Effect of early life exposure to air pollutants on the incidence of eczema in children under 2 years

Zhiping Wang[1], Yuxiu Liang[1], Shaoqian Lin[2], Xiaodong Zhao[2], Shuoxin Bai[1], Jiatao Zhang[1], Shuang Du[1], and Yanling Wu[1]

[1]Shandong University Cheeloo College of Medicine
[2]Jinan Municipal Center for Disease Control and Prevention

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Abstract

Background: The incidence of eczema is higher in children aged 0-2 years, but the long-term effect of air pollutants exposure in early life on the risk of eczema development is unclear. **Methods**: We conducted a birth cohort study in Jinan, China, to explore the effect of early life air pollutant exposure on the risk of eczema in younger children. An inverse distance weighting method was used for individual exposure assessment. Binary and multivariate logistic models were used to investigate the effects of air pollutants on eczema, the distributed lag model to find sensitive windows of exposure, weighted quantile sum model and principal component analysis to explore the combined effects of multiple pollutants. **Results**: The cumulative incidence rate for eczema among 5819 children aged 2 was 19.8%. Exposure to high levels of O_3 during pregnancy (*OR* 1.12, 95% *CI* 1.06-1.19) and during the first year after birth (*OR* 1.24, 95% *CI* 1.03-1.50) increased the risk of eczema. $PM_{2.5\text{-}10}$ during pregnancy (*OR* 1.31, 95% *CI* 1.20-1.43), $PM_{2.5}$ (*OR* 1.08, 95% *CI* 1.01-1.15) and $PM_{2.5\text{-}10}$ (*OR* 1.07, 95% *CI* 1.00-1.14) during the first year after birth also increased the risk of eczema. The critical window for O_3 and PM exposure was the third trimester and early postnatal period. Moreover, in the combined effect of multiple pollutants, O_3 played a dominant role during pregnancy (weighting > 0.3), with a predominantly O_3 principal component associated with eczema risk (adjusted *OR* 1.011, 95% *CI* 1.007-1.015). **Conclusions**: Exposure to air pollutants O_3 and PM in early life increased the risk of eczema at 0-2 years of age, and the sensitivity window appeared earlier. O_3 exposure during pregnancy played a key role in the combined effect of pollutants on eczema risk.

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[a] Department of Occupational and Environmental Health, School of Public Health, Cheeloo College of Medicine, Shandong University, 44 Wenhua Xi Road, Jinan, Shandong 250012, PR China.

[b] Jinan Municipal Center for Disease Control and Prevention, Jinan, Shandong, P.R. China.

[c] Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, 44 Wenhua Xi Road, Jinan, Shandong 250012, PR China.

[*]Correspondence to:

Zhiping Wang. School of Public Health, Cheeloo College of Medicine, Shandong University, 44 Wenhua Xi Road, Jinan, Shandong 250012, PR China. E-mail address:*zhipingw@sdu.edu.cn.*

Yanling Wu. School of Public Health, Cheeloo College of Medicine, Shandong University, 44 Wenhua Xi Road, Jinan, Shandong 250012, PR China. E-mail address:*ling1984@sdu.edu.cn*.

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Keyword : Eczema, Air pollution, Cohort study, Early life, Joint effect

1. Introduction

Eczema (also known as atopic dermatitis, AD) is a common chronic, recurrent skin allergic disorder in children, with approximately one in five children suffering from eczema. Eczema mostly occurs in early life, with 50% of patients diagnosed within the first year of life(Fishbein, Silverberg, Wilson, & Ong, 2020). In recent years, the incidence of eczema has been on the rise worldwide(Sun et al., 2019), and the intense itching and rash of eczema attacks severely affect the quality of life of affected children(Bosma, Ouwerkerk, & Middelkamp-Hup, 2021). More importantly, children with eczema are more likely to develop other atopic diseases, such as food allergies, asthma, and allergic rhinitis(Hill & Spergel, 2018; Martin et al., 2015). One review estimated that children with eczema are as much as six times more likely to develop a food allergy compared to their healthy peers(Tsakok et al., 2016). Another Canadian study found that children with eczema had 1.65 times the risk of asthma, 7.37 times the risk of food allergies, and 2.36 times the risk of allergic rhinitis at age 3 compared to healthy children(Dharma et al., 2018).

Numerous factors influence the development of eczema in infants and children, including genetic factors and a variety of prenatal and postnatal environmental factors, such as parental allergy history(Venter et al., 2021), maternal diet during pregnancy(Tan et al., 2023), antibiotic use(F. Q. Huang, Lu, Wu, Gong, & Zhao, 2020), and air pollutants. Air pollutants have been shown to increase the risk of allergic diseases, and a 2020 Canadian study showed that NO_2 and O_3 exposure within the first three years of life increased the risk of asthma and eczema in children(T. To et al., 2020). A Wuhan, China study showed that PM exposure in the early life, especially during pregnancy, increased the risk of childhood asthma(Y. Zhang et al., 2021). A pooled study of two Swedish birth cohorts found that exposure to environmental $PM_{2.5}$, PM_{10}, and NO_2before the age of 2 years was associated with increased expression of inflammatory protein levels such as IL-12B, IL-8, and IFN-gamma(He et al., 2022).

Fewer studies have been conducted on the association between exposure to air pollutants and eczema, and most of them have used the number of eczema outpatient visits as the study outcome. A 2022 time-series

study in Guangzhou, China, found that high PM_{10} exposure in the short term (3 days) increased the number of eczema outpatient visits, with more pronounced effects in children(J. Zhang et al., 2022). A 2022 study in Shanghai, China, found that O_3, $PM_{2.5}$, and NO_2 exposure increased eczema outpatient visits, especially in children aged 0-7 years(Ye et al., 2022). A time series study in Chongqing, China, found that short-term (5 days) exposure to ambient air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO) increased the number of eczema clinic visits in children aged 0-18 years, especially in children aged 0-3 years(Luo et al., 2022). A 2018 Korean study found that short-term (6 months) exposure to high PM exacerbated atopic dermatitis in preschool children living in industrial urban areas(Oh et al., 2018). A 2015 study from Taiwan, China, found that high CO exposure throughout pregnancy, especially in early pregnancy, increased the risk of eczema in infants at 6 months of life(C. C. Huang et al., 2015). Most of the above studies are about the short-term effects of exposure to air pollutants on eczema, and there is a lack of evidence to assess the effects of long-term exposure to pollutants throughout early life, and the types of pollutants that play a major effect on childhood eczema are not exactly the same in different studies in different regions, moreover, there is a lack of evidence for the combined effects of pollutants. In addition, most of the relevant studies in China are in southern cities such as Guangzhou and Shanghai, and there is a lack of evidence related to the cohort of children in northern cities of China.

Therefore, this study relied on the Jinan birth cohort in a northern Chinese city to investigate the effect of exposure to air pollutants in early life (including pregnancy and two years after birth) on the risk of childhood eczema, and to find its critical window period by distribution lag model (DLM), and to analyze the combined effect of 6 pollutants in different periods by Weighted Quantile Sum (WQS) regression model and Principal component analysis (PCA). The results of the study may provide epidemiological evidence for preventing the development of eczema and improving the physical fitness of children.

2. Materials and methods

2.1 Study population

The study population was subjects who completed 2-year follow-up in the Jinan Birth Cohort, a baseline population recruited from January 2018 to December 2019 from 15 vaccination clinics selected in urban areas of Jinan, Shandong Province, and surveyed at the second vaccination of infants at 1 month of age for hepatitis B vaccine according to the national immunization plan. The details of the cohort were described in the previously published article(Bai et al., 2023; Du et al., 2022).

Each mother of the infant was informed of the purpose and content of the study and signed an informed consent. The study was approved by the Ethics Committee of Preventive Medicine of Shandong University (Approved number: 20170315).

2.2 Definition of eczema

Physician-diagnosed eczema within the first 12 months of life, as reported by the child's mother, were defined as eczema at age 1. At the two-year follow-up, physician-diagnosed eczema within the past 12 months, as reported by the mother, was defined as eczema at age 2. Study participants were divided into four groups based on eczema at age 1 and eczema at age 2, including no eczema, only eczema at age 1, only eczema at age 2, and persistent eczema.

2.3 Exposure assessment of the air pollutants

The ambient air pollutant data were obtained from dynamic monitoring data of air pollutants collected at 17 ambient air quality monitoring stations in Jinan. Daily 24-hour average concentrations of SO_2, NO_2, CO, PM_{10}, $PM_{2.5}$, and daily maximum 8-hour average concentrations of O_3 were obtained for the birth cohort population between the date of the last menstrual period of the earliest pregnant mother and the date of birth of the latest child who had reached the age of 2 years. Then obtained the $PM_{2.5\text{-}10}$ concentration by subtracting the $PM_{2.5}$ concentration from the PM_{10} concentration. The residence address of the mother during pregnancy and after the birth of the child, the date of the mother's last menstrual period for the current pregnancy and the date of birth of the child were collected through questionnaires at the baseline and

follow-up surveys of the cohort study, and the pollutant concentrations measured at 17 monitoring stations were weighted according to the spatial distance between the home address and the concentration at the monitoring station using the Inverse Distance Weighting (IDW) model to obtain the individual pollutant concentrations for each study subject(Rishikeshan, Katiyar, Mahesh, & Ieee, 2014).

2.4 Covariate

Child information Gender, birth weight, breastfeeding, birth mode, use of masks, and preterm birth.

Parental information Parental atopy, maternal age at delivery, work during pregnancy, maternal primipara.

Family information House decoration, home dampness, use of carpet, pets, monthly household income, open windows often, air purifier use.

Parental atopy was defined as either parent having had an allergic disease, including eczema, allergic rhinitis, food and drug allergy, or asthma. Working during pregnancy was defined as the act of the mother continuing to work in the workplace during pregnancy. Home dampness was defined as having at least one of the following dampness-related exposures in the dwelling environment: visible mold stains, visible damp stains, damp clothing/bedding, condensation on windows, or moldy odors. Open windows often was defined as three or more window openings in a week by the child's cohabitants.

2.5 Statistical analysis

Descriptive analysis Median, interquartile range (IQR), percentile and mean ± standard deviation was used to characterize the air pollutants. Spearman's correlation analysis was used to detect the magnitude of correlation between each environmental factor. Independent samples t-test or Mann-Whitney U rank sum test, Chi-square test or Fisher exact test were used to compare the differences in characteristics between the eczema group and the non-eczema group.

Generalized linear models (GLM) It is a direct generalization of the common linear models, and logistic regression analysis was implemented by the link function. The binary logistic model was used to estimate the effects of pollutant exposure during pregnancy on one-year-old eczema, two-year-old eczema, and cumulative eczema; and a multiple logistic model was used to estimate the effect of pollutant exposure during pregnancy and two years postnatally on no eczema, only eczema at age 1, only eczema at age 2, and persistent eczema (no eczema group: OR =1), the process was implemented through the 'nnet' package in the R software.

The distributed lag model (DLM) A sensitive period is a time when the effects of exposure on development and disease risk are stronger at one time than at others. In this study, the distributed lag model was used to find the sensitive window period of air pollutants on the onset of eczema. The vulnerable sensitive window period was identified by dividing the exposure time by week, based on the generalized linear model, and adding cross-sectional basis functions of the study variables to assess the lag effect of exposure factors and the relationship of exposure response. The process was implemented through the 'dlnm' package in R software.

Weighted quantile sum (WQS) model To evaluate the joint effect of exposure to air pollutants on the onset of eczema in children over different time periods(Garcia-Serna et al., 2022). Inclusion of all pollutants in the model and analysis of their positive association with childhood eczema, the WQS index (a weighted linear index) is obtained, which is considered as an overall mixture effect, while weight of each pollutant indicated how much a certain pollutant contributed to the WQS index, and the values of the weights range from 0 to 1. When constructing the model, the model parameter "q" was set to 4, which indicates that the effect is obtained after each quantile increase, the number of bootstrap (b) samples used in the parameter estimation of the model was set to 1000. The process was implemented through the 'gWQS' package in the R software.

Principal component analysis (PCA) PCA is a multivariate statistical method that classifies multiple air pollutants with correlations into a set of uncorrelated variables, called principal components (PCs),

representing the most important characteristics of the raw data, which are arranged in descending order of variance. The process was implemented through the 'factoextra' package in R software.

Sensitivity analysis : To verify the robustness of the WQS model, firstly, the model parameter "q" was changed from 4 to 10, representing the joint effect of exposure to air pollutants on childhood eczema for each 10-percentile increase. Secondly, the number of bootstrap (b) samples used in the parameter estimation of the model were set to 100, 1000, 2000 and 3000 respectively. If there was no significant difference in the results of sensitivity analysis, it indicated the robustness of the model.

Variance Inflation Factor (VIF) was used to diagnose the covariate covariates in each multifactorial model, and statistical analysis was performed in this study with P <0.05 as the test level, and all statistical analyses were performed in R 4.1.2.

3.Results

3.1 Characteristics of study population in the Jinan birth cohort

We presented in Figure 1 the distribution of monitoring stations, the home addresses of study subjects, and the locations of outpatients. A Global Moran's I analysis of eczema prevalence in the five districts showed an index of -0.610, Z=-0.718, P =0.472, and no statistically significant spatial autocorrelation.

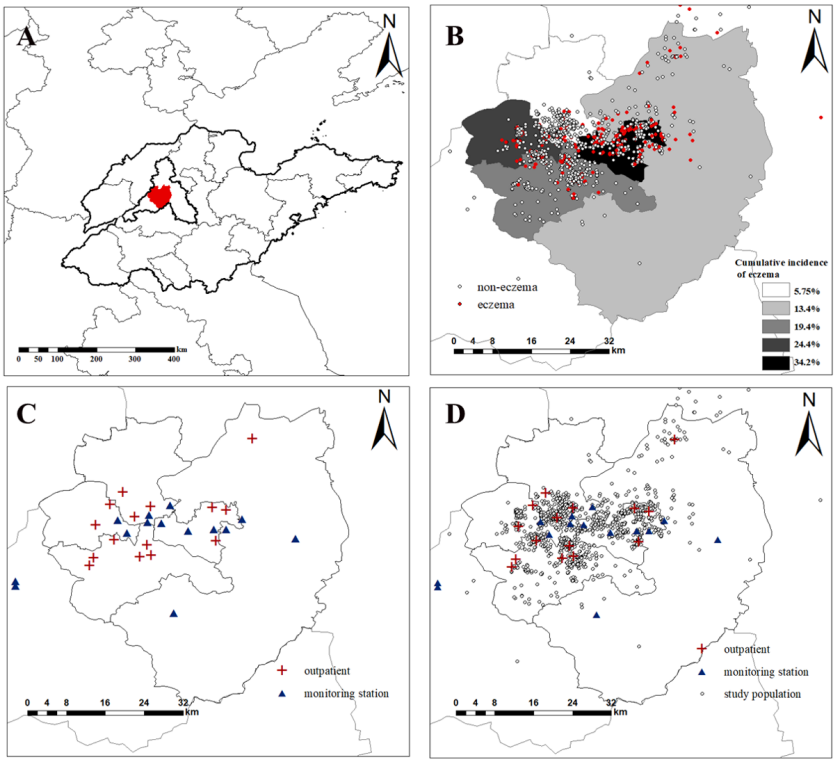

Figure 1 The locations for study area(A), home addresses of subjects (B, D), outpatient clinics and monitoring stations (C, D), and the incidence of eczema in five different districts(B).

6640 mothers of newborns without congenital disease participated in the survey, of whom 139 were multiples, and after further exclusion, a total of 6501 singleton births without congenital disease served as the baseline population for the birth cohort, and after 2 years of follow-up, a total of 5819 study subjects completed follow-up, with a 10.5% (682/6501) lost to follow-up rate over 2 years. A total of 1155(19.8%) of the 5819 study subjects had eczema before the age of 2 years, with 996(17.1%) children with eczema at 1 year of age

and 229 (3.9%) with eczema at 2 years of age (Figure 2). A higher proportion of children with eczema had a history of parental atopy (22.08% vs 18.83%), maternal working during pregnancy (65.71% vs 60.06%), high monthly household income (89.52% vs 86.60%), maternal primipara (53.77% vs 47.81%), infrequent window opening (51.95% vs 60.50%), and use of air purifiers (23.64% vs 20.44%) compared with non-eczema study subjects(P <0.05) (Table1).

Classification of eczema	n
Eczema at only 1 year old	926
Eczema at only 2 year old	159
Persistent eczema	70
1 year old eczema	926+70=996
2 year old eczema	159+70=229
Cumulative eczema	926+70+159=1155

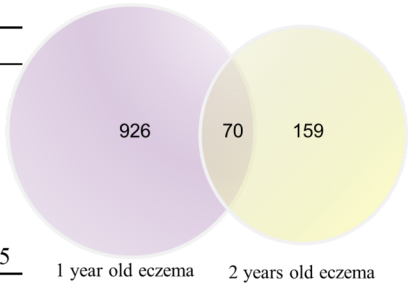

Figure 2 The proportion of eczema in the Jinan birth cohort.

Table 1 Characteristics of study population in the Jinan Birth Cohort.

Characteristics	Eczema	Non-eczema	P
Total (n, %)	1155(19.8)	4664(80.2)	
Characteristics of children			
Gender (n, %)			0.329
male	612(52.99)	2394(51.33)	
female	543(47.01)	2270(48.67)	
Birth weight (g, mean ± SD)	3404.7±474.21	3389.4±487.9	0.144
Breastfeeding			0.328
<12months	162(14.03)	601(12.89)	?¿?
12 months	993(85.97)	4063(87.11)	
Birth mode (n, %)			0.124
Vaginal delivery	654(56.62)	2521(54.05)	
Cesarean delivery	501(43.38)	2143(45.95)	
Use of masks (n, %)			0.379
Yes	741(64.16)	3059(65.59)	
Preterm birth (n, %)			0.645
Yes	55(4.76)	205(4.40)	
Characteristics of parents			
Parental atopy (n, %)			**0.014**
Yes	255(22.08)	878(18.83)	
Maternal age at delivery (years, n, %)			0.747
<35	942(81.56)	3782(81.09)	?¿?
35	213(18.44)	882(18.91)	
Maternal work during pregnancy (n, %)			**<0.001**
Yes	759(65.71)	2801(60.06)	
Maternal Primipara (n, %)			**<0.001**
Yes	621(53.77)	2230(47.81)	
Family characteristics			
House decoration (n, %)			0.155
Yes	44(3.81)	226(4.85)	

Characteristics	Eczema	Non-eczema	*P*
Home dampness (n, %)			0.830
Yes	43(3.72)	165(3.54)	
Use of carpet (n, %)			0.255
Yes	51(4.42)	170(3.65)	
Pets (n, %)			0.250
Yes	33(2.86)	104(2.23)	
Monthly household income (RMB, n, %)			**0.009**
<6000	121(10.48)	625(13.40)	?¿?
6000	1034(89.52)	4039(86.60)	
Open windows often (n, %)			**<0.001**
Yes	600(51.95)	2821(60.50)	
Use an air purifier (n, %)			**0.019**
Yes	273(23.64)	953(20.44)	

3.2 Concentrations of air pollutant exposure in the early life

The exposure to pollutants during pregnancy, 1 year after birth and 2 years after birth of the study subjects was shown in Table 2. Higher levels of pollutant exposure during pregnancy than after birth and higher levels of pollutant exposure in the first year after birth than in the second year after birth (all P -values < 0.001). In Table 3, the pollutant exposure of eczema and non-eczema subjects in different exposure periods was compared. Only pollutant concentrations during pregnancy differed significantly between eczema and non-eczema populations (P <0.001), with only NO_2concentrations differing during the other periods. In Figure S1, we showed changes in the concentration of pollutants during pregnancy among subjects at different conception dates. Figure S2 showed the correlation between the pollutants at different exposure periods, with a strong correlation between the pollutants.

Table 2 Exposure concentrations of air pollutants in different stages of early life.

Air pollutant concentration	Mean ± SD	P $_{25}$	P_{50} [IQR]	P $_{75}$	Mean ± SD	P $_{25}$	P $_{50}$ [IQR]	P $_{75}$
	During entire pregnancy	**During entire pregnancy**	**During entire pregnancy**	**During entire pregnancy**	**During age 0-2 y**	**During age 0-2 y**	**During age 0-2 y**	**During age 0-2 y**
NO_2(μg/m^3)	45.4 ± 5.5	41.1	45.7 [8.1]	49.3	38.4 ± 3.1	36.6	38.4 [3.6]	40.3
SO_2(μg/m^3)	14.8 ± 2.0	13.5	14.5 [2.1]	15.7	12.5 ± 0.9	11.8	12.4 [1.3]	13.1
O_3(μg/m^3)	109.1 ± 13.6	97.0	109.0 [23.3]	120.4	107.6 ± 6.2	102.7	108.9 [10.6]	113.3
CO (mg/m^3)	0.87 ± 0.07	0.83	0.88 [0.08]	0.91	0.83 ± 0.03	0.81	0.83 [0.04]	0.85
PM_{10}(μg/m^3)	113.4 ± 11.6	104.5	112.9 [18.1]	122.6	99.6 ± 5.9	95.8	99.8 [7.8]	103.6

Air pollutant concentration	Mean ± SD	P 25	P50 [IQR]	P 75	Mean ± SD	P 25	P 50 [IQR]	P 75
$PM_{2.5}$(μg/m^3)	54.9 ± 7.0	49.3	55.3 [11.1]	60.4	48.8 ± 3.3	46.5	48.5 [4.3]	50.7
$PM_{2.5\text{-}10}$(μg/m^3)	58.5 ± 5.6	54.7	58.5 [7.6]	62.3	50.8 ± 3.3	48.8	51.1 [4.1]	52.9
	During age 0-1y	**During age 0-1y**	**During age 0-1y**	**During age 0-1y**	**During age 1-2y**	**During age 1-2y**	**During age 1-2y**	**During age 1-2y**
NO_2(μg/m^3)	40.1±4.6	37.3	39.4 [5.3]	42.6	36.6±2.2	35.5	37.3 [2.5]	38.0
SO_2(μg/m^3)	12.6±1.3	11.8	12.4 [1.6]	13.4	12.3±0.79	11.6	12.4 [1.4]	13.0
O_3(μg/m^3)	113.0±4.6	111.0	115.0 [5.5]	116.0	102.0±11.3	92.6	106.0 [19.0]	112.0
CO (mg/m^3)	0.85±0.04	0.82	0.85 [0.05]	0.87	0.81±0.04	0.78	0.81 [0.05]	0.83
PM_{10}(μg/m^3)	101.0±9.2	94.8	99.4 [12.4]	107.0	97.9±6.8	92.9	97.3 [10.1]	103.0
$PM_{2.5}$(μg/m^3)	51.5±4.5	48.5	50.5 [5.5]	53.9	46.0±2.7	44.1	45.8 [3.8]	47.9
$PM_{2.5\text{-}10}$(μg/m^3)	49.8±5.2	46.2	48.7 [6.3]	52.5	51.9±6.0	47.0	52.0 [9.7]	56.7

* P -value for the Mann-Whitney U test of pollutant concentration during pregnancy and 2 years after birth.

P -value for the Mann-Whitney U test of pollutant concentration in the first and second years after birth.

Table 3 Median and IQR of air pollutants at different stages in early life in the eczema and non-eczema population.

Air pollutant	**During entire pregnancy**	**During entire pregnancy**	**During entire pregnancy**	**During ag**
	Non-eczema	Eczema	P	Non-eczema
NO_2(μg/m^3)	46.03(8.02)	44.01(8.03)	<0.001	38.47(3.60)
SO_2(μg/m^3)	14.55(1.83)	14.22(2.25)	<0.001	12.41(1.27)
O_3(μg/m^3)	108.41(23.23)	110.96(24.09)	<0.001	108.87(10.5
CO (mg/m^3)	0.88(0.08)	0.87(0.08)	<0.001	0.83(0.04)
PM_{10}(μg/m^3)	113.19(18.00)	111.50(18.33)	<0.001	99.75(7.66)
$PM_{2.5}$(μg/m^3)	55.53(10.99)	54.18(11.25)	<0.001	48.49(4.21)
$PM_{2.5\text{-}10}$(μg/m^3)	58.51(7.65)	58.27(7.60)	0.522	51.05(4.07)
	During age 0-1y	**During age 0-1y**	**During age 0-1y**	
NO_2(μg/m^3)	39.44(5.31)	38.97(5.28)	<0.001	37.34(2.46)
SO_2(μg/m^3)	12.35(1.62)	12.40(1.74)	0.375	12.36(1.37)
O_3(μg/m^3)	114.55(5.45)	114.58(5.59)	0.669	105.83(18.9
CO (mg/m^3)	0.85(0.05)	0.85(0.05)	0.998	0.81(0.05)
PM_{10}(μg/m^3)	99.32(12.04)	99.59(13.43)	0.457	97.45(10.12
$PM_{2.5}$(μg/m^3)	50.48(5.38)	50.81(5.66)	0.500	45.83(3.72)
$PM_{2.5\text{-}10}$(μg/m^3)	48.68(6.19)	48.91(6.71)	0.419	52.11(9.76)

3.3 Relationship between air pollutant exposure in early life and the risk of childhood eczema

Pollutant concentrations were divided according to quartiles and binary logistic regression analysis was performed (Table 4). In the single pollutant model, the results showed that increased O_3concentrations during pregnancy were a risk factor for cumulative eczema [1.12(1.06-1.19)], one-year-old eczema [1.10(1.04-1.17)], and two-year-old eczema [1.15(1.02-1.29)]. In the multi-pollutant model, $PM_{2.5}$, $PM_{2.5\text{-}10}$ and $PM_{10}$with VIF values >5 were considered to have multicollinearity and were not included in the model at the same time, and after adjusting for other pollutants and six variables that were statistically significant in the univariate analysis: parental allergy, work during pregnancy, monthly household income, maternal primipara, frequent window opening and air purifier use, PM_{10}exposure during pregnancy had a significant effect on cumulative eczema [1.27(1.14-1.41)], 1-year old eczema [1.22(1.09-1.36)], and 2-year-old eczema [1.30(1.04-1.62)]. Dividing PM_{10}into $PM_{2.5}$ and $PM_{2.5\text{-}10}$, $PM_{2.5\text{-}10}$ remained positively associated with the risk of cumulative eczema [1.31(1.20-1.43)], 1-year old eczema [1.31(1.19-1.44)], and 2-year-old eczema [1.20(1.01-1.44)], while $PM_{2.5}$ had no significant effect.

Table 4 *OR* and 95% *CI* of air pollutant exposure during pregnancy for eczema risk in the binary logistic regression model.

Pollutants during pregnancy (μg/m^3)	Pollutants during pregnancy (μg/m^3)	Cumulative eczema	Eczema at age 1	Eczema at age 2
Model 1	PM_{10}	0.92(0.86-0.97)	0.92(0.87-0.98)	0.88(0.78-0.99)
	$PM_{2.5\text{-}10}$	0.98(0.92-1.04)	0.89(0.79-1.01)	0.99(0.94-1.06)
	$PM_{2.5}$	0.88(0.83-0.93)	0.85(0.75-0.96)	0.88(0.83-0.94)
	O_3	**1.12(1.06-1.19)**	**1.10(1.04-1.17)**	**1.15(1.02-1.29)**
	CO	0.86(0.82-0.92)	0.89(0.84-0.95)	0.74(0.65-0.83)
	SO_2	0.83(0.78-0.88)	0.85(0.78-0.90)	0.81(0.72-0.91)
	NO_2	0.82(0.77-0.87)	0.84(0.79-0.89)	0.76(0.67-0.86)
Model 2	PM_{10}	**1.27(1.14-1.41)**	**1.22(1.09-1.36)**	**1.30(1.04-1.62)**
	O_3	1.04(0.94-1.14)	1.02(0.92-1.13)	0.89(0.73-1.08)
	CO	0.94(0.87-1.02)	0.98(0.90-1.07)	0.73(0.62-0.86)
	SO_2	0.85(0.79-0.92)	0.86(0.79-0.93)	0.86(0.73-1.02)
	NO_2	0.80(0.72-0.88)	0.81(0.72-0.90)	0.76(0.62-0.93)
Model 3	$PM_{2.5\text{-}10}$	**1.31(1.20-1.43)**	**1.31(1.19-1.44)**	**1.20(1.00-1.45)**
	O_3	0.98(0.90-1.07)	0.98(0.89-1.08)	0.83(0.69-1.00)
	CO	0.95(0.88-1.03)	0.99(0.91-1.08)	0.74(0.63-0.87)
	SO_2	0.88(0.82-0.95)	0.88(0.81-0.95)	0.90(0.77-1.06)
	NO_2	0.74(0.66-0.82)	0.73(0.66-0.82)	0.75(0.60-0.93)
Model 4	$PM_{2.5}$	1.06(0.95-1.17)	1.02(0.91-1.13)	1.08(0.87-1.34)
	O_3	0.98(0.88-1.08)	0.96(0.86-1.07)	0.84(0.69-1.03)
	CO	0.94(0.87-1.02)	0.99(0.90-1.07)	0.73(0.62-0.86)
	SO_2	0.89(0.82-0.96)	0.90(0.82-0.98)	0.90(0.76-1.08)
	NO_2	0,87(0.79-0.95)	0.87(0.79-0.96)	0.83(0.69-1.01)

Odd ratios were calculated per IQR increase in exposure.

Model 1, single-pollutant mode. No adjustment for other pollutants and covariates. The role of each pollutant in the mixing effect was obtained.

In the multi-pollutant models, the VIF value of PM_{10}, $PM_{2.5\text{-}10}$ and $PM_{2.5}$ was over 5, which was multicollinearity and not included in the model at the same time. PM_{10} model (Model 2), $PM_{2.5\text{-}10}$ model (Model 3), and $PM_{2.5}$ model (Model 4) were adjusted for paternal atopy, maternal work during pregnancy, maternal primipara, monthly household income, open windows often, and use an air purifier.

In the multiple logistic regression model of the effect of pollutants during pregnancy on childhood eczema, results from the single-pollutant model showed that O_3 exposure was significant for the risk of developing eczema at age 1 year only [1.11(1.04-1.19)] and age 2 years only [1.23(1.06-1.42)]. After adjusting for other pollutants and covariates in the multi-pollutant model, the results showed that PM_{10} exposure was significant for 1-year old eczema only [1.25(1.11-1.40)] and 2-years old eczema only [1.51(1.16-1.95)]. Dividing PM_{10} into $PM_{2.5}$ and $PM_{2.5\text{-}10}$, $PM_{2.5\text{-}10}$ remained positively associated with the risk of 1-year old eczema only [1.32(1.20-1.45)] and 2-year-old eczema only [1.24(1.00-1.54)], while $PM_{2.5}$ had no significant effect (Table 5).

In the multivariate logistic regression model in the first year of life(Table 5), the results of the single-pollutant model showed that PM_{10}[1.08(1.02-1.15)], CO[1.07(1.00-1.14)], and SO_2 [1.07(1.00-1.14)]exposure were all positively associated with only eczema at age 1, and after dividing PM_{10} into $PM_{2.5}$ and $PM_{2.5\text{-}10}$, both $PM_{2.5}$[1.08(1.01-1.15)]and $PM_{2.5\text{-}10}$[1.07(1.00-1.14)] were still positively associated with only eczema at age 1, and in the multi-pollutant model, CO [1.08(1.00-1.18)]was still positively associated with only eczema at age 1. O_3 concentration was positively associated with only eczema at age 2, in both the single-pollutant model [1.26(1.09-1.46)] and the multi-pollutant model [1.24(1.03-1.50)] with statistical significance.

Table 5 *OR* and 95% *CI* for the effect of air pollutant exposure during pregnancy on childhood eczema in the multiple logistic regression model.

Pollutants concentration	Pollutants concentration	Model 1	Model 1	Model 1	Model 1		Model 2	Model 2	Model 2
		No eczema (n=4664)	Only eczema at age 1 (n=926)	Only eczema at age 2 (n=159)	Persistent eczema (n=70)		No eczema (n=4664)	Only eczema at age 1 (n=926)	Only eczema at age 2 (n=159)
During the pregnancy	PM_{10}	1	0.93(0.87-0.99)	0.91(0.79-1.04)	0.79(0.64-0.98)	0.79(0.64-0.98)	1	**1.25(1.11-1.40)**	**1.51(1.16-1.95)**
	$PM_{2.5}$	1	0.89(0.84-0.95)	0.87(0.76-1.00)	0.75(0.61-0.94)	0.75(0.61-0.94)	1	1.05(0.93-1.17)	1.25(0.97-1.61)
	$PM_{2.5\text{-}10}$	1	1.00(0.94-1.07)	0.91(0.79-1.05)	0.87(0.70-1.08)	0.87(0.70-1.08)	1	**1.32(1.20-1.45)**	**1.24(1.00-1.54)**
	O_3	1	**1.11(1.04-1.19)**	**1.23(1.06-1.42)**	1.05(0.85-1.29)	1.05(0.85-1.29)	1	1.07(0.96-1.19)	1.12(0.88-1.42)
	CO	1	0.90(0.85-0.96)	0.75(0.64-0.86)	0.68(0.55-0.85)	0.68(0.55-0.85)	1	1.01(0.92-1.10)	0.79(0.65-0.96)
	SO_2	1	0.84(0.79-0.89)	0.81(0.70-0.93)	0.74(0.59-0.92)	0.74(0.59-0.92)	1	0.86(0.79-0.93)	0.84(0.69-1.03)
	NO_2	1	0.84(0.79-0.90)	0.77(0.67-0.89)	0.67(0.54-0.84)	0.67(0.54-0.84)	1	0.81(0.73-0.91)	0.78(0.61-1.00)
In the first years of life	PM_{10}	1	**1.08(1.02-1.15)**	0.81(0.71-0.94)	0.97(0.79-1.20)	0.97(0.79-1.20)	1	1.06(0.92-1.21)	1.00(0.73-1.37)
	$PM_{2.5}$	1	**1.08(1.01-1.15)**	0.83(0.72-0.95)	1.05(0.85-1.30)	1.05(0.85-1.30)	1	1.02(0.91-1.14)	1.02(0.79-1.33)
	$PM_{2.5\text{-}10}$	1	**1.07(1.00-1.14)**	0.80(0.70-0.93)	1.00(0.91-1.24)	1.00(0.91-1.24)	1	0.98(0.86-1.12)	0.97(0.71-1.31)
	O_3	1	0.98(0.92-1.04)	**1.26(1.09-1.46)**	0.92(0.75-1.14)	0.92(0.75-1.14)	1	1.03(0.95-1.12)	**1.24(1.03-1.50)**

Pollutants concentration	Pollutants concentration	Model 1	Model 1	Model 1	Model 1		Model 2	Model 2	Model 2
	CO	1	**1.07(1.00-1.14)**	0.74(0.64-0.86)	1.02(0.82-1.25)	1.02(0.82-1.25)	1	**1.08(1.00-1.18)**	0.78(0.64-0.94)
	SO_2	1	**1.06(1.01-1.14)**	0.84(0.72-0.96)	0.97(0.79-1.20)	0.97(0.79-1.20)	1	1.01(0.88-1.17)	1.09(0.80-1.50)
	NO_2	1	0.92(0.87-0.98)	0.91(0.79-1.04)	0.88(0.71-1.08)	0.88(0.71-1.08)	1	0.91(0.85-0.97)	0.99(0.85-1.15)

Odd ratios were calculated per IQR increase in exposure.

Model 1, single-pollutant mode.

Model 2, models were adjusted for other pollutants, paternal atopy, maternal work during pregnancy, maternal primipara, monthly household income, open windows often, and use an air purifier. The VIF value of PM_{10}, $PM_{2.5}$, and $PM_{2.5\text{-}10}$ was over 5, which was multicollinearity and not included in the model at the same time.

3.4 Identification of critical windows for $PM_{2.5\text{-}10}$ and O_3 exposure to childhood eczema

In the DLM with eczema at 2 years of age as an outcome, the exposure period was the entire life course before the date of eczema onset at 2 years of age. Finding the sensitive window during pregnancy and after birth separately through DLM. PM_{10}, $PM_{2.5\text{-}10}$ and O_3 exposure was divided by weeks. There was no significant sensitivity window for PM_{10} and $PM_{2.5\text{-}10}$ exposure during pregnancy, but 0-23 weeks postnatal for PM_{10} and 3-13 weeks postnatal for $PM_{2.5\text{-}10}$ were critical risk windows for eczema at 2 years of age. O_3 exposure at 32-42 weeks of pregnancy, 0-10 weeks and 91-105 weeks postnatal were critical risk windows (Figure 3).

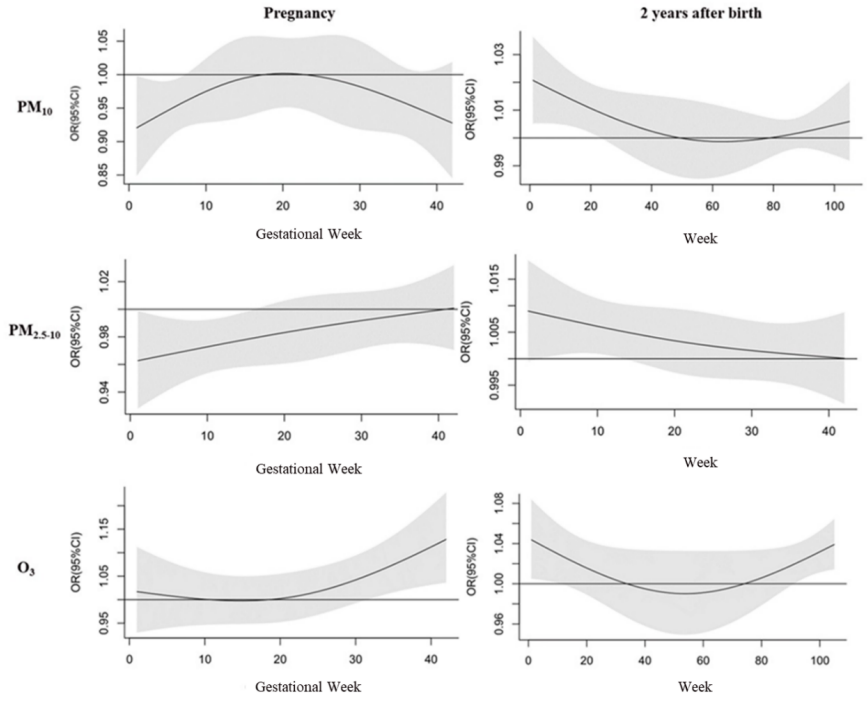

Figure 3 The effect of PM_{10}, $PM_{2.5\text{-}10}$, and O_3 exposure during pregnancy and postnatal period on eczema

at 2 years of age. The binomial logistic was used as a linking function, comparing 2-year-old eczema patients with children who have not had eczema. The lag-response relationship between pollutant and eczema was modeled by natural cubic spline, according to the AIC value, with all the above degrees of freedom (DF) being 3. All pollutants were referenced at the 25th percentile to obtain their risk effects at the 75th percentile. All models were adjusted for paternal atopy, maternal work during pregnancy, maternal primipara, monthly household income, open windows often, and use air purifier.

3.5 Combined effects of different periods of exposure to air pollutants on eczema in children

Pollutants during pregnancy and the first year after birth were included in the WQS model. For per 25 percentiles increased in the WQS index of combined exposure to pollutants, the risk of eczema at 1 year of age was increased by 1.38 times (95%CI : 1.14-1.66), O_3during pregnancy played a major role in the combined effect, and SO_2, O_3, CO and PM in the first year of birth also played an important role (Figure 4).

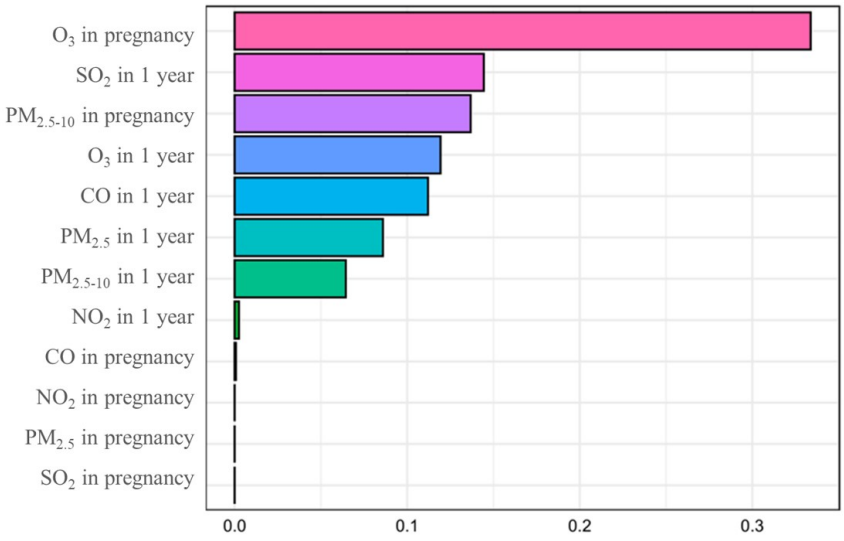

Figure 4. Effect of combined exposure to air pollutants during pregnancy and in the first year of life on the risk of eczema at 1 year of age. The direction of the association between exposure to air pollutants and childhood eczema was set as positive. The model was adjusted for paternal atopy, maternal work during pregnancy, maternal primipara, monthly household income, open windows often, and use air purifier.

Pollutants during pregnancy, one year after birth, and the second year after birth were all included in the WQS model. For per 25 percentiles increased in the WQS index of combined exposure to pollutants, the risk of cumulative eczema in children before 2 years of age increased by 1.28 times (95%CI : 1.06-1.55), in which O_3 in pregnancy played a major role (Figure 5).

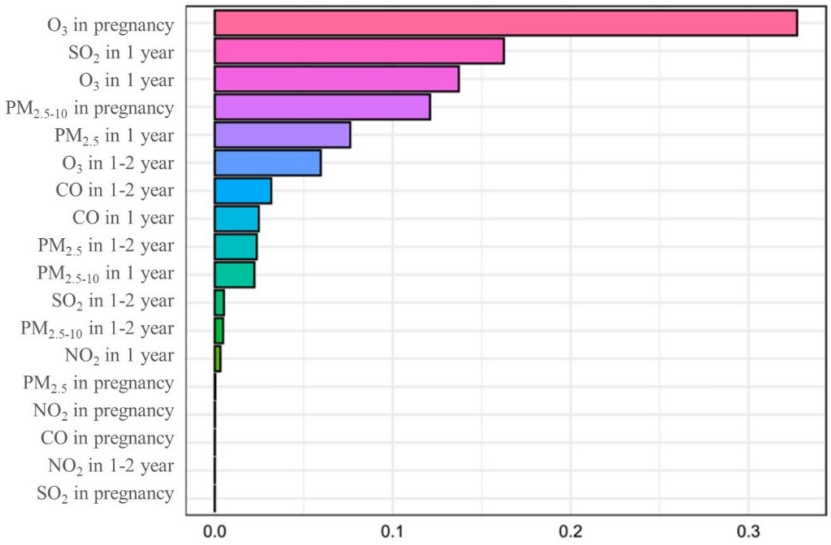

Figure 5 Effect of combined exposure to air pollutants during pregnancy and two years after birth on the risk of cumulative eczema under 2 years of age. The direction of the association between exposure to air pollutants and childhood eczema was set as positive. Model was adjusted for paternal atopy, maternal work during pregnancy, maternal primipara, monthly household income, open windows often, and use air purifier.

3.6 Principal component analysis of pollutants during pregnancy

In the WQS model, O_3 during pregnancy was found to play an important role in the onset of eczema before two years of age, so we conducted a Principal Component Analysis of the pollutants during pregnancy, with a cumulative contribution of 93.2% from PC1 and PC2 (Figure 6), the largest coefficient component in PC1 was O_3 (0.838), and the largest coefficient component in PC2 was $PM_{2.5\text{-}10}$ (0.718). Including PC1 and PC2 in the logistic regression model, PC1 was positively associated with the risk of cumulative eczema (a*OR* 1.011, 95% *CI* 1.007-1.015) (Table 6).

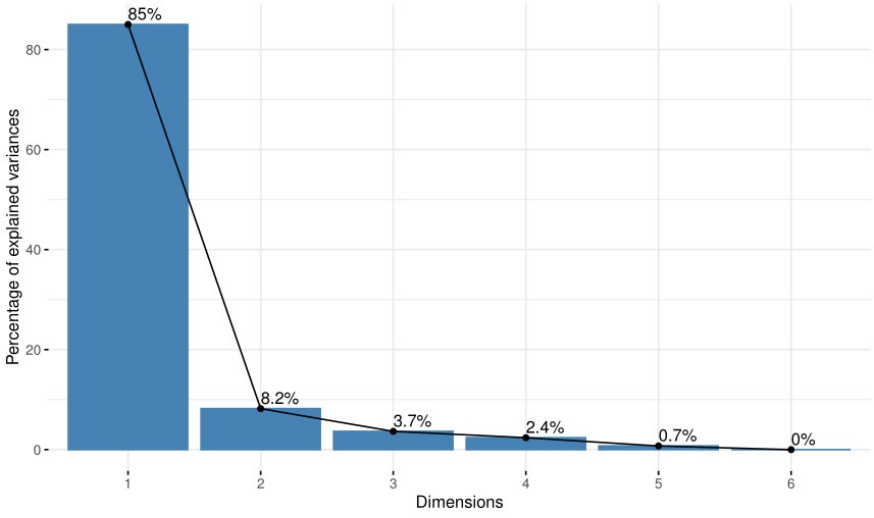

Figure 6 Percentage of variance explained by extracted principal components.

Table 6 Principal component analysis of pollutants during pregnancy

	c*OR* (95%CI)	a*OR* (95%CI) *	O_3	$PM_{2.5\text{-}10}$	$PM_{2.5}$	CO	NO_2	SO_2
PC1	1.002(1.001-1.002)	1.011(1.007-1.015)	**0.838**	-0.248	-0.390	-0.003	-0.283	-0.067
PC2	1.000(0.998-1.002)	1.004(0.991-1.017)	0.483	**0.718**	-0.248	-0.001	0.414	0.116

*Adjusted for paternal atopy, maternal work during pregnancy, maternal primipara, monthly household income, open windows often, and use air purifier.

3.6 Results of sensitivity analysis

In the WQS model of the combined effect of pollutants during pregnancy and at 1 year of age on the risk of eczema at 1 year of age, the risk of eczema at 1 year of age increased by 1.14 times (95%CI: 1.06-1.23) for per 10 percentiles increased in the WQS index of combined exposure to pollutants. O_3 in pregnancy still played a major role (Figure S3). In the WQS model of the effects of pollutant exposure during pregnancy and 2 years after birth on the cumulative eczema risk within two years, for per 10 percentiles increased in the WQS index of pollutant combined exposure, the cumulative eczema risk of children before two years of age increased by 1.11 times (95%CI: 1.04-1.20). O_3 in pregnancy still played a major role (Figure S4). There was no significant difference between the sensitivity analysis results and the main results of this study. Secondly, the number of bootstrap (b) samples used in the parameter estimation of the model were set to 100, 1000, 2000 and 3000 respectively (Figure S5, Figure S6). After 1000 times bootstrap, the model results were relatively stable. The WQS model had robustness.

4. Discussions

In this study, we included 5819 children from the Jinan birth cohort who completed two years of follow-up, with a cumulative eczema incidence of 19.8%. We found that O_3 exposure in the early life was positively associated with the risk of eczema at 0-2 years of age, particularly O_3 exposure during pregnancy (*OR*1.12, 95% *CI* 1.06-1.19). A Canadian study found that exposure to oxidant air pollutants before the age of 3 was associated with an increased risk of eczema(Teresa To et al., 2020). Another Belarusian study found that higher average annual ground-level ozone was associated with a high incidence of eczema in infants(Belugina, Yagovdik, Belugina, & Belugin, 2018). Consistent with the results of our study. The DLM model was used to find sensitive windows for O_3 exposure and found that 32-42 weeks of gestation, 0-10 and 91-105 weeks of postnatal life were critical risk windows. The joint effect of pollutants on eczema risk at different periods was analyzed by the WQS model, O_3 exposure during pregnancy played a dominant role in this joint effect (weighting >0.3). The same result was found in the PCA, with PC1 (the largest coefficient for O_3) positively associated with the risk of eczema (a*OR* 1.011, 95% CI 1.007-1.015. It has been shown that O_3 exposure increased both transcript and protein levels of the main inflammasome complex, such as ASC and caspase-1, and O_3 can activate cutaneous inflammasome in a redox dependent manner(Ferrara et al., 2020). This pathway may play a role in the increased risk of eczema from O_3 exposure.

In our study, PM exposure was also found to increase the risk of eczema. When PM_{10} was divided into $PM_{2.5}$ and $PM_{2.5\text{-}10}$ by particle size, only large $PM_{2.5\text{-}10}$ particles had an effect during pregnancy, while small $PM_{2.5}$ particles had no significant effect, however, both $PM_{2.5}$ and $PM_{2.5\text{-}10}$ had a significant effect during the first year of life. It is speculated that the mother may provide some protection against PM-induced fetal harm. A study in Guangzhou, China, reported that high three-day exposure to PM_{10} and $PM_{2.5}$ was positively associated with the number of eczema outpatient visits in children under 12 years of age(J. Zhang et al., 2022). Another study found that $PM_{2.5}$ exposure during pregnancy combined with postnatal tobacco exposure increased the risk of eczema(Jedrychowski et al., 2011). A Korean study found that PM_{10} exposure increased the risk of eczema, while $PM_{2.5}$ had no significant effect(Min et al., 2020). The different findings on the effects of PM_{10} and $PM_{2.5}$ on childhood eczema may be due to the differences in chemical composition and emission sources. The DLM was used to find the critical window of PM exposure during pregnancy and postnatal period respectively and found that the risk window for PM_{10} was 0-23 weeks postnatal and for $PM_{2.5\text{-}10}$ was 3-13 weeks postnatal. This may reveal that newborns are more vulnerable in the first six months of life when PM exposure is more likely to increase the risk of eczema.

A 2018 review mentioned that the atopic march begins with eczema(Hill & Spergel, 2018). It is noteworthy that, we found the sensitivity window for eczema also appeared early, during the third trimester (O_3) and the first 6 months of life ($O_3$and PM). A Mexican study found that the window of sensitivity for $PM_{2.5}$ exposure to recurrent wheeze was 6 to 39 weeks after birth(Rivera Rivera et al., 2021). A Chinese study found that the critical window of O_3 exposure for asthma and wheezing was 31-37 weeks of gestation and 1-105 weeks after birth(Bai et al., 2023). Eczema has an earlier window of sensitivity to air pollutants than other allergic diseases. Therefore, prevention of eczema is also important for the prevention of other allergic diseases.

The study population was divided into four groups based on eczema at 1 year of age and eczema at 2 years of age. Air pollutant exposure during pregnancy and the first year after birth increased the risk of eczema only at age 1 and eczema only at age 2 compared to the no eczema group, but had no significant effect on persistent eczema. The risk of eczema is influenced by a combination of environmental and genetic factors(Shi et al., 2021), and we speculate that genetic factors may play a key role in the development of persistent eczema.

The incidence of eczema in this study was 19.8% and the pollutants positively associated with the risk of eczema were $O_3$and PM. The cumulative eczema incidence in children aged 3-6 years was 26.8% in a 2019 study from Hubei(Deng et al., 2019), which showed that $PM_{2.5}$ and PM_{10} during pregnancy increased the risk of eczema, and this study had a $PM_{2.5}$concentration of 72.11 ± 5.12μg/m^3, higher than 54.9 ± 7.0μg/m^3 in our study, meanwhile, PM_{10}concentrations of 114.65 ± 9.63μg/m^3, close to our study. A 2016 study in Shanghai reported a cumulative eczema incidence of 21.1% in children aged 4-6 years (Liu et al., 2016), which found that pregnancy NO_2 exposure increased the risk of eczema, while PM_{10} had no significant effect, the NO_2 concentration during pregnancy in that study was 54.9 ± 10.5μg/m^3, in our study was 45.37 ± 5.5μg/m^3, the PM_{10} concentration was 82.7 ± 7.7μg/m^3, and in our study was 113.4 ± 11.6μg/m^3. Differences in pollutant concentrations between regions may be one reason why the types of pollutants affecting the risk of eczema vary between studies.

The main strength and novelty of our study lies in its prospective birth cohort design, to explore the impact of long-term exposure to air pollutants in the early life on eczema at 0-2 years of age. Secondly, we found effects of O_3 and PM exposure on eczema risk and identified critical risk windows. Thirdly, we explored the combined effect of air pollutants on eczema by WQS and PCA, and the dominant role of O_3 exposure during pregnancy was found. The limitation of this study is that eczema before one year of age is a mother-reported symptom of eczema and there is no specific date of onset. Secondly, the pregnancy information was obtained from the mother's recollection after the birth of the child, which may lead to recall bias. Finally, our study only considered outdoor exposure to air pollutants and lacked an assessment of indoor exposure.

5.Conclusion

In conclusion, we found that exposure to air pollutants O_3 and PM in early life increased the risk of eczema at 0-2 years of age, and the sensitivity window appeared earlier. Importantly, under combined exposure to air pollutants, O_3 exposure during pregnancy played a key role on eczema risk.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Preventive Medicine of Shandong University (Approved number: 20170315). Each mother of subject was informed of the purpose and content of the study and signed the informed consent.

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Authors' contribution

Yuxiu Liang: investigation, software, writing-original draft preparation. Shuoxin Bai: investigation, visualization. Jiatao Zhang: investigation, resources. Shuang Du: investigation, visualization. Zhiping Wang:

project administration, methodology, conceptualization.

Declarations of interest

None.

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References

Bai, S., Cui, L., Du, S., Zhao, X., Lin, S., Yang, X., . . . Wang, Z. (2023). A life course approach to asthma and wheezing among young children caused by ozone: A prospective birth cohort in northern China.*Environmental research, 226* , 115687. doi:10.1016/j.envres.2023.115687

Belugina, I. N., Yagovdik, N. Z., Belugina, O. S., & Belugin, S. N. (2018). Outdoor environment, ozone, radionuclide-associated aerosols and incidences of infantile eczema in Minsk, Belarus. *J Eur Acad Dermatol Venereol, 32* (11), 1977-1985. doi:10.1111/jdv.15063

Bosma, A. L., Ouwerkerk, W., & Middelkamp-Hup, M. A. (2021). Children with atopic eczema experiencing increased disease severity in the pollen season more often have hay fever at a young age and a dark skin type.*J Dermatol, 48* (4), 470-475. doi:10.1111/1346-8138.15750

Deng, S., Huang, D., Wang, W., Yan, H., Li, S., & Xiang, H. (2019). Associations of gestational and the first year of life exposure to ambient air pollution with childhood eczema in Hubei, China.*Environ Sci Pollut Res Int, 26* (23), 23842-23849. doi:10.1007/s11356-019-05633-w

Dharma, C., Lefebvre, D. L., Tran, M. M., Lou, W. Y. W., Subbarao, P., Becker, A. B., . . . investigators, C. S. (2018). Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: Effects on allergic diseases. *Clin Exp Allergy, 48* (1), 48-59. doi:10.1111/cea.13063

Du, S., Bai, S., Zhao, X., Lin, S., Zhai, Y., Wang, Z., & Wang, Z. (2022). The effect and its critical window for ambient temperature and humidity in pregnancy on term low birth weight. *Environ Sci Pollut Res Int* . doi:10.1007/s11356-022-19512-4

Ferrara, F., Pambianchi, E., Pecorelli, A., Woodby, B., Messano, N., Therrien, J. P., . . . Valacchi, G. (2020). Redox regulation of cutaneous inflammasome by ozone exposure. *Free Radic Biol Med, 152* , 561-570. doi:10.1016/j.freeradbiomed.2019.11.031

Fishbein, A. B., Silverberg, J. I., Wilson, E. J., & Ong, P. Y. (2020). Update on Atopic Dermatitis: Diagnosis, Severity Assessment, and Treatment Selection. *J Allergy Clin Immunol Pract, 8* (1), 91-101. doi:10.1016/j.jaip.2019.06.044

Garcia-Serna, A. M., Martin-Orozco, E., Jimenez-Guerrero, P., Hernandez-Caselles, T., Perez-Fernandez, V., Cantero-Cano, E., . . . Group, N. S. (2022). Cytokine profiles in cord blood in relation to prenatal traffic-related air pollution: The NELA cohort. *Pediatr Allergy Immunol, 33* (2), e13732. doi:10.1111/pai.13732

He, S., Klevebro, S., Baldanzi, G., Pershagen, G., Lundberg, B., Eneroth, K., . . . Gruzieva, O. (2022). Ambient air pollution and inflammation-related proteins during early childhood.*Environmental research, 215* (Pt 2), 114364. doi:10.1016/j.envres.2022.114364

Hill, D. A., & Spergel, J. M. (2018). The atopic march: Critical evidence and clinical relevance. *Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology, 120* (2), 131-137. doi:10.1016/j.anai.2017.10.037

Huang, C. C., Wen, H. J., Chen, P. C., Chiang, T. L., Lin, S. J., & Guo, Y. L. (2015). Prenatal air pollutant exposure and occurrence of atopic dermatitis. *Br J Dermatol, 173* (4), 981-988. doi:10.1111/bjd.14039

Huang, F. Q., Lu, C. Y., Wu, S. P., Gong, S. Z., & Zhao, Y. (2020). Maternal exposure to antibiotics increases the risk of infant eczema before one year of life: a meta-analysis of observational studies. *World J Pediatr, 16* (2), 143-151. doi:10.1007/s12519-019-00301-y

Jedrychowski, W., Perera, F., Maugeri, U., Mrozek-Budzyn, D., Miller, R. L., Flak, E., . . . Spengler, J. D. (2011). Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. *Int Arch Allergy Immunol, 155* (3), 275-281. doi:10.1159/000320376

Liu, W., Cai, J., Huang, C., Hu, Y., Fu, Q., Zou, Z., . . . Sundell, J. (2016). Associations of gestational and early life exposures to ambient air pollution with childhood atopic eczema in Shanghai, China. *Sci Total Environ, 572* , 34-42. doi:10.1016/j.scitotenv.2016.07.197

Luo, P., Wang, D., Luo, J., Li, S., Li, M. M., Chen, H., . . . Zhou, L. (2022). Relationship between air pollution and childhood atopic dermatitis in Chongqing, China: A time-series analysis. *Front Public Health, 10* , 990464. doi:10.3389/fpubh.2022.990464

Martin, P. E., Eckert, J. K., Koplin, J. J., Lowe, A. J., Gurrin, L. C., Dharmage, S. C., . . . Allen, K. J. (2015). Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clinical and Experimental Allergy : Journal of the British Society For Allergy and Clinical Immunology, 45* (1), 255-264. doi:10.1111/cea.12406

Min, K. D., Yi, S. J., Kim, H. C., Leem, J. H., Kwon, H. J., Hong, S., . . . Kim, S. Y. (2020). Association between exposure to traffic-related air pollution and pediatric allergic diseases based on modeled air pollution concentrations and traffic measures in Seoul, Korea: a comparative analysis. *Environ Health, 19* (1), 6. doi:10.1186/s12940-020-0563-6

Oh, I., Lee, J., Ahn, K., Kim, J., Kim, Y. M., Sun Sim, C., & Kim, Y. (2018). Association between particulate matter concentration and symptoms of atopic dermatitis in children living in an industrial urban area of South Korea. *Environmental research, 160* , 462-468. doi:10.1016/j.envres.2017.10.030

Rishikeshan, C. A., Katiyar, S. K., Mahesh, V. N. V., & Ieee. (2014, Nov 14-16). *Detailed evaluation of DEM interpolation methods in GIS using DGPS data.* Paper presented at the 6th International Conference on Computational Intelligence and Communication Networks, Bhopal, INDIA.

Rivera Rivera, N. Y., Tamayo-Ortiz, M., Mercado Garcia, A., Just, A. C., Kloog, I., Tellez-Rojo, M. M., . . . Rosa, M. J. (2021). Prenatal and early life exposure to particulate matter, environmental tobacco smoke and respiratory symptoms in Mexican children. *Environmental research, 192* , 110365. doi:10.1016/j.envres.2020.110365

Shi, H., Wan, G., Wang, T., Zhu, J., Jiang, L., Ma, S., . . . Dong, H. (2021). Prevalence and influencing risk factors of eczema among preschool children in Urumqi city: a cross-sectional survey. *BMC Pediatr, 21* (1), 347. doi:10.1186/s12887-021-02819-5

Sun, C., Zhang, J., Huang, C., Liu, W., Zhang, Y., Li, B., . . . Sundell, J. (2019). High prevalence of eczema among preschool children related to home renovation in China: A multi-city-based cross-sectional study. *Indoor Air, 29* (5), 748-760. doi:10.1111/ina.12586

Tan, T., Xiao, D., Li, Q., Zhong, C., Hu, W., Guo, J., . . . Yang, N. (2023). Maternal yogurt consumption during pregnancy and infantile eczema: a prospective cohort study. *Food Funct, 14* (4), 1929-1936. doi:10.1039/d2fo02064e

To, T., Zhu, J., Stieb, D., Gray, N., Fong, I., Pinault, L., . . . Dell, S. (2020). Early life exposure to air pollution and incidence of childhood asthma, allergic rhinitis and eczema. *Eur Respir J, 55* (2). doi:10.1183/13993003.00913-2019

To, T., Zhu, J., Stieb, D., Gray, N., Fong, I., Pinault, L., . . . Dell, S. (2020). Early life exposure to air pollution and incidence of childhood asthma, allergic rhinitis and eczema. *The European respiratory journal, 55* (2). doi:10.1183/13993003.00913-2019

Tsakok, T., Marrs, T., Mohsin, M., Baron, S., du Toit, G., Till, S., & Flohr, C. (2016). Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol, 137* (4), 1071-1078. doi:10.1016/j.jaci.2015.10.049

Venter, C., Palumbo, M. P., Sauder, K. A., Glueck, D. H., Liu, A. H., Yang, I. V., . . . Dabelea, D. (2021). Incidence and timing of offspring asthma, wheeze, allergic rhinitis, atopic dermatitis, and food allergy and association with maternal history of asthma and allergic rhinitis. *World Allergy Organ J, 14* (3), 100526. doi:10.1016/j.waojou.2021.100526

Ye, C., Gu, H., Li, M., Chen, R., Xiao, X., & Zou, Y. (2022). Air Pollution and Weather Conditions Are Associated with Daily Outpatient Visits of Atopic Dermatitis in Shanghai, China. *Dermatology, 238* (5), 939-949. doi:10.1159/000522491

Zhang, J., Yang, Y., Fu, L., Jing, D., Sun, B., Chen, Y., . . . Shen, S. (2022). Short-term exposure of PM(2.5) and PM(10) increases the number of outpatients with eczema in Guangzhou: A time-series study.*Front Public Health, 10* , 930545. doi:10.3389/fpubh.2022.930545

Zhang, Y., Wei, J., Shi, Y., Quan, C., Ho, H. C., Song, Y., & Zhang, L. (2021). Early-life exposure to submicron particulate air pollution in relation to asthma development in Chinese preschool children. *J Allergy Clin Immunol, 148* (3), 771-782.e712. doi:10.1016/j.jaci.2021.02.030