



Associations of gestational and early life exposures to ambient air pollution with childhood atopic eczema in Shanghai, China



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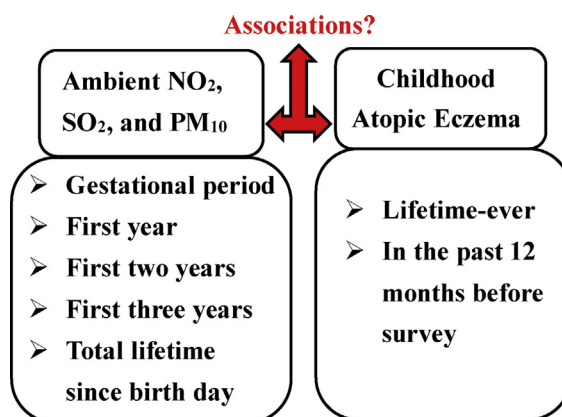
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HIGHLIGHTS

- We first studied effects of ambient NO₂, SO₂, and PM₁₀ on childhood eczema in China.
- We compared differences in effect of pollutants in various periods on child's eczema.
- Exposure to NO₂ in various periods were significantly associated with child's eczema.
- No significant association was found of ambient SO₂ and PM₁₀ with childhood eczema.

GRAPHICAL ABSTRACT



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ABSTRACT

Whether ambient air pollution is associated with childhood atopic eczema is controversial. In this paper, we selected 3358 preschool children who had not altered residences since pregnancy from a cross-sectional study during 2011–2012 in Shanghai, China, and obtained parent-reported data regarding childhood atopic eczema using an improved ISAAC questionnaire. We recorded daily concentrations of SO₂, NO₂, and PM₁₀ throughout the child's lifetime (2006–2012), and calculated period-averaged concentrations for each district where the child lived to represent the child's exposure levels of these pollutants during different periods. In the multiple logistic

Abbreviations: ISAAC, International Study of Asthma and Allergies in Childhood; CCHH, China, Children, Homes, Health; SO₂, sulphur dioxide; NO₂, nitrogen dioxide; PM₁₀, particulate matter with an aerodynamic diameter ≤ 10 μm; OR, odds ratio; CI, confidence interval; IQR, interquartile range; ETS, environmental tobacco smoke.

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regression analyses adjusted for potential confounders as well as for the other pollutants in the same periods, childhood atopic eczema was significantly associated with increments of NO₂ in the approximate interquartile range (20 µg/m³) during gestational period (adjusted OR, 95% CI for eczema lifetime-ever: 1.80, 1.29–2.49; for eczema in the year prior to the survey: 2.32, 1.57–3.43) and during the first year of life (2.00, 1.40–2.84; 2.16, 1.43–3.28). Exposure to elevated NO₂ in the first two years, three years and total lifetime, as well as exposure to mixtures containing NO₂ in each of these periods, were consistently associated with increased likelihood of childhood eczema. The highest odds ratios were found between exposure to a mixture of SO₂ and NO₂ during total lifetime (increment: 35 µg/m³) and childhood eczema (adjusted OR, 95% CI: 2.80, 1.75–4.48; 3.50, 1.98–6.19). No significant associations were found between childhood eczema and ambient SO₂ and PM₁₀ individually or in mixtures. This study indicates that gestational and lifetime exposures to ambient NO₂ are risk factors for atopic eczema in childhood. Exposure to ambient SO₂ and PM₁₀ may enhance the effect of NO₂ exposure on childhood eczema.

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1. Introduction

Atopic eczema (also known as atopic dermatitis) is a common skin disease in childhood affecting a child's life-quality (Weidinger and Novak, 2015). Several studies have reported that the childhood prevalence of atopic eczema has been increasing world-wide (Asher et al., 2006; Duggan et al., 2012; Grize et al., 2006; Weidinger and Novak, 2015). The childhood prevalence of atopic eczema in China has greatly increased in the past 20 years (Gu et al., 2004; Xu et al., 2012; Zhang et al., 2013).

Serious outdoor air pollution is presently a hot topic in China (Kan et al., 2012; Zhang et al., 2012). Studies have not consistently found associations between air pollution and children's eczema (Ahn, 2014; Flohr and Mann, 2014; Kim et al., 2013b; Kim and Hong, 2012; Lee et al., 2008, 2013; Myers and Hershey, 2010; Song et al., 2011; Torres-Borrego et al., 2008). Several studies have found that exposure to ambient air pollutants increases the risk of atopic eczema in childhood (Hasunuma et al., 2014; Sbihi et al., 2015; Weir et al., 2013) or exacerbates atopic eczema symptoms (Brunekeef et al., 2009; Kim et al., 2013a; Song et al., 2011). However, other studies have reported that exposure to ambient air pollutants had no significant associations with atopic eczema in childhood (Aguilera et al., 2013; Anderson et al., 2010; Brauer et al., 2007; Gehring et al., 2010; Yura and Shimizu, 2001).

Few of these studies have been conducted in China (Lee et al., 2008, 2013). To our best knowledge, no studies have investigated gestational and early life exposures to ambient air pollutants and childhood prevalence of atopic eczema in China. Therefore, we used daily concentration data of outdoor SO₂, NO₂, and PM₁₀ from the Shanghai Environmental Monitoring Center (SEMC), with our data for childhood atopic eczema from the questionnaire-based cross-sectional survey in the China, Children, Homes, Health (CCHH) study in Shanghai to investigate associations between pollutant exposure and the prevalence of atopic eczema. We studied exposures to outdoor SO₂, NO₂, and PM₁₀ individually and in various mixtures (SO₂ + NO₂, NO₂ + PM₁₀, SO₂ + PM₁₀, and SO₂ + NO₂ + PM₁₀) during different periods of the child's life (from gestation to the survey day) and their associations with the risk of lifetime-ever atopic eczema and eczema in the year prior to the survey. We hypothesized that exposures to ambient air pollutants individually and in various mixtures are associated with childhood atopic eczema.

2. Materials and methods

2.1.1. Questionnaire and participants

During April 2011 to April 2012, we multi-stage hierarchically sampled 17,898 preschool children from 72 kindergartens in five districts (Urban: Jing-An, Zha-Bei, and Hong-kou; Suburban: Bao-Shan and Feng-Xian) selected from 18 districts of Shanghai city (phase one of CCHH). We surveyed parents or guardians at teacher-parent meetings using a standard questionnaire or *via* post to the children's teachers,

who distributed questionnaires along with explanatory guidance for parents or guardians. We updated the questions for children's health status from those in the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 1995), and modified questions about home environment and lifestyle behaviors from those of the Dampness in Building and Health (DBH) study in Sweden (Bornehag et al., 2004a). Our previous articles (Cai et al., 2016; Huang et al., 2015; Hu et al., 2014; Liu et al., 2013) provide more information about the questionnaire and survey method for the CCHH study in Shanghai. The ethical committee of the School of Public Health, Fudan University in Shanghai, China approved the questionnaire and detailed proposal for the CCHH study. By oral presentation or written explanation, we thoroughly informed participants of the purpose and potential concerns of the study. All participants verbally consented to respond to the survey.

For the present study, we selected data from 3358 four to six year-old children who were born during 2006–2008 in Shanghai city, provided specific date of birth, and who were living in the same residences as during their gestational period. To investigate the gestational period, data for 2527 children were selected (Fig. 1). Because questionnaires for children in Zha-Bei district and Hong-kou district did not include a question for the specific birthdate, the selected children were from the other three districts (Jing-An, Bao-Shan, and Feng-Xian) of Shanghai city. Jing-An district, in center city, has a high density of residences and traffic roads; Bao-Shan district, a suburb near downtown, has a vast iron and steel mill; and Feng-Xian district, a suburb far from downtown, has a low density of residences and population and no large industrial factories. The distribution of kindergartens and monitoring stations of outdoor air quality in these districts are described in a previous article (Liu et al., 2016).

2.1.2. Exposures and outcomes

The Shanghai Environmental Monitoring Center (SEMC) provided daily mean concentrations of SO₂, NO₂, and PM₁₀, from January 1, 2006 to April 30, 2012 for each of the 18 districts in Shanghai city. Daily measurements of outdoor SO₂, NO₂ and PM₁₀ in every district were uniformly and respectively made by the Ultraviolet Fluorescence, Chemiluminescence methods, and a Tapered Element Oscillating Microbalance. We classified the child's exposure periods as gestational period, first year, first two years, first three years, and total years since birth (from the birth day to the surveyed day). We calculated the period-averaged values of daily concentrations of SO₂, NO₂, and PM₁₀ during these periods in the district where the child's residence is located to represent exposure levels of ambient SO₂, NO₂, and PM₁₀ during different periods. The period-averaged concentration was the arithmetically-averaged value of cumulative daily concentrations divided by number of days in the time segments. For example, assuming the child's residence is located in Jing-An district, we calculated the averaged values of daily concentrations of SO₂, NO₂, and PM₁₀ individually and in various mixtures in Jing-An district from the pregnancy day to the birth day as the child's exposure level for these pollutants in gestational period. Then

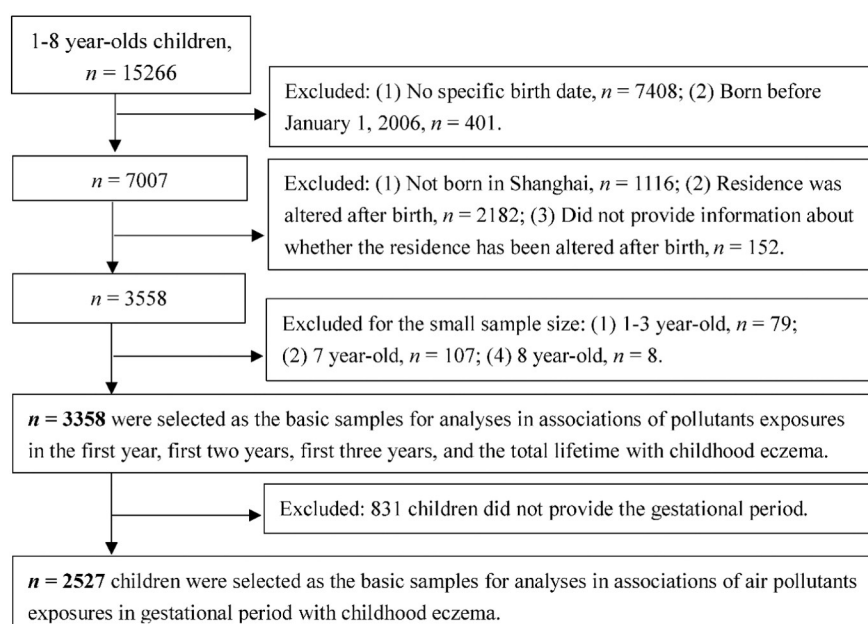


Fig. 1. Flowchart for selection of samples for analyses.

these averaged values for each child were used to calculate the mean concentration of the studied pollutants in various periods and were used to analyze associations of the studied pollutants with childhood atopic eczema.

Questions in the survey about atopic eczema were as follows: (1) Eczema, lifetime-ever: Has your child ever had an itchy skin rash (eczema), which was coming and going for at least 6 months (yes vs. no); (2) Eczema, in the last 12 months: Has your child had eczema (itchy skin rash that comes and goes for the least 6 months) in the last 12 months (yes vs. no). Children were classified as having eczema (lifetime-ever or in the last 12 months) when their questionnaires were answered “yes” in the corresponding question. The original ISAAC questionnaire did not include the word “eczema” with respect to childhood eczema. In our questionnaire, we improved these questions by adding this word and adding a specific description to explain what is defined as eczema.

2.1.3. Covariates and statistical analyses

From literature studies (Fann et al., 2011; Mendell et al., 2011) and our own previous analyses (Cai et al., 2016; Liu et al., 2016), we denoted the following factors to be covariates: sex (boys vs. girls), age (4 vs. 5 vs. 6 year-old), family history of atopy (yes vs. no), ownership of the residence (owner vs. renter), breastfeeding (≤ 6 vs. >6 months), household dampness-related exposures (yes vs. no), environmental tobacco smoke (ETS) at home (yes vs. no), distance of residence from the nearest main traffic road (<200 m vs. ≥ 200 m), use of heating during winter (yes vs. no), and renovation or purchase of new large furniture during early lifetime (yes vs. no). We defined family history of atopy as at least one of the child's family members (siblings, parents, and/or grandparents) having had at least one of the following diseases: asthma, eczema, and rhinitis. Ownership of the current residence was used as a proxy of family socioeconomic status (Hiroshi et al., 2013). We defined household dampness-related exposures as reports of at least two of the following dampness-related indicators: visible mold spots, visible damp stains, damp clothing/beddings, water damage, condensation on windows, and moldy odor. ETS at home was defined as at least one family member smoking. The questions we used for these factors have been provided in a previous article (Zhang et al., 2013).

SPSS 17.0 (SPSS Ltd., USA) was used for statistical analyses. Pearson's chi-square test was used to compare differences in eczema prevalences.

Multi-sample Kruskal-Wallis test (Ruxton and Beauchamp, 2008) was used to compare differences in period-mean concentrations of individual air pollutants and mixtures of pollutants among children from different districts. Logistic regression analysis was used to investigate associations of period-mean concentrations of individual pollutants and their mixtures with childhood eczema. Bivariate logistic regression was used to investigate crude associations (model 1). Multiple logistic regression analyses were performed to adjust these crude associations in two successive regression models: firstly, adjusted for all covariates mentioned above (model 2); secondly, model 2 adjusted for the other studied air pollutants in the same exposure period or for the air pollutant not included in the pair of two pollutants in the same exposure period (as a continuous variable) (model 3). We excluded those children whose questionnaires lacked a response for any covariate in the multiple logistic regression analyses.

We investigated the increased risk of eczema in increments of approximate interquartile ranges (IQR, concentration at 75% percentile minus concentration at 25% percentile) for each air pollutant or each mixture of pollutants during each exposure period. To compare the effects of air pollutants on childhood eczema during different exposure periods, we set the same increment (approximate IQR) in the period-mean concentration for each air pollutant or each mixture of the studied pollutants. We accepted associations for odds ratios (OR) with 95% confidence interval (CI) as significant for p -value < 0.05 .

3. Results

Table 1 shows demographic information and prevalence of childhood eczema for the 2527 children. The children's average age was 5.1 ± 0.8 year-old, with approximately equal numbers of boys and girls. Their residences were generally located in Jing-An, Bao-Shan, and Feng-Xian districts, with about two-thirds being owned by the occupants. A total of 21.7% of the children had a family history of atopy and 38.3% had home dampness-related exposures in the current residence. About 58% had ≤ 6 months breastfeeding and 57.9% were exposed to smoking in the home. A total of 38.6% lived <200 m from a main traffic road and 86.5% used home heating during winter. A total of 38.6% of the children's residences were renovated or had added new large furniture during early lifetime. In total, 21.1% and 13.4% of the studied children had eczema lifetime-ever and in the last year before the survey, respectively. Prevalences of eczema were significantly

Table 1
Demographic data and prevalences of the studied diseases among 2527 children.

Items	Sample size, <i>n</i> (%) ^a	Eczema, lifetime-ever (Total: <i>N</i> = 504, 21.1%)		Eczema, in the last year before survey (Total: <i>N</i> = 329, 13.4%)	
		Prevalence, <i>n</i> (%)	<i>p</i> -value ^b	Prevalence, <i>n</i> (%)	<i>p</i> -value ^b
(1) Age during the survey					
4 years-old	875 (34.6)	191 (22.8)	0.195	127 (14.9)	0.099
5 years-old	1306 (51.7)	243 (19.6)		152 (12.0)	
6 years-old	346 (13.7)	70 (22.0)		50 (15.0)	
(2) Sex					
Boys	1284 (51.0)	247 (20.6)	0.532	154 (12.4)	0.141
Girls	1232 (49.0)	255 (21.6)		173 (14.4)	
(3) Family history of atopy					
Yes	538 (21.7)	188 (36.5)	<0.001	135 (25.6)	<0.001
No	1944 (78.3)	306 (16.6)		189 (10.0)	
(4) Ownership of the residence					
Owner	1661 (66.8)	338 (21.4)	0.559	110 (13.8)	0.659
Renter	825 (33.2)	158 (20.4)		214 (13.2)	
(5) Home dampness-related exposures					
Yes	818 (38.3)	200 (25.7)	<0.001	126 (15.8)	0.022
No	1316 (61.7)	229 (18.4)		157 (12.3)	
(6) Duration of breastfeeding					
≤6 months	1440 (58.0)	369 (20.3)	0.804	234 (12.5)	0.598
>6 months	1043 (42.0)	257 (19.9)		174 (13.2)	
(7) Environmental tobacco smoke (ETS) at home					
Yes	1435 (57.9)	271 (20.0)	0.198	174 (12.5)	0.187
No	1043 (42.1)	219 (22.1)		145 (14.3)	
(8) Distance of residence from the nearest main traffic road					
<200 m	976 (38.6)	195 (20.9)	0.898	130 (13.6)	0.789
≥200 m	1551 (61.4)	309 (21.2)		199 (13.2)	
(9) Use of heating during winter					
Yes	2186 (86.5)	455 (22.0)	0.004	293 (13.8)	0.131
No	341 (13.5)	49 (15.1)		36 (10.8)	
(10) Renovated the residence or bought new large furniture during early lifetime					
Yes	854 (33.8)	184 (22.3)	0.277	121 (14.4)	0.314
No	1673 (66.2)	320 (20.4)		208 (12.9)	
(8) Location of the residence					
Jing-An district	625 (27.9)	179 (30.1)	<0.001	121 (20.1)	<0.001
Bao-Shan district	789 (35.2)	158 (21.1)		102 (13.2)	
Feng-Xian district	826 (36.9)	116 (15.0)		70 (8.7)	

^a Due to the missing data in the questionnaire, the summation of the sample sizes in various options for different items could be smaller than the total 2527 children.^b Pearson's chi-square test for the difference of prevalence between various options for different items (*n**2 times tables, where *n* is the total number of options in different items).

different among children with family history of atopy and home dampness-related exposures, and among children from different districts. The prevalence of eczema did not differ with age, sex or any other covariates.

The average concentrations of SO₂, NO₂, and PM₁₀ for all exposure periods were approximately 45.0 µg/m³, 55.0 µg/m³, and 82.0 µg/m³, respectively (Table 2). The period-mean concentrations of NO₂ had the largest standard deviation (SD) and interquartile range. These

Table 2
Individual air pollutant concentrations in various districts and exposure periods.

Pollutants	Geometric mean ± standard deviation (interquartile range)				<i>p</i> -value ^a
	Total	Jing-An district	Bao-Shan district	Feng-Xian district	
(1) During gestational period (<i>N</i> = 2527)					
SO ₂	45.2 ± 7.1 (13.6)	44.4 ± 1.0 (1.5)	55.1 ± 2.0 (3.7)	38.7 ± 1.5 (2.5)	<0.001
NO ₂	54.9 ± 10.5 (22.0)	64.7 ± 1.7 (2.0)	62.8 ± 3.7 (2.6)	42.4 ± 4.2 (1.3)	<0.001
PM ₁₀	82.7 ± 7.7 (11.0)	84.3 ± 5.2 (5.5)	88.8 ± 5.4 (6.2)	75.4 ± 4.2 (5.5)	<0.001
(2) During the first year of life (<i>N</i> = 3358)					
SO ₂	44.4 ± 6.7 (14.0)	43.4 ± 1.5 (2.1)	54.1 ± 2.6 (3.4)	38.7 ± 1.2 (1.9)	<0.001
NO ₂	54.2 ± 10.7 (22.3)	64.6 ± 1.0 (1.2)	63.3 ± 1.2 (1.5)	41.4 ± 1.5 (1.2)	<0.001
PM ₁₀	82.7 ± 6.0 (10.3)	84.5 ± 2.6 (4.4)	88.6 ± 3.0 (5.2)	76.2 ± 2.3 (3.2)	<0.001
(3) During the first two years of life (<i>N</i> = 3358)					
SO ₂	44.4 ± 6.6 (15.2)	43.0 ± 1.0 (1.8)	54.4 ± 0.7 (1.1)	38.8 ± 0.5 (0.5)	<0.001
NO ₂	53.8 ± 10.8 (22.1)	64.2 ± 0.8 (1.4)	63.0 ± 0.7 (1.3)	40.9 ± 1.4 (1.4)	<0.001
PM ₁₀	81.8 ± 5.5 (10.1)	83.8 ± 1.5 (1.6)	87.6 ± 1.8 (3.3)	75.4 ± 1.4 (1.8)	<0.001
(4) During the first three years of life (<i>N</i> = 3358)					
SO ₂	44.0 ± 6.5 (14.2)	42.4 ± 0.9 (1.4)	54.0 ± 0.8 (1.7)	38.7 ± 0.5 (0.6)	<0.001
NO ₂	53.7 ± 10.7 (22.5)	63.9 ± 0.6 (1.1)	62.9 ± 0.4 (0.8)	40.7 ± 1.4 (0.5)	<0.001
PM ₁₀	81.2 ± 5.4 (10.0)	83.1 ± 1.6 (2.7)	87.0 ± 1.6 (2.7)	74.9 ± 1.4 (2.0)	<0.001
(5) During total lifetime since the birth's day (<i>N</i> = 3358)					
SO ₂	43.2 ± 6.5 (14.5)	41.3 ± 0.6 (0.9)	53.2 ± 0.4 (0.8)	38.1 ± 0.4 (0.3)	<0.001
NO ₂	53.6 ± 10.7 (22.5)	63.5 ± 0.3 (0.5)	63.1 ± 0.2 (0.3)	40.8 ± 1.3 (0.3)	<0.001
PM ₁₀	79.4 ± 5.1 (10.7)	81.2 ± 0.8 (1.3)	85.0 ± 0.8 (1.4)	73.2 ± 0.9 (1.1)	<0.001

^a Multi-sample Kruskal-Wallis test for the concentration difference in different districts.

period-averaged concentrations were significantly different depending on the district (p -values <0.001). Jing-An district had the highest averaged concentrations of NO₂. Bao-Shan district had the highest averaged concentrations of SO₂ and PM₁₀ and had the highest averaged concentrations of four different mixtures of the studied pollutants (Table A.1). Feng-Xian district had the lowest averaged concentrations of the studied pollutants individually and in various mixtures (Table A.1) in all lifetime periods. Exposure to pairs of pollutants within and between various periods had moderate or strong correlations (Pearson's correlation coefficient $r = 0.603$ – 0.994) (Table 3). Except for the gestational period, correlations between NO₂ and PM₁₀ were stronger than correlations between SO₂ and PM₁₀, followed by correlations between SO₂ and NO₂ both within and between various periods.

Table 4 shows interquartile associations between SO₂, NO₂, and PM₁₀ and atopic eczema in childhood during different exposure periods. In the crude logistic regression analyses (Model 1), all studied air pollutants had significant associations with the increased risk of eczema, except for PM₁₀ during gestational period with eczema in the last year, and except for SO₂ during lifetime since the child's birth with eczema lifetime-ever and in the last year. After adjusting for the potential confounders of the child's demographic characteristics and indoor environmental exposures (model 2), these associations and their statistical significances changed very little. However, when the associations were adjusted for the other air pollutants in the same periods (model 3), all significant associations of SO₂ and PM₁₀ with increased risk of eczema disappeared. Only NO₂ with increments in approximate interquartile ranges during all studied exposure periods had significant and positive associations with increased risk of eczema ever and in the last year (Table 4). Among children from different districts (Table A.2), similar trends for the associations were found in the multiple logistic regression analyses (model 3) for associations of different quartiles of pollutants during different periods with childhood eczema. To summarize, exposure to ambient NO₂, but not SO₂ and PM₁₀, with increments in interquartile ranges during all periods had positive associations with increased risk of eczema lifetime-ever and in the last year.

We found similar trends in the associations of mixtures with childhood eczema (Table 5). All associations were strong and statistically significant in the bivariate logistic regression analyses (model 1). After adjusting for the covariates (model 2), associations were still statistically significant but odds ratios were smaller than in the bivariate logistic regression analyses. After further adjusting for the one pollutant not included in the pollutant mixture (model 3), all studied associations of the various mixtures including NO₂ with childhood eczema were still statistically significant and the odds ratios for these associations were larger than in model 2, but all associations of the mixture of SO₂ and PM₁₀ with childhood eczema lost statistical significance. The highest odds ratios were found for associations of the mixture of SO₂ and NO₂ during

total lifetime with childhood eczema during lifetime-ever (OR, 95% CI: 2.80, 1.75–4.48) and in the last year before survey (OR, 95% CI: 3.50, 1.98–6.19). The trends were similar irrespective of district (Table A.3). To summarize, only exposure to all mixtures with NO₂, but not the mixture of SO₂ and PM₁₀, were positively associated with increased eczema risk, during all studied periods.

4. Discussion

In this study, we found that exposures to ambient SO₂, NO₂, and PM₁₀ during various periods were significantly associated with the increased risk of eczema in the crude logistic regression analyses. However, when the crude associations were adjusted for the potential confounders and further mutually adjusted for the other air pollutants in the same periods, only exposures to ambient NO₂ during various periods were significantly and positively associated with increased risk of eczema ever and in the last year prior to the survey. We also found that all associations of exposures to the various pollutant mixtures that included NO₂ with increased risk of childhood eczema lifetime-ever and in the last year were significant, whereas no significant associations were found between exposures to the mixture of SO₂ and PM₁₀ at any studied period and childhood eczema.

Worldwide, several studies have been conducted on associations between exposures to ambient SO₂, NO₂, and PM₁₀ during different periods of lifetime and childhood prevalence of atopic eczema (Anderson et al., 2010; Brauer et al., 2007; Brunekreef et al., 2009; Gehring et al., 2010; Hasunuma et al., 2014; Lee et al., 2008; Weir et al., 2013;), or the incidence of atopic eczema among infants (Aguilera et al., 2013; Sbihi et al., 2015), or the increased symptoms of atopic eczema among eczematous children (Kim et al., 2013a; Song et al., 2011). Several previous studies (Anderson et al., 2010; Brunekreef et al., 2009; Hasunuma et al., 2014; Lee et al., 2008; Sbihi et al., 2015; Weir et al., 2013) reported similar findings as in the present study, whereas the findings from some studies differed from those of the present study (Aguilera et al., 2013; Gehring et al., 2010; Kim et al., 2013a; Song et al., 2011).

Specifically, Hasunuma et al. (2014) used daily data regarding outdoor NO₂ for about 619 thousand preschool children in 28 regions of Japan from 1997 to 2009, and found that an increment of 1 ppb for NO₂ during lifetime could increase the year-averaged prevalence of atopic dermatitis by 0.39%. In four Canadian cities, a study identified 2477 approximately 1-year-old infants and found that exposure to ambient NO₂ during the first year of life was significantly associated with the development of atopy to allergens (Sbihi et al., 2015). In the 2005–2006 National Health and Nutrition Examination Survey (NHANES) in the United States, Weir et al. (2013) found that exposure to ambient NO₂ in higher annually-averaged concentration were

Table 3
Correlations between two air pollutants during different periods [Pearson's correlation coefficient, r].

Pollutant	GP			F1			F2			F3			TL		
	SO ₂	NO ₂	PM ₁₀	SO ₂	NO ₂	PM ₁₀	SO ₂	NO ₂	PM ₁₀	SO ₂	NO ₂	PM ₁₀	SO ₂	NO ₂	PM ₁₀
GP	SO ₂														
	NO ₂	0.699	0.603	0.899	0.694	0.765	0.932	0.697	0.775	0.924	0.705	0.818	0.923	0.708	0.827
	PM ₁₀		0.710	0.655	0.969	0.794	0.644	0.974	0.864	0.638	0.981	0.863	0.631	0.979	0.904
F1	SO ₂			0.671	0.669	0.449	0.624	0.673	0.601	0.648	0.692	0.609	0.628	0.690	0.689
	NO ₂				0.693	0.712	0.978	0.691	0.805	0.965	0.688	0.795	0.955	0.693	0.830
	PM ₁₀					0.827	0.676	0.994	0.901	0.657	0.982	0.890	0.647	0.982	0.914
F2	SO ₂						0.758	0.832	0.925	0.730	0.815	0.919	0.733	0.821	0.908
	NO ₂							0.678	0.813	0.982	0.673	0.817	0.977	0.678	0.838
	PM ₁₀								0.902	0.658	0.989	0.899	0.648	0.988	0.919
F3	SO ₂									0.798	0.887	0.962	0.792	0.891	0.970
	NO ₂										0.666	0.813	0.988	0.669	0.834
	PM ₁₀											0.902	0.653	0.993	0.922
TL	SO ₂												0.804	0.898	0.978
	NO ₂													0.664	0.829
	PM ₁₀														0.924

GP, gestational period; F1, first year; F2, first two years; F3, first three years; TL, total lifetime since birth. All p -values are lower than 0.001.

Table 4

Associations of exposure to individual air pollutants in different periods with childhood eczema.

Pollutants ^a (Increment)	OR, 95%CI ^b					
	Eczema, lifetime-ever			Eczema, in the last year before survey		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
(1) During gestational period						
SO ₂ (15)	1.44, 1.23–1.68	1.33, 1.12–1.58	1.10, 0.84–1.44	1.45, 1.21–1.74	1.36, 1.10–1.66	1.05, 0.76–1.43
NO ₂ (20)	1.80, 1.45–2.24	1.53, 1.21–1.94	1.80, 1.29–2.49	1.97, 1.52–2.57	1.71, 1.28–2.29	2.32, 1.57–3.43
PM ₁₀ (10)	1.19, 1.03–1.37	1.10, 0.94–1.28	0.87, 0.70–1.07	1.17, 0.99–1.38	1.08, 0.90–1.31	0.83, 0.65–1.06
(2) During the first year of life						
SO ₂ (15)	1.20, 1.06–1.36	1.12, 0.98–1.28	0.83, 0.69–1.01	1.20, 1.04–1.39	1.14, 0.97–1.33	0.80, 0.63–1.01
NO ₂ (20)	1.90, 1.57–2.30	1.66, 1.34–2.05	2.00, 1.40–2.84	2.06, 1.63–2.60	1.80, 1.40–2.33	2.16, 1.43–3.28
PM ₁₀ (10)	1.33, 1.17–1.52	1.27, 1.10–1.47	0.98, 0.76–1.25	1.37, 1.18–1.60	1.32, 1.11–1.58	1.00, 0.75–1.34
(3) During the first two years of life						
SO ₂ (15)	1.58, 1.32–1.89	1.50, 1.24–1.83	1.37, 0.98–1.89	1.56, 1.26–1.92	1.44, 1.14–1.81	1.06, 0.73–1.52
NO ₂ (20)	1.93, 1.60–2.34	1.69, 1.37–2.09	2.49, 1.61–3.85	2.11, 1.67–2.67	1.86, 1.44–2.40	2.63, 1.57–4.40
PM ₁₀ (10)	1.59, 1.39–1.82	1.48, 1.27–1.72	1.25, 0.89–1.75	1.71, 1.46–2.00	1.62, 1.36–1.94	1.37, 0.93–2.01
(4) During the first three years of life						
SO ₂ (15)	1.63, 1.36–1.96	1.47, 1.21–1.80	1.05, 0.74–1.47	1.62, 1.30–2.01	1.47, 1.16–1.86	0.86, 0.58–1.27
NO ₂ (20)	1.89, 1.56–2.29	1.65, 1.34–2.03	1.83, 1.26–2.68	2.04, 1.62–2.57	1.78, 1.38–2.29	1.83, 1.17–2.86
PM ₁₀ (10)	1.36, 1.19–1.55	1.29, 1.11–1.51	0.90, 0.65–1.25	1.41, 1.20–1.65	1.37, 1.14–1.64	0.99, 0.68–1.46
(5) During total lifetime since birth day						
SO ₂ (15)	1.19, 1.00–1.41	1.16, 0.96–1.40	0.90, 0.65–1.23	1.23, 1.00–1.51	1.20, 0.96–1.50	0.99, 0.68–1.44
NO ₂ (20)	1.88, 1.56–2.28	1.63, 1.33–2.00	1.59, 1.11–2.29	2.05, 1.63–2.58	1.78, 1.38–2.28	1.74, 1.13–2.68
PM ₁₀ (10)	1.90, 1.56–2.31	1.64, 1.33–2.04	1.37, 0.61–3.10	2.03, 1.60–2.57	1.78, 1.37–2.31	1.20, 0.48–3.01

^a Increment is the approximate interquartile range which is presented in the Table 2.^b Model 1 is bivariate logistic regression analyses (crude associations). Model 2 is multiple logistic regression analyses adjusted for age, sex, family history of atopy, ownership of the residence, breastfeeding, home dampness, ETS at home, distance of residence from the nearest main traffic road, use of heating during winter, and renovated residence or bought new large furniture during early lifetime. Model 3 is Model 2 multiple logistic regression and further adjusted for other air pollutants in the same exposure period (as a continuous variable). Bold indicates significance.

consistently associated with increased risk of allergic sensitization during lifetime (OR, 95% CI for increment of 10 ppb: 1.15, 1.04–1.27). In phase three of the ISAAC, Brunekreef et al. (2009) suggested that frequency of truck traffic on the street close to the residence was positively

associated with the prevalence of eczema during childhood among 6–7 and 13–14 years-old children. Since NO₂ is the main pollutant of truck traffic (Sbihi et al., 2015), we therefore inferred that this study (Brunekreef et al., 2009) might indicate that NO₂ has a dose-response

Table 5

Associations of exposure to various mixed air pollutants in different periods with childhood eczema.

Pollutants ^a (Increment)	OR, 95%CI ^b					
	Eczema, lifetime-ever			Eczema, in the last year before survey		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
(1) During gestational period						
SO ₂ + NO ₂ (35)	1.83, 1.47–2.29	1.61, 1.26–2.05	1.88, 1.37–2.56	2.00, 1.53–2.63	1.79, 1.33–2.41	2.35, 1.61–3.42
SO ₂ + PM ₁₀ (25)	1.48, 1.21–1.82	1.34, 1.07–1.68	0.95, 0.69–1.32	1.48, 1.16–1.89	1.33, 1.02–1.74	0.83, 0.57–1.20
NO ₂ + PM ₁₀ (30)	1.73, 1.39–2.15	1.48, 1.16–1.88	1.61, 1.18–2.19	1.88, 1.44–2.46	1.65, 1.23–2.21	1.97, 1.36–2.84
SO ₂ + NO ₂ + PM ₁₀ (45)	1.78, 1.43–2.22	1.51, 1.19–1.92		1.88, 1.44–2.46	1.61, 1.20–2.16	
(2) During the first year of life						
SO ₂ + NO ₂ (35)	1.90, 1.57–2.31	1.68, 1.35–2.06	1.99, 1.38–2.87	2.00, 1.58–2.53	1.77, 1.37–2.29	1.93, 1.25–2.98
SO ₂ + PM ₁₀ (25)	1.92, 1.58–2.33	1.70, 1.37–2.10	1.61, 0.90–2.88	2.04, 1.61–2.58	1.81, 1.40–2.34	1.29, 0.67–2.50
NO ₂ + PM ₁₀ (30)	1.92, 1.58–2.34	1.67, 1.34–2.06	2.10, 1.59–2.79	2.07, 1.63–2.62	1.82, 1.40–2.36	2.43, 1.74–3.40
SO ₂ + NO ₂ + PM ₁₀ (45)	1.94, 1.59–2.35	1.69, 1.36–2.09		2.07, 1.63–2.62	1.83, 1.41–2.37	
(3) During the first two years of life						
SO ₂ + NO ₂ (35)	1.92, 1.58–2.33	1.67, 1.35–2.07	2.76, 1.75–4.37	2.03, 1.61–2.57	1.79, 1.39–2.31	2.78, 1.61–4.81
SO ₂ + PM ₁₀ (25)	1.90, 1.56–2.31	1.65, 1.34–2.05	1.22, 0.65–2.30	2.02, 1.59–2.56	1.78, 1.37–2.30	1.00, 0.48–2.06
NO ₂ + PM ₁₀ (30)	1.88, 1.55–2.29	1.62, 1.31–2.01	1.88, 1.43–2.48	2.04, 1.60–2.59	1.78, 1.37–2.31	2.24, 1.62–3.11
SO ₂ + NO ₂ + PM ₁₀ (45)	1.90, 1.56–2.31	1.64, 1.33–2.03		2.03, 1.60–2.57	1.78, 1.37–2.31	
(4) During the first three years of life						
SO ₂ + NO ₂ (35)	1.94, 1.60–2.35	1.71, 1.39–2.11	2.52, 1.63–3.89	2.10, 1.66–2.65	1.86, 1.44–2.40	2.68, 1.59–4.52
SO ₂ + PM ₁₀ (25)	1.95, 1.60–2.37	1.70, 1.37–2.11	1.51, 0.75–3.06	2.04, 1.61–2.59	1.80, 1.39–2.34	1.04, 0.48–2.28
NO ₂ + PM ₁₀ (30)	1.89, 1.55–2.30	1.63, 1.32–2.02	1.93, 1.48–2.53	2.04, 1.61–2.59	1.79, 1.38–2.33	2.28, 1.65–3.15
SO ₂ + NO ₂ + PM ₁₀ (45)	1.92, 1.58–2.34	1.68, 1.36–2.08		2.05, 1.62–2.61	1.82, 1.40–2.36	
(5) During total lifetime since birth day						
SO ₂ + NO ₂ (35)	1.99, 1.64–2.41	1.74, 1.41–2.14	2.80, 1.75–4.48	2.14, 1.69–2.70	1.90, 1.47–2.45	3.50, 1.98–6.19
SO ₂ + PM ₁₀ (25)	1.89, 1.56–2.30	1.65, 1.33–2.04	1.22, 0.59–2.53	2.00, 1.58–2.54	1.77, 1.36–2.28	0.96, 0.43–2.16
NO ₂ + PM ₁₀ (30)	1.87, 1.54–2.28	1.62, 1.31–2.01	1.95, 1.49–2.54	2.02, 1.59–2.56	1.77, 1.36–2.29	2.27, 1.65–3.12
SO ₂ + NO ₂ + PM ₁₀ (45)	1.87, 1.54–2.27	1.63, 1.32–2.02		1.97, 1.56–2.49	1.74, 1.35–2.25	

^a Increment is the approximate interquartile range presented in the Table A.1.^b Model 1 is bivariate logistic regression analyses (crude associations). Model 2 is multiple logistic regression analyses adjusted for age, sex, family history of atopy, ownership of the residence, breastfeeding, home dampness, ETS at home, distance of residence from the nearest main traffic road, use of heating during winter, and renovated residence or bought new large furniture during early lifetime. Model 3 is Model 2 multiple logistic regression and further adjusted for the other air pollutant which is not involved in the pollutants mixture in the same exposure period (as a continuous variable). Bold indicates significance.

relationship with the childhood prevalence of eczema among the studied children. A survey in Taiwan for >317,000 middle-school students from 1995 to 1996 also indicated that atopic eczema was significantly associated with traffic-related NO₂ (Lee et al., 2008). In phase one of the ISAAC study, Anderson et al. (2010) found that exposure to ambient PM₁₀ during the child's lifetime was not significantly associated with the childhood prevalence of eczema.

However, a longitudinal study in Seoul, Korea evaluated the effects of outdoor air pollution on skin symptoms among young children (mean age during enrollment: 35 months) with atopic eczema and found that exposure to high concentration of PM₁₀, but not NO₂, was significantly associated with an increase in the skin symptoms of atopic eczema (0.44% increased risk of symptoms for an increment of 1 µg/m³) (Kim et al., 2013a). Another longitudinal study in Seoul, Korea for forty-one 8–12 years-old children with diagnosed atopic eczema also found that daily exposures to ambient ultrafine particles may exacerbate skin symptoms in these children (Song et al., 2011). Our findings that exposures to ambient PM₁₀ during various periods of lifetime had no associations with childhood eczema are inconsistent with these findings. Also, a birth-cohort study for 2199 infants of 12–18 months-old in Spain also suggested that early exposure to ambient NO₂ was not significantly associated with atopic eczema among these infants (Aguilera et al., 2013). A prospective birth cohort study with eight-years follow-up for 3863 children in the Netherlands also concluded that exposure to ambient NO₂ during lifetime was not significantly associated with atopic eczema among these children (Gehring et al., 2010). Our findings of positive and significant relationships of exposure to ambient NO₂ differ from these findings.

These differences between findings in the present study and findings in some previous studies might be partly explained by differences in the period-averaged concentrations of the studied pollutants. The averaged concentrations of NO₂ in the present study (Table 2) and in similar studies on associations between ambient air pollution and childhood asthma from China (Cai et al., 2014; Deng et al., 2015) were notably larger than in the studies from European countries (Aguilera et al., 2013; Gehring et al., 2010), Korea (Kim et al., 2013a; Song et al., 2011), Japan (Hasunuma et al., 2014), Canada (Sbihi et al., 2015), and United States (Weir et al., 2013). Ambient air quality in developed European countries, Korea, Japan, Canada, and United States, is better than in the developing cities of China (Zhang et al., 2012). Odds ratios of risk for childhood eczema for increments in the interquartile range of NO₂ concentration from the present study (Table 4 and Table 5) were higher and more statistically significant than on similar studies from other countries (Aguilera et al., 2013; Gehring et al., 2010; Hasunuma et al., 2014; Sbihi et al., 2015; Weir et al., 2013). Our findings also suggest that exposure to NO₂ is a risk factor for childhood eczema, and possibly suggests that ambient NO₂ exposure has a concentration threshold for its risk for childhood eczema. More studies are warranted to test these suggestions.

For ambient PM₁₀, we “unexpectedly” found no significant associations with the prevalence of childhood eczema, consistent with a previous worldwide study (Anderson et al., 2010). However, the mean concentrations of ambient PM₁₀ in the present study were higher than in Seoul, Korea, where two longitudinal studies concluded that exposure to ambient PM₁₀ aggravated skin symptoms in children with atopic eczema (Kim et al., 2013a; Song et al., 2011). Although these Korean studies indicate that exposure to PM₁₀ may aggravate eczema skin symptoms, but not induce atopic eczema, more studies are required to give a robust conclusion. With respect to ambient SO₂, we did not find any previous studies on exposure to and childhood eczema. Our findings seemingly suggest that exposure to ambient SO₂ had no robust effect on the prevalence of childhood eczema, but additional studies are warranted.

Furthermore, in the multiple logistic regression analyses adjusted for other pollutants, the statistical significance of exposure to ambient SO₂ and PM₁₀ and childhood eczema disappeared. These findings suggest

that the effect of one ambient air pollutant on childhood diseases can be confounded and modified by other air pollutants in the same exposure period. Thus we suggest that confounding and effect-modification among different kinds of air pollutants should be considered in studies of air pollution and human health (Fann et al., 2011). These findings also suggest that exposure to ambient NO₂, but not SO₂ and PM₁₀, during early and lifetime are risk factors for childhood eczema. Besides, this deduction is supported by our novel findings that only those mixtures containing NO₂ were significantly associated with childhood eczema, whereas no significant associations were found between exposures to the mixture of SO₂ and PM₁₀ in all studied periods and childhood eczema. These findings suggest that SO₂ and PM₁₀, while not individually risk factors, could enhance the effect of exposure to ambient NO₂ on childhood eczema. Ambient NO₂ has been widely suggested as a proxy of traffic-generated air pollution (Delfino et al., 2014; Gehring et al., 2015; Oftedal et al., 2009; Weinmayr et al., 2010), while ambient SO₂ is a proxy for industry-related air pollution (Kim et al., 2013b; Parker et al., 2009). The coarse fraction of PM₁₀ comes mainly from abrasive and crushing processes typified by construction (Wilhelm et al., 2008) and the fine fraction of PM₁₀ is generated by combustion (Kim et al., 2013b; Wilhelm et al., 2008). These findings also suggest that traffic-related air pollution may have a stronger impact on childhood eczema than industrial air pollution and air pollution from other sources.

The exact mechanism for how exposure to ambient NO₂ increases risk of postnatal atopic eczema is still unclear (Weidinger and Novak, 2015). It has been hypothesized that NO₂ exposure may influence the development of the immune system thereby increasing susceptibility to virally induced infections in childhood (Sly and Holt, 2011; Flohr and Mann, 2014). Altering developmental steps during pregnancy could shift the balance between the T helper type 1 (Th1) and T helper type 2 (Th2) in the immune system thereby increasing Th2 responses after birth which would increase the risk of childhood atopic eczema (Prescott et al., 2003). Some studies have also demonstrated that NO₂ may induce permeability and inflammatory of bronchial epithelial cell cultures, another possible mechanism for air pollutants to impact allergic diseases (D'Amato et al., 2015; Ezratty et al., 2014).

This study has some limitations. Firstly, as in all questionnaire-based cross-sectional epidemiological studies, no causal inferences can be made about the studied associations. Secondly, the data for childhood eczema as well as for the adjusted covariates in the logistic regression analyses are from parents-reported questionnaires so that our findings may have been influenced by reporter error and/or bias. Thirdly, we used period-averaged concentrations of air pollutants from ambient monitors in different district, where the child's residence was located, to represent the child's exposure level during various periods. Although many previous studies have used air pollution data from ambient monitors as a proxy for personal exposures to investigate the potential health effect of these exposures to ambient air pollution (Dockery et al., 1993; Cai et al., 2014; Wu et al., 2016a, 2016b; Kloog et al., 2015; Lu et al., 2015; Deng et al., 2015), these period-averaged concentrations in residence-located district might differ from the real personal exposure levels (Cai et al., 2014; Lu et al., 2015; Wu et al., 2016a) and there is no validation of the exposure assessment, thus this paper might have the potential exposure misclassification. Fourthly, because concentrations of the studied air pollutants were strongly correlated with each other (Table 3), we were unable to precisely discern the relative importance of various exposure periods. Fifthly, many studies on environmental exposures and childhood allergic diseases have proposed a hygiene hypothesis: children who come from “dirty” rural areas and had greater and more diverse exposure to microbes would have lower prevalences of allergic diseases than children from the “clean” urban districts (Bloomfield et al., 2006; Daley, 2014; Liu, 2015; Strachan, 1989; von Mutius, 2007). In the present study, consistent with this hypothesis, we found that children from rural district (Feng-Xian district) had

significantly lower prevalence of atopic eczema than children from urban district (Jing-An district) (Table 1). Therefore, although the present study shows that exposure to ambient NO₂ exposure differed, there may be other environmental exposures that differ between children from rural areas and children from urban areas, and that have strong associations with the risk of childhood atopic eczema (Bornehag et al., 2004b; Flohr and Mann, 2014). However, we had limited capacity to consider the hygiene hypothesis and these environmental exposures in the present study.

Nevertheless, this study had several strengths. Firstly, to our best knowledge, the present study is the first study investigating associations between exposures to ambient air pollutants individually and in various mixtures and the childhood prevalence of atopic eczema among 4–6 year-old children in China. ISAAC questionnaire responses to childhood eczema questions have been validated with respect to physician assessment (Jenkins et al., 1996). We also improved the eczema questions by adding the word “eczema” in the questions and adding a specific description to explain what is defined as eczema to parents. Therefore, our parent-reported data on childhood eczema should give believable data. Secondly, although using air pollution data from central air-monitoring stations as a proxy for personal exposure to ambient air pollution may introduced a non-differential exposure measurement error, a study suggested that such an error most likely causes a bias toward the null hypothesis that would underestimate the potential health effect of ambient air pollution (Zeger et al., 2000). Therefore, the real associations of ambient air pollution exposures (SO₂, NO₂, and PM₁₀) with childhood eczema may be stronger than our estimated associations. Thus, our estimated odds ratios with both the odds ratio and 95% confidence intervals > 1.00 likely indicate at least the direction of health effects of ambient air pollution and remind us that the studied pollutant probably is a risk factor for the studied diseases. Thirdly, the studied children's residences remained the same from gestation until the present day. The lifetime exposure times were therefore the last 5–7 years for these 4–6 year-old children. According to a requirement of the Environmental Protection Agency in China for the ambient air quality monitoring station locations should not be in the direct vicinity of traffic or industrial sources (Cai et al., 2014; Deng et al., 2015). Therefore, our air pollution data characterizes the general ambient air pollution level, and the district-averaged concentrations can be used to approximate the child's exposure level over the long-term exposures. Fourthly, we considered several residential living activities, such as home dampness-related exposures, household ETS, and residence renovation or purchase of new large furniture during early lifetime, which have been reported to modify or confound the effect of our studied pollutants on childhood health (Cai et al., 2016; Liu et al., 2016), as covariates in the multiple logistic regression analyses. Fifthly, the studied districts of Shanghai had widely different population densities and industrial plants, so that there were quite different concentrations of NO₂ and SO₂ (Table 2). This gave us an excellent situation in which to study associations between different ambient air pollutants and childhood eczema.

5. Conclusions

This study indicates gestational and lifetime exposure to ambient NO₂ individually and its mixtures with other pollutants is a risk factor for atopic eczema in childhood among preschool children in Shanghai, China. Exposure to ambient SO₂ and PM₁₀, while not risk factors individually or in mixture may enhance the effect of NO₂ exposure on childhood eczema. Confounding and effect-modification among different kinds of air pollutants should be considered in the study on air pollution and childhood diseases.

Conflict of interest

The authors declare that they have no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.scitotenv.2016.07.197>.

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Supplemental materials

Associations of Gestational and Early Life Exposures to Ambient Air Pollution with Childhood Atopic Eczema in Shanghai, China

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Table A.3 Associations of exposure to mixed air pollutants with childhood eczema, stratified by district.

Table A.1 Mean concentration ($\mu\text{g}/\text{m}^3$) of various mixed air pollutants during different exposure periods.

Mixed air Pollutants	Geometric mean $\pm$ standard deviation (interquartile range)				<i>p</i> -value ^a
	Total	Jing-An district	Bao-Shan district	Feng-Xian district	
(1) During gestational period (<i>N</i> = 2,527)					
SO ₂ + NO ₂	101.7 $\pm$ 16.1 (34.4)	108.6 $\pm$ 2.6 (2.4)	115.5 $\pm$ 8.1 (4.3)	82.4 $\pm$ 6.9 (2.3)	<0.001
SO ₂ + PM ₁₀	128.8 $\pm$ 13.2 (23.7)	129.1 $\pm$ 6.2 (7.9)	141.9 $\pm$ 7.5 (6.6)	115.2 $\pm$ 5.9 (7.4)	<0.001
NO ₂ + PM ₁₀	139.1 $\pm$ 16.6 (30.5)	149.1 $\pm$ 6.0 (7.1)	150.5 $\pm$ 8.1 (8.1)	119.5 $\pm$ 9.2 (8.8)	<0.001
SO ₂ + NO ₂ + PM ₁₀	184.8 $\pm$ 21.4 (43.5)	193.5 $\pm$ 6.5 (7.7)	204.1 $\pm$ 10.3 (8.2)	158.6 $\pm$ 10.1 (8.6)	<0.001
(2) During the first year of life (<i>N</i> = 3,358)					
SO ₂ + NO ₂	100.2 $\pm$ 16.1 (34.0)	107.4 $\pm$ 2.9 (3.6)	115.2 $\pm$ 7.0 (5.4)	81.2 $\pm$ 5.5 (1.6)	<0.001
SO ₂ + PM ₁₀	127.8 $\pm$ 11.7 (24.5)	128.4 $\pm$ 3.8 (5.5)	140.8 $\pm$ 6.3 (4.3)	115.7 $\pm$ 4.3 (2.9)	<0.001
NO ₂ + PM ₁₀	138.3 $\pm$ 16.1 (32.3)	149.1 $\pm$ 3.6 (4.2)	150.8 $\pm$ 5.3 (5.9)	118.8 $\pm$ 6.6 (3.9)	<0.001
SO ₂ + NO ₂ + PM ₁₀	183.1 $\pm$ 21.4 (44.7)	192.5 $\pm$ 4.2 (5.8)	203.5 $\pm$ 8.4 (6.6)	157.9 $\pm$ 7.9 (4.1)	<0.001
(3) During the first two years of life (<i>N</i> = 3,358)					
SO ₂ + NO ₂	99.8 $\pm$ 16.0 (35.9)	106.7 $\pm$ 2.4 (3.2)	115.2 $\pm$ 6.5 (1.7)	80.8 $\pm$ 5.4 (1.6)	<0.001
SO ₂ + PM ₁₀	126.9 $\pm$ 11.5 (25.0)	127.2 $\pm$ 3.3 (3.4)	139.9 $\pm$ 6.2 (3.3)	114.9 $\pm$ 3.9 (2.4)	<0.001
NO ₂ + PM ₁₀	137.0 $\pm$ 15.9 (32.2)	147.9 $\pm$ 2.7 (3.0)	149.5 $\pm$ 4.7 (4.5)	117.6 $\pm$ 6.5 (3.0)	<0.001
SO ₂ + NO ₂ + PM ₁₀	181.9 $\pm$ 21.3 (46.4)	190.9 $\pm$ 3.6 (4.6)	202.4 $\pm$ 8.2 (4.1)	156.7 $\pm$ 7.8 (3.6)	<0.001
(4) During the first three years of life (<i>N</i> = 3,358)					
SO ₂ + NO ₂	99.3 $\pm$ 15.8 (35.9)	105.9 $\pm$ 2.3 (2.6)	116.4 $\pm$ 6.5 (2.1)	80.5 $\pm$ 5.3 (1.0)	<0.001
SO ₂ + PM ₁₀	125.9 $\pm$ 11.3 (25.0)	127.2 $\pm$ 3.3 (4.2)	138.9 $\pm$ 6.1 (2.9)	114.3 $\pm$ 3.9 (1.8)	<0.001
NO ₂ + PM ₁₀	136.2 $\pm$ 15.8 (32.4)	146.9 $\pm$ 2.8 (3.9)	148.7 $\pm$ 4.4 (3.3)	116.9 $\pm$ 6.5 (2.8)	<0.001
SO ₂ + NO ₂ + PM ₁₀	180.7 $\pm$ 21.0 (46.8)	189.4 $\pm$ 3.6 (5.0)	201.1 $\pm$ 8.1 (3.1)	155.9 $\pm$ 7.6 (2.5)	<0.001
(5) During total lifetime since birth's day (<i>N</i> = 3,358)					
SO ₂ + NO ₂	98.5 $\pm$ 15.8 (36.7)	104.6 $\pm$ 1.9 (1.6)	114.0 $\pm$ 6.6 (1.0)	80.0 $\pm$ 5.2 (0.6)	<0.001
SO ₂ + PM ₁₀	123.3 $\pm$ 11.1 (25.4)	123.0 $\pm$ 2.6 (2.4)	136.2 $\pm$ 6.0 (1.8)	112.0 $\pm$ 3.5 (1.2)	<0.001
NO ₂ + PM ₁₀	134.4 $\pm$ 15.6 (32.7)	144.7 $\pm$ 2.1 (1.8)	147.0 $\pm$ 4.2 (1.8)	115.3 $\pm$ 6.3 (1.4)	<0.001
SO ₂ + NO ₂ + PM ₁₀	178.1 $\pm$ 20.8 (47.3)	186.1 $\pm$ 2.8 (2.8)	198.6 $\pm$ 8.1 (2.1)	153.6 $\pm$ 7.4 (1.6)	<0.001

^a Multi-sample Kruskal-Wallis test for the concentration difference in different districts.

Table A.2 Associations of exposure to individual air pollutants with childhood eczema, stratified by district.

Pollutants ^a (Increment)	Adjusted OR ^b , 95%CI (Model 3)					
	Eczema, lifetime-ever			Eczema, in the last year before survey		
	Jing-An	Bao-Shan	Feng-Xian	Jing-An	Bao-Shan	Feng-Xian
(1) During gestational period						
SO ₂	0.81, 0.31-2.11	0.98, 0.43-2.26	0.81, 0.31-2.11	0.81, 0.24-2.76	1.47, 0.82-2.65	0.81, 0.24-2.76
NO ₂	1.17, 0.49-2.82	1.74, 1.05-2.89	1.17, 0.49-2.82	1.46, 0.53-4.04	1.56, 0.55-4.42	1.46, 0.53-4.04
PM ₁₀	0.58, 0.36-1.01	0.97, 0.67-1.42	0.58, 0.36-1.03	0.75, 0.43-1.31	0.78, 0.50-1.21	0.75, 0.43-1.31
(2) During the first year of life						
SO ₂	0.70, 0.23-2.19	1.07, 0.40-2.87	1.00, 0.63-1.57	0.45, 0.14-1.48	1.08, 0.68-1.73	1.28, 0.72-2.27
NO ₂	1.53, 0.86-2.70	1.22, 0.81-1.82	1.58, 0.84-2.97	1.39, 0.74-2.59	1.24, 0.75-2.08	1.69, 0.77-3.73
PM ₁₀	1.20, 0.86-2.70	0.99, 0.69-1.43	0.74, 0.14-4.00	0.57, 0.10-3.22	1.01, 0.65-1.56	1.03, 0.10-5.44
(3) During the first two years of life						
SO ₂	1.33, 0.89-2.01	0.91, 0.68-1.42	0.88, 0.15-5.10	1.03, 0.65-1.62	0.95, 0.29-3.18	0.97, 0.13-7.33
NO ₂	2.09, 0.23-19.29	1.49, 0.50-4.48	1.53, 0.35-6.65	1.23, 0.69-2.17	1.57, 0.53-4.64	1.51, 0.13-17.34
PM ₁₀	1.02, 0.61-1.70	0.87, 0.33-2.31	1.18, 0.85-1.64	1.12, 0.12-10.51	1.17, 0.39-3.46	1.00, 0.67-1.50
(4) During the first three years of life						
SO ₂	1.04, 0.67-1.61	1.14, 0.43-2.98	1.07, 0.21-5.55	0.90, 0.55-1.48	0.91, 0.30-2.75	0.67, 0.07-6.75
NO ₂	1.25, 0.37-2.97	1.73, 0.66-4.54	1.35, 0.08-21.87	1.35, 0.34-4.07	1.39, 0.77-2.49	1.26, 0.11-14.06
PM ₁₀	0.96, 0.36-2.52	1.19, 0.72-1.94	0.81, 0.14-4.55	0.70, 0.25-1.95	1.13, 0.39-3.31	0.57, 0.17-2.04
(5) During total lifetime since birth day						
SO ₂	0.91, 0.58-1.43	1.04, 0.41-2.67	0.40, 0.09-1.75	1.16, 0.70-1.93	1.09, 0.36-3.28	0.49, 0.05-4.86
NO ₂	2.35, 0.27-7.91	1.78, 0.66-4.81	1.34, 0.61-3.17	2.24, 0.33-7.27	1.30, 0.42-4.05	1.38, 0.12-15.65
PM ₁₀	1.03, 0.65-1.67	1.10, 0.28-4.37	0.91, 0.17-4.93	1.03, 0.37-2.91	0.90, 0.19-4.32	0.59, 0.14-6.80

^a Increment is the interquartile range which is presented in the Table 2.

^b Multiple logistic regression analyses with adjusted for age, sex, family history of atopy, ownership of the residence, breastfeeding, home dampness, ETS at home, distance of residence from the nearest main traffic road, use of heating during winter, and renovated the residence or bought new large furniture during early lifetime, as well as mutually for other air pollutants in the same exposure period (as a continuous variable). Bold indicates significance.

Table A.3 Associations of exposure to mixed air pollutants with childhood eczema, stratified by district.

Pollutants ^a	Adjusted OR, 95%CI ^b					
	Eczema, lifetime-ever			Eczema, in the last year before survey		
	Jing-An	Bao-Shan	Feng-Xian	Jing-An	Bao-Shan	Feng-Xian
(1) During gestational period						
SO ₂ + NO ₂	1.08, 0.65-1.64	1.17, 0.76-1.80	1.31, 0.83-2.05	1.06, 0.64-1.49	1.23, 0.74-2.04	1.33, 0.76-2.34
SO ₂ + PM ₁₀	0.92, 0.64-1.31	0.86, 0.56-1.34	0.83, 0.55-1.26	0.87, 0.58-1.31	0.78, 0.49-1.22	0.82, 0.48-1.40
NO ₂ + PM ₁₀	1.06, 0.67-1.48	1.25, 0.85-1.82	1.15, 0.75-1.65	1.07, 0.75-1.43	1.05, 0.67-1.65	1.16, 0.58-1.85
SO ₂ + NO ₂ + PM ₁₀	1.09, 0.75-1.31	1.18, 0.81-1.73	1.13, 0.62-1.84	1.05, 0.68-1.46	1.26, 0.85-1.86	1.08, 0.65-1.88
(2) During the first year of life						
SO ₂ + NO ₂	1.50, 1.00-2.25	1.25, 0.80-1.95	1.07, 0.65-1.53	1.17, 0.75-1.83	1.17, 0.79-1.75	1.07, 0.63-1.66
SO ₂ + PM ₁₀	0.97, 0.68-1.38	0.95, 0.65-1.39	0.89, 0.61-1.30	0.96, 0.64-1.43	0.95, 0.68-1.32	0.95, 0.60-1.52
NO ₂ + PM ₁₀	1.21, 0.89-1.66	1.15, 0.56-1.90	1.12, 0.77-1.89	1.24, 0.87-1.76	1.11, 0.68-1.95	1.16, 0.69-1.54
SO ₂ + NO ₂ + PM ₁₀	1.07, 0.74-1.54	1.13, 0.78-1.88	1.16, 0.69-1.86	1.16, 0.77-1.76	1.06, 0.69-1.58	1.17, 0.75-1.73
(3) During the first two years of life						
SO ₂ + NO ₂	1.02, 0.66-1.57	1.13, 0.57-1.70	1.19, 0.72-1.96	1.06, 0.65-1.73	1.10, 0.72-1.55	1.08, 0.55-1.93
SO ₂ + PM ₁₀	0.89, 0.56-1.33	0.70, 0.49-1.01	0.83, 0.57-1.21	0.76, 0.54-1.23	0.98, 0.63-1.50	0.85, 0.54-1.36
NO ₂ + PM ₁₀	1.02, 0.72-1.45	1.09, 0.63-1.56	1.25, 0.80-1.96	1.15, 0.77-1.74	1.10, 0.73-1.89	1.21, 0.69-2.11
SO ₂ + NO ₂ + PM ₁₀	1.23, 0.82-1.84	1.17, 0.64-1.86	1.38, 0.93-2.05	1.27, 0.84-1.91	1.23, 0.74-2.05	1.17, 0.71-1.92
(4) During the first three years of life						
SO ₂ + NO ₂	1.21, 0.77-1.92	1.03, 0.69-1.52	1.08, 0.76-1.54	1.06, 0.59-1.53	1.05, 0.63-1.61	1.07, 0.68-1.76
SO ₂ + PM ₁₀	0.82, 0.52-1.25	0.85, 0.45-1.35	1.04, 0.67-1.59	0.76, 0.41-1.31	0.91, 0.56-1.46	0.93, 0.54-1.61
NO ₂ + PM ₁₀	1.50, 0.96-2.37	1.11, 0.79-1.62	1.07, 0.65-1.75	1.65, 0.99-2.75	1.07, 0.68-1.56	1.04, 0.56-1.93
SO ₂ + NO ₂ + PM ₁₀	1.09, 0.70-1.70	1.08, 0.69-1.53	1.20, 0.73-1.97	1.10, 0.67-1.82	1.10, 0.68-1.78	1.22, 0.65-2.27
(5) During total lifetime since birth day						
SO ₂ + NO ₂	1.09, 0.71-1.68	1.08, 0.75-1.50	1.07, 0.64-1.54	1.15, 0.69-1.61	1.14, 0.64-1.63	1.08, 0.76-1.86
SO ₂ + PM ₁₀	0.89, 0.64-1.35	0.82, 0.53-1.27	0.92, 0.46-1.43	0.84, 0.67-1.55	0.94, 0.56-1.57	0.85, 0.36-1.39
NO ₂ + PM ₁₀	1.47, 0.98-2.21	1.16, 0.63-1.95	1.24, 0.73-2.09	1.56, 0.99-2.46	1.06, 0.65-1.64	1.22, 0.63-2.34
SO ₂ + NO ₂ + PM ₁₀	1.37, 0.91-2.10	1.12, 0.65-1.76	1.24, 0.80-1.94	1.42, 0.89-2.25	1.14, 0.67-1.75	1.25, 0.72-2.16

^a Increment is the interquartile range which is presented in the Table A.1.

^b Multiple logistic regression analyses with adjusted for age, sex, family history of atopy, ownership of the residence, breastfeeding, home dampness, ETS at home, distance of residence from the nearest main traffic road, use of heating during winter, and renovated the residence or bought new large furniture during early lifetime, as well as mutually for other air pollutants in the same exposure period (as a continuous variable) except for regarding the mixture SO₂ + NO₂ + PM₁₀. Bold indicates significance.