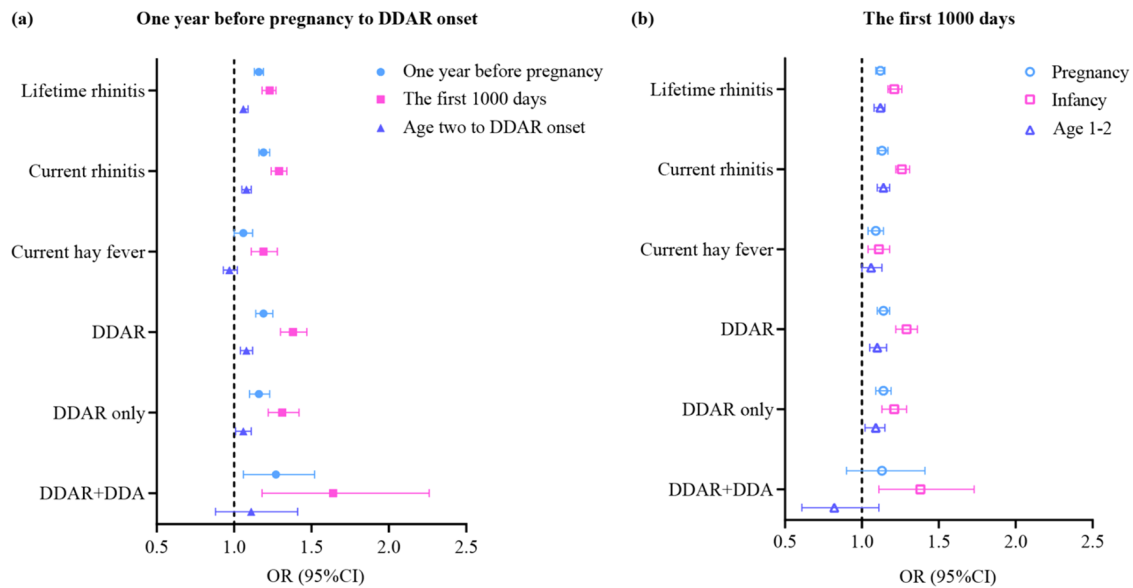


Figure 1. Associations (OR, 95%CI) of O₃ exposure in different time periods with the onset of AR/symptoms. Note: (a) Associations of O₃ exposure in 3 exposure windows with the onset of DDAR from 1 year before pregnancy to DDAR onset. (b) Associations of O₃ in 3 exposure windows within the first 1000 days with the onset of AR symptoms. MLBR models were applied, adjusting for temperature, age, gender, exclusive breastfeeding, FHA, single child, living area (urban), home dampness, SSE, and per capita income. City was set as the random effect variable.

breastfeeding length (<6 months vs ≥6 months), living in southern region (vs northern region), FHA (yes vs no), single child (yes vs no), urban residency (vs suburban/rural residency), and gender (boys vs girls), respectively. The O₃-AR association was compared between subgroups, and those with significantly different ORs between subgroups indicated the existence of effect modification. Risk differences between subgroups were calculated using the following formula³⁸

$$(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{SE_1^2 + SE_2^2} \quad (3)$$

\hat{Q}_1 and \hat{Q}_2 are the regression coefficients in different subgroups, respectively, and SE_1 and SE_2 are the standard errors in each subgroup.

2.5.5. E-R Curves for O₃ in the SEW and AR/Symptoms. To characterize the E-R relationship between O₃ in the SEW and AR/symptoms, we employed restricted cubic splines (RCS) analysis in the subgroups stratified by significant modifiers. This approach enabled the flexible modeling of potential nonlinear associations through piecewise polynomial regression. The number of knots in the RCS curve was set to 3, with the median concentration selected as the reference point for the effect estimation. To assess the potential nonlinearity, a likelihood ratio test was performed to evaluate the linearity assumption. Furthermore, adjustments were made for potential confounding factors consistent with the approach used in the MLBR model.

All analyses used R software (v4.1.1) with the dplyr/pcor/lme4 packages in data processing, dlnm for lag modeling, and rms for E-R curves. ORs (MLBR) and HRs (DLNM) were presented per interquartile range (IQR) increase of O₃ exposure (95% confidence interval (CI)).

3. RESULTS

3.1. Demographics and Prevalence of AR and Symptoms

In the total subjects ($n = 38,176$), the mean age was 4.8 years, and 48.1% were girls. The prevalence of DDAR was 11.9% consisting of 7.0% DDAR only and 1.3% DDRA + DDA (with DDAR earlier diagnosed than DDA). For lifetime rhinitis, current rhinitis, and current hay fever, the positive reports accounted for 31.2, 25.9, and 7.1%, respectively (Figure S2).

Southern cities, in particular Wuhan, Shanghai, and Nanjing, showed consistently higher prevalence than northern cities.

Compared to non-DDAR children, DDAR children were more likely to be boys (58.0 vs 51.1%) and single child (67.5 vs 55.5%). They lived more in the southern region (83.8 vs 70.9%) and had higher proportions of FHA (68.7 vs 34.0%). They reported more on exposure to poor housing conditions (renovation, dampness, mold, SSE) while less exclusive breastfeeding (>6 months) (56.8 vs 63.5%) (Table 1).

3.2. Assessment of O₃, PM, and NO₂

Across 7 cities, we observed distinct spatial variations in the level of exposure to O₃. For example, during the first 1000 days of life, Shanghai and Nanjing exhibited the highest average O₃ concentrations (83.4 and 78.9 μg/m³, respectively), while Urumqi showed the lowest level (54.7 μg/m³) (Figure S3). The above spatial variation characteristics remained consistent across 3 time periods. For PM, Shanghai had the lowest concentrations, while Wuhan had the highest concentrations of PM_{1.0} and PM_{2.5}. Urumqi and Taiyuan recorded peak PM_{2.5-10} and PM₁₀, respectively (Table S1). NO₂ concentrations showed minimal variations among cities. All IQR values were provided in Table S2.

Within the same exposure period, O₃ had weak correlations with PM and temperature (both $r < 0.6$) (Figure S4). Across different exposure periods, O₃ concentration was strongly correlated with itself ($0.6 < r < 0.9$) (Figure S5).

3.3. Regression Analysis

3.3.1. MLBR Analysis in Multiple Exposure Windows.

Among 3 periods for O₃ exposure, the first 1000 days of life, from pregnancy until age 2, emerged as the most critical exposure window for O₃-AR association in MLBR, compared to the other two periods—one year before pregnancy and from age 2 to the AR onset (Figure 1a). Notably, each IQR (15.2 μg/m³, Table S2) increase of O₃ in this period was associated with significantly elevated risks of DDAR (OR = 1.38, 95% CI: 1.30,1.47), DDAR only (OR = 1.31, 95% CI: 1.22,1.42), and

Table 2. Multilevel Log Binomial Regression (MLBR) Analysis (OR, 95%CI) for O₃ and AR/Symptoms Adjusting for the Second Co-Pollutant^a

Health outcomes	Single-Pollutant model	+PM ₁	+PM _{2.5}	+PM _{2.5-10}	+PM ₁₀	+NO ₂
The first 1000 days						
Lifetime rhinitis	1.23(1.18,1.27)***	1.10(1.05,1.15)***	1.19(1.14,1.24)***	1.21(1.16,1.26)***	1.15(1.10,1.20)***	1.25(1.21,1.30)***
Current rhinitis	1.29(1.24,1.34)***	1.13(1.08,1.18)***	1.23(1.18,1.28)***	1.25(1.20,1.31)***	1.18(1.13,1.24)***	1.32(1.27,1.37)***
Current hay fever	1.19(1.11,1.28)***	1.07(0.99,1.16)	1.14(1.05,1.23)***	1.15(1.06,1.24)***	1.07(0.99,1.16)	1.31(1.24,1.39)***
DDAR	1.38(1.30,1.47)***	1.20(1.12,1.28)***	1.32(1.24,1.40)***	1.34(1.26,1.43)***	1.24(1.16,1.33)***	1.42(1.33,1.51)***
DDAR only	1.31(1.22,1.42)***	1.18(1.08,1.27)***	1.26(1.17,1.36)***	1.28(1.18,1.38)***	1.18(1.09,1.28)***	1.34(1.24,1.45)***
DDAR + DDA	1.64(1.18,2.26)**	1.68(1.22,2.32)**	1.61(1.16,2.22)**	1.44(0.97,2.13)	1.45(1.01,2.08)*	1.55(1.10,2.19)*
Infancy						
Lifetime rhinitis	1.21(1.17,1.26)***	1.09(1.05,1.13)***	1.22(1.18,1.26)***	1.23(1.18,1.27)***	1.16(1.11,1.20)***	1.23(1.18,1.27)***
Current rhinitis	1.26(1.22,1.31)***	1.11(1.07,1.16)***	1.29(1.26,1.32)***	1.28(1.23,1.33)***	1.19(1.15,1.24)***	1.28(1.23,1.33)***
Current hay fever	1.11(1.04,1.18)**	0.96(0.89,1.03)	1.08(1.01,1.16)*	1.09(1.01,1.16)*	1.01(0.94,1.08)	1.13(1.06,1.20)***
DDAR	1.29(1.22,1.36)***	1.10(1.03,1.16)**	1.28(1.21,1.35)***	1.28(1.21,1.36)***	1.18(1.11,1.25)***	1.30(1.23,1.37)***
DDAR only	1.21(1.13,1.29)***	1.05(0.98,1.13)	1.20(1.13,1.28)***	1.21(1.13,1.29)***	1.10(1.03,1.18)**	1.21(1.14,1.30)***
DDAR + DDA	1.38(1.11,1.73)**	1.39(1.11,1.73)**	1.34(1.07,1.69)*	1.28(0.95,1.71)	1.33(1.02,1.73)*	1.35(1.07,1.70)*

^a**P* < 0.05, ***P* < 0.01, ****P* < 0.001. The above results showed that most of the significant associations for O₃ found in the single-pollutant model remained significant in the two-pollutant model, adjusting for PM_{1.0}, PM_{2.5}, PM_{2.5-10}, PM₁₀, and NO₂, respectively.

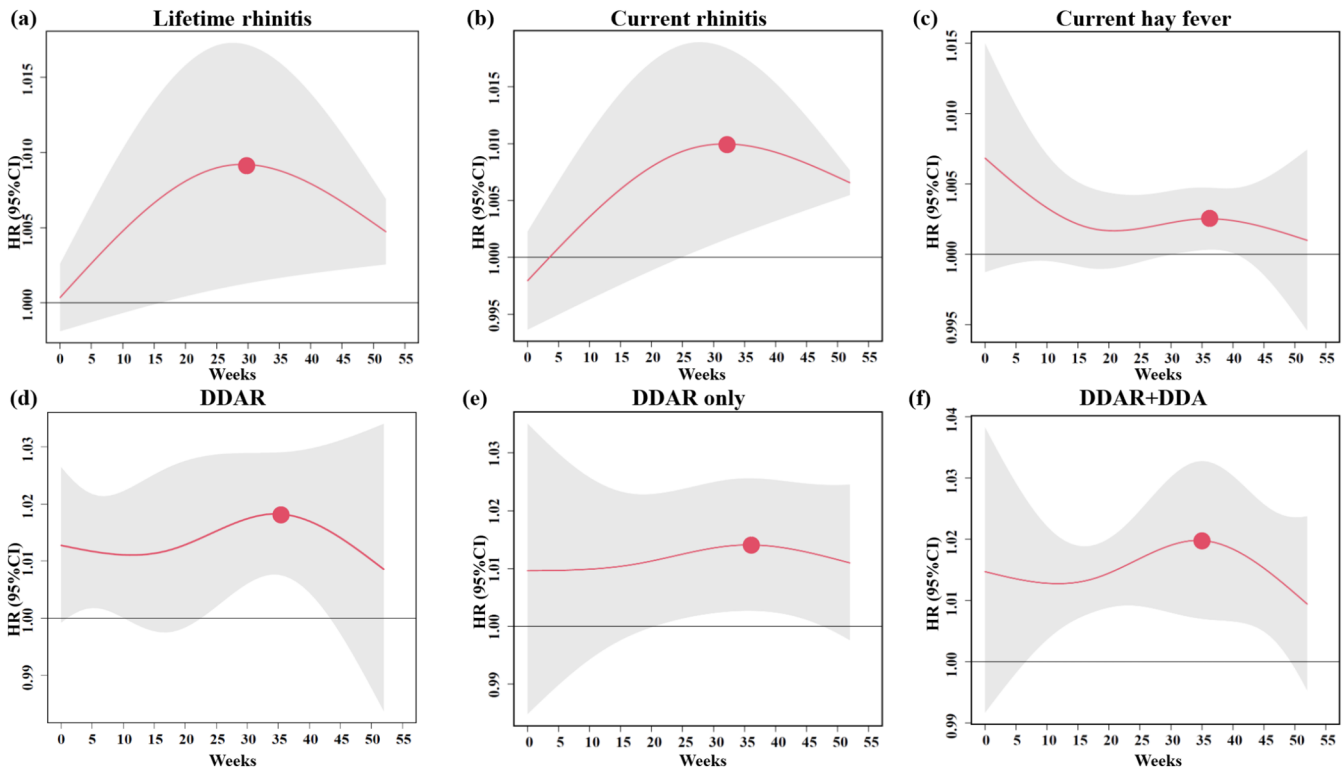


Figure 2. DLNM analysis (HR, 95%CI) on O₃ exposure in infancy and AR/symptoms in preschool children. Note: HR: hazards ratio. The covariates adjusted in the model were the same as those shown in Figure 1. The red curve in each subfigure is the HR value, the gray interval is the 95%CI, and the time windows at 30–38 weeks after birth, before and after the red dots, were the time windows with the highest risk in infancy. Panels (a)–(f) represent 6 health outcomes of interest.

comorbid DDAR and DDA (OR = 1.64, 95% CI: 1.18,2.26), respectively.

Within the 1,000-day window, the infancy period (aged 0–1 year) demonstrated the strongest association with O₃ exposure, compared to pregnancy and from age 1 to 2 (Figure 1b). Each IQR (10.1 μg/m³, Table S2) increase in O₃ exposure in infancy was associated with significantly elevated risks of DDAR (OR = 1.29, 95% CI:1.22,1.36), DDAR only (OR = 1.21,95% CI:1.13,1.29), and comorbid DDAR and DDA (OR = 1.38, 95% CI:1.11,1.73), respectively. We further performed two-pollutant model analyses during the high-risk exposure

windows of the first 1000 days and infancy, controlling for co-exposures to other air pollutants (PM_{1.0}, PM_{2.5}, PM_{2.5-10}, PM₁₀, and NO₂). Notably, the observed association between O₃ exposure and AR/symptoms remained robust (Table 2).

3.3.2. DLNM Analysis for SEW. The DLNM analysis in the first 1000 days of life (totally 143 weeks) corroborated the MLBR findings, consistently identifying infancy (40–92 weeks after pregnancy) as the most vulnerable exposure window for AR onset (Figure S7, pink background). Within infancy, we further performed the DLNM analysis and revealed that a more precise SEW appeared in 30–38 weeks postpartum

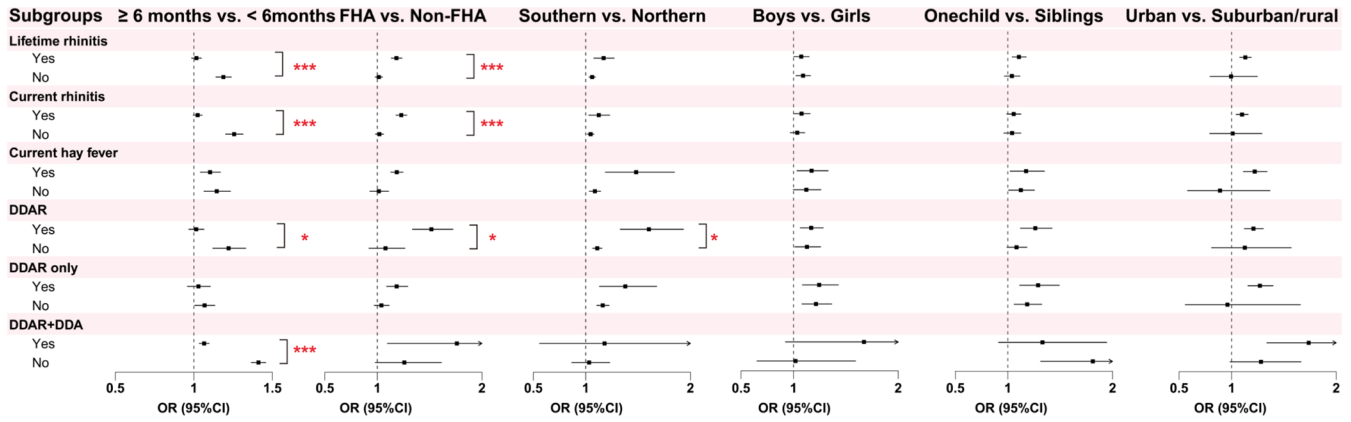


Figure 3. Subgroup analysis of the association between infancy O₃ exposure and AR/symptoms in children. Note: **P* < 0.05, ***P* < 0.01, ****P* < 0.001. These statistical significance tests refer to the comparisons of O₃-AR/symptoms associations between subgroups with or without the 6 variates: exclusive breastfeeding length (<6 months vs ≥6 months), living in southern region (vs northern region), FHA (yes vs no), single child (yes vs no), urban residency (vs suburban/rural residency), and gender (boys vs girls), respectively. In the regression model, the covariates adjusted in the model were consistent with those shown in Figure 1, except for the grouping variables, which were excluded. “Yes” and “No” refer to with or without the stratification variable labeled in the upper middle of each forest line graph. For example, the “Yes” and “No” under “Lifetime rhinitis” in the left line refer to “with exclusive breastfeeding ≥6 months”, while “No” as “with exclusive breastfeeding <6 months”, respectively.

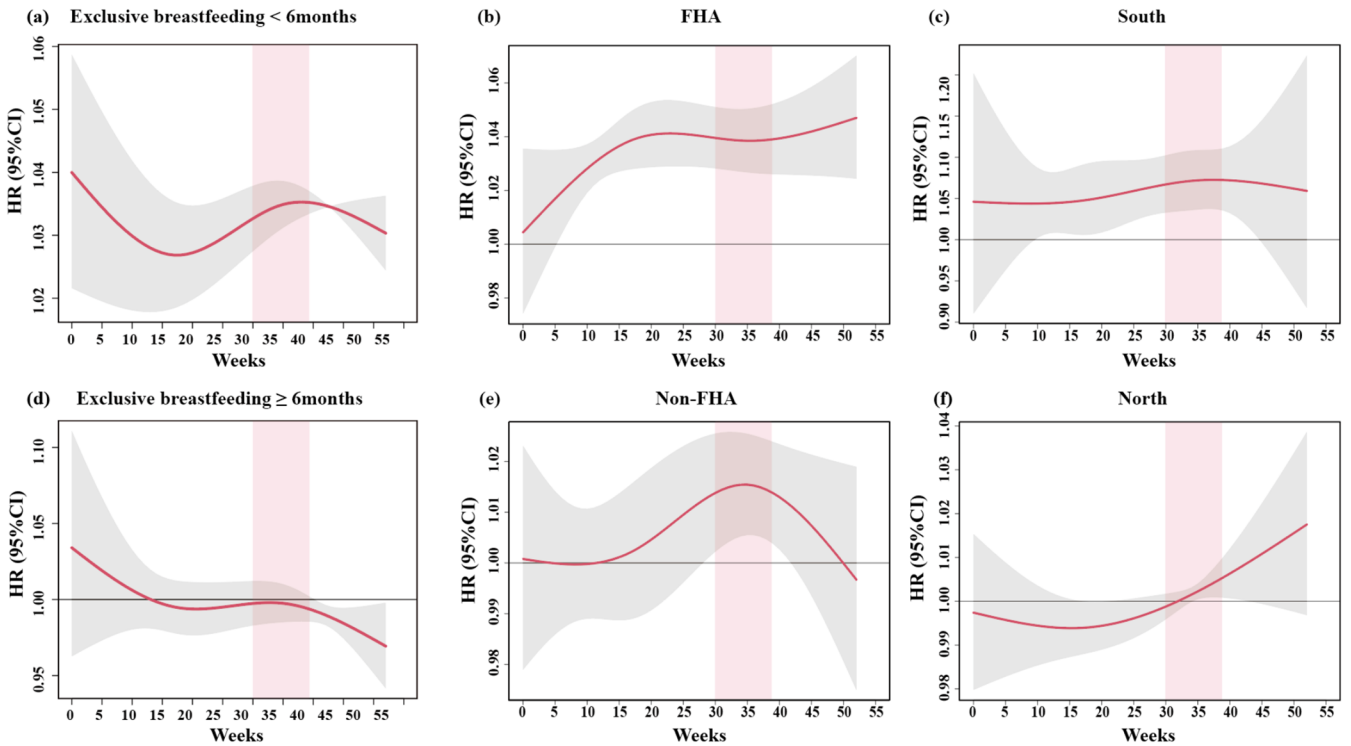


Figure 4. DLNM analysis of the association between infancy O₃ exposure and DDAR onset in 3 pairs of subgroups. Note: The covariates adjusted in the model were consistent with those shown in Figure 1, except for the grouping variables, which were excluded. In each subplot, the sensitive exposure window (postnatal weeks 30–38) is highlighted in red shading.

(7.5–9.5 months) with the highest association with AR risk (Figure 2). This refined specific SEW existed for AR and symptoms of interest, with DDAR, DDAR only, and DDAR + DDA exhibiting a more pronounced risk than AR symptoms. This SEW in late infancy suggested a potential developmental vulnerability that might predispose children to AR.

3.3.3. Subgroup Analyses. In the analysis of all 6 subgroups, 3 subgroups revealed significantly elevated AR/symptoms risks with O₃ exposure in infancy: the subgroups with less than 6 months of exclusive breastfeeding, FHA, and living in the southern region (Figure 3).

By DLNM analysis in each subgroup (Figure 4), for children with <6 months of exclusive breastfeeding, with FHA, and living in the southern region, the whole infancy had increased O₃-DDAR associations, while for those with ≥6 months of exclusive breastfeeding, such associations totally disappeared; for those without FHA, the risks largely decreased in the whole infancy but still remained significant for O₃ exposure in the SEW at 30–38 weeks, and for those living in the northern region, a very slight significant risk still remained in the SEW. Among 3 modifiable factors, only ≥6 months of exclusive

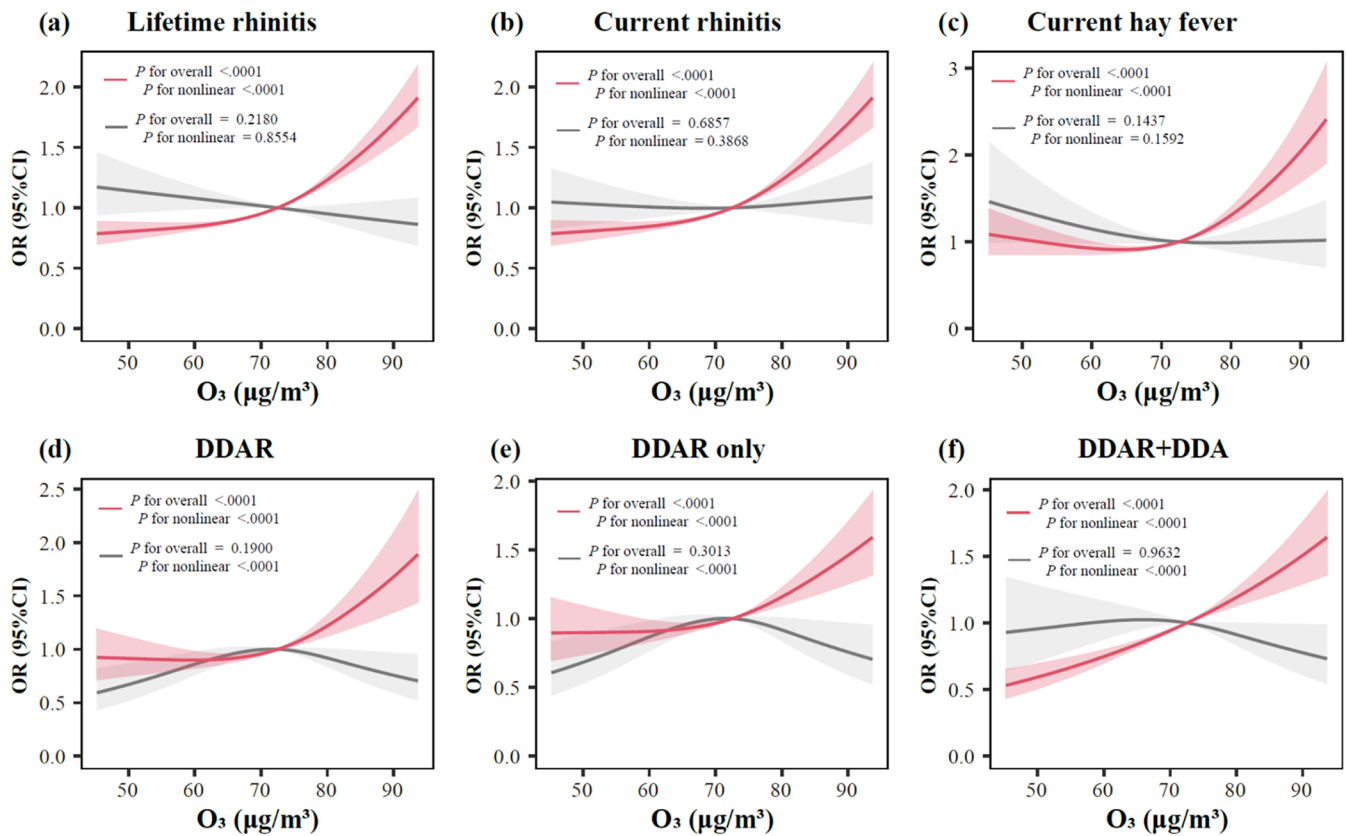


Figure 5. Exposure–response relationships stratified by exclusive breastfeeding (≥ 6 months vs < 6 months) in the identified SEW (postnatal 30–38w). Note: The covariates adjusted in the model were consistent with those shown in Figure 1, except for exclusive breastfeeding. Red lines with red shading refer to the RCS curve for those with exclusive breastfeeding < 6 months, while gray lines with gray shading refer to those with exclusive breastfeeding ≥ 6 months.

breastfeeding provided effective protection by offsetting the O_3 risks in the SEW in association with DDAR onset (Figure 4).

3.3.4. E–R Curve for O_3 in the SEW and AR/Symptoms. Focusing on O_3 exposure in SEW, the E–R curve revealed a significant J-shaped relationship between O_3 and AR/symptoms (all P -overall < 0.05), with no evidence of a threshold effect (Figure S8). We further depicted the E–R curves for exposure to the O_3 in the SEW in each subgroup with or without 6 months of exclusive breastfeeding, respectively. The similar J-shaped curves were observed, but only in those with < 6 months of exclusive breastfeeding (Figure 5). No significant E–R association was observed in the group with ≥ 6 months of exclusive breastfeeding.

4. DISCUSSION

This multicenter nationwide study identified postnatal 30–38 weeks (7.5–9.5 months of age) as the critical SEW for early-life O_3 exposure associated with the onset of AR in preschool children. Among all evaluated factors, ≥ 6 months of exclusive breastfeeding demonstrated significant alleviation effects in reducing the O_3 -associated AR risk within this SEW. The E–R relationship for O_3 in this window exhibited a J-shaped curve with no detectable safety threshold.

Epidemiological studies have consistently identified O_3 as a harmful secondary air pollutant that can impair immune function and increase susceptibility to allergic diseases. Supporting evidence comes from the Taiwan Birth Cohort (OR = 2.02, 95%CI: 1.05,3.88) and German LISA Study (OR = 1.30, 95%CI: 1.02,1.64), both demonstrating that elevated

O_3 exposure significantly increased AR risk in children under 6 years.^{39,40} Our study advanced this understanding by identifying infancy (0–1 year) as a vulnerable period for O_3 -associated AR risk, specifically in the postnatal 30–38 weeks (7.5–9.5 months of age) in late infancy as the SEW with the highest susceptibility. These findings are supported by the Canadian T-CHEQ cohort, where infant O_3 exposure (mean $43 \mu\text{g}/\text{m}^3$) was associated with increased risks of both asthma (HR = 1.22, 95%CI: 1.04,1.43) and AR (HR = 1.15, 95%CI: 1.00,1.31), while postinfancy exposure (after age 3) showed no significant effects.⁴¹ Similarly, a seven-city study in Northeast China reported that early-life O_3 exposure (mean $86.9\text{--}92.6 \mu\text{g}/\text{m}^3$) elevated AR risk in school-aged children (adjusted OR = 1.13, 95%CI: 1.07,1.18).⁴² Compared to other pollutants, O_3 played a distinct role in both exacerbating and initiating AR. On one hand, O_3 demonstrated a stronger association with the risk of AR compared to other pollutants (see Table S4); On the other hand, O_3 might generate more toxic secondary products—such as aldehydes and superoxide radicals—that amplified inflammatory responses and promoted a pronounced Th2 bias.⁴³ In addition, O_3 could act as an adjuvant, interacting with other allergens to collectively trigger allergic diseases.⁴⁴ Collectively, these features demonstrated the profound impact of O_3 on AR.

Subgroup analysis revealed that when FHA, geographical region, and exclusive breastfeeding (≥ 6 months vs < 6 months) modified the associations between O_3 exposure and AR onset, only ≥ 6 months of exclusive breastfeeding demonstrated statistically significant protective effects in attenuating or even

eliminating AR risk associated with O₃ in the identified SEW. These findings show remarkable consistency with our previous finding on the protective role of ≥ 6 months of exclusive breastfeeding in decreasing the risks of early-life PM exposure on asthma development in Shanghai preschoolers,²³ despite the sample size being smaller ($n = 16,009$) than in this study ($n = 38,176$). Most notably, the robust protective effects of exclusive breastfeeding (≥ 6 months) in counteracting O₃-associated AR risks strengthened the importance of breastfeeding, not only in balancing the nutrition in infants but in mitigating the adverse health impacts of air pollution during this vulnerable developmental period. The potential mechanisms underlying the formation of the SEW might be closely linked to developmental characteristics of the infant's respiratory tract, behavioral habits, and transitions in feeding practices during this period. Due to the immature immune system and increased exposure to particles, pathogens, and allergens, infants might experience more pronounced immune disturbances in response to these adverse factors.^{45,46}

The protective role of breastfeeding against air pollution-induced allergic disorders is supported by existing literature. Dong et al. demonstrated that extended breastfeeding (>3 months) significantly mitigated O₃-associated wheezing risk (OR = 0.99, 95%CI: 0.86,1.15) compared to a shorter duration (<3 months; OR = 1.23, 95%CI: 1.00,1.50).⁴⁷ Complementary evidence also came from a Canadian cohort revealing lower breastfeeding rates in children with early onset chronic asthma (7.5%) compared to healthy controls (10.1%).⁴⁸ Different from previous studies as mentioned above and in alignment with WHO guidelines,⁴⁹ our study specifically evaluated a 6-month duration of exclusive breastfeeding and its significant protective effect against O₃ exposure in the SEW-associated AR development. These consistent findings across studies underscore the importance of breastfeeding in respiratory allergy prevention and highlight the need for further research to elucidate the underlying biological mechanisms. Although previous studies have also suggested that infants with eczema or known food allergies may introduce allergens and other foods before 4 months of age,^{50,51} these studies do not recommend discontinuing breastfeeding. This is because breast milk serves not only as a nutritional source but also as a microbial ecosystem that plays a critical role in shaping the infant's gut microbiota, providing anti-inflammatory protection, and promoting immune system maturation.^{52,53} Exclusive breastfeeding beyond six months provides crucial support for strengthening the immune system and promoting a healthy gut microbiome, partly by counteracting increased exposure to bacteria and other harmful microorganisms inhaled or ingested at SEW (30–38 weeks, around 7–9 months after birth), thereby helping to offset the risks during the sensitive exposure window.⁵⁴

In the SEW, the *E–R* relationship between O₃ and AR demonstrated a distinct J-shaped nonlinear association, consistent with previous U.S. studies reporting similar threshold-free, J-shaped curves for O₃-asthma relationships in pediatric populations.^{18,55} This observed pattern might reflect two synergistic pathological mechanisms: (1) The co-occurrence of elevated O₃ levels with usually higher ambient temperatures likely exacerbates oxidative stress and airway inflammation;⁵⁶ and (2) the concurrent presence of highly reactive particulate components—including polycyclic aromatic hydrocarbons (PAHs), organic carbon (OC), and elemental carbon (EC)—might further potentiate respiratory

toxicity through combined exposure effects.⁵⁷ The absence of a clear exposure threshold in these associations suggests that even a low level of O₃ exposure during this critical developmental window may confer measurable AR risk.

This study made three significant contributions to environmental health research. First, through a large-scale, multicenter design utilizing high-resolution spatiotemporal O₃ exposure data in mainland China, we have precisely identified postnatal 30–38 weeks (7.5–9.5 months in infancy) as a critical window of susceptibility for the development of the O₃-associated AR in preschool children. Second, our study provided a comprehensive characterization of the *E–R* relationship between O₃ in the SEW and pediatric allergic respiratory diseases in the Chinese population, with a novel finding of a threshold-free J-shaped association. Third, and most importantly, we demonstrated that among multiple evaluated protective factors, exclusive breastfeeding for ≥ 6 months uniquely attenuated the O₃-associated AR risk during this vulnerable period. The above findings carry important implications for both public health policy by informing improved air quality standards and infant nutrition guidelines, and future research directions to the biological mechanisms underlying pollution-diet interactions during critical developmental periods.

This study also has several limitations. First, AR and related symptoms were assessed through parent-reported questionnaires without clinical examinations in each subject. This might have introduced potential recall errors or misreporting. However, we applied the standardized and validated questionnaire with its advantages of good feasibility and acceptability. Second, we focused on the onset of AR and did not examine the longitudinal trajectory or pattern of AR development. Variations in AR progression over time might influence the identification of the SEW. Third, although we employed a high-resolution O₃ exposure model based on individual residential addresses, we did not collect data on children's time-activity patterns, which might have led to exposure misclassification.

5. CONCLUSIONS

This large multicenter study identified postnatal 30–38 weeks (7.5–9.5 months) as the critical exposure window for O₃-associated AR risk in preschoolers, showing a threshold-free J-shaped exposure–response relationship. Exclusive breastfeeding for at least 6 months significantly attenuated this risk, providing evidence of early-life prevention strategies. This population-level evidence established a significant link between early-life O₃ exposure during infancy and AR development, offering a scientific foundation for developing targeted preventive measures targeted at this critical window.

■ ASSOCIATED CONTENT

Data Availability Statement

If you are interested in our data, please contact the corresponding author to obtain the original data based on the innovative research proposal proposed by the data applicants.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/envhealth.5c00319>.

Characteristics and distribution of O₃, other air pollutants and meteorological factors in each of 7 cities

and in different exposure windows (Table S1–S2); construction and selection of MLBR model (Table S3); associations (OR, 95% CI) of O₃ and other pollutants in relation to AR/symptoms in the two-pollutant model during infancy (Table S4); graphical distribution of participants (Figure S1); city-level prevalence of AR/symptoms (Figure S2); O₃ exposure in 6-time windows (Figure S3); partial correlations between pollutants and meteorology (Figure S4); partial correlations of O₃ levels across different exposure windows (Figure S5); directed Acyclic Graph (DAG) for variable selections (Figure S6); DLNM analysis of O₃ exposure during the first 1000 days (Figure S7); Exposure–response curve for O₃ exposure in the SEW (Figure S8) (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The study was funded by the National Natural Science Foundation of China (No. 82473591, 82504367), Natural Science Foundation of Shanghai (25ZR1402090), Shanghai International Science and Technology Partnership Project (No. 21230780200), Shanghai B&R Joint Laboratory Project (No. 22230750300), China National Postdoctoral Program for Innovative Talents (BX20240069), and China Postdoctoral Science Foundation (2025M770734).

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