



Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema



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ARTICLE INFO

Article history:

Received 13 November 2015

Received in revised form

26 May 2016

Accepted 28 May 2016

Available online 6 June 2016

Keywords:

Allergy

Traffic-related air pollution

Fetal origins

Prenatal exposure

Multi-pollutant and trimester model

ABSTRACT

Background: Mounting evidence suggests that exposure to ambient air pollution is associated with the development of childhood allergic diseases, but the effect of prenatal exposure to air pollution on the risk of childhood asthma and allergy is unclear.

Objectives: We evaluated the association between maternal exposure to outdoor air pollution during different trimesters of pregnancy and incidence of asthma, allergic rhinitis, and eczema in 2598 pre-school children aged 3–6 years in China.

Methods: Children's lifetime incidence of allergic diseases was obtained using questionnaire. Individual exposure to outdoor air pollutants during trimesters of pregnancy was estimated by an inverse distance weighted (IDW) method based on the measured concentrations at monitoring stations. We used multiple logistic regression method to estimate the odds ratio (OR) of asthma, allergic rhinitis, and eczema for per interquartile range (IQR) increase in the exposure to air pollutant in each trimester, which was adjusted for the effect of other air pollutants and its effect in other trimesters by a multi-pollutant/trimester model.

Results: Incidence of asthma (6.8%), allergic rhinitis (7.3%), and eczema (28.6%) in children was associated with maternal exposure to traffic-related pollutant NO₂ during entire pregnancy with OR (95% confidence interval [CI]) respectively 1.63 (0.99–2.70), 1.69 (1.03–2.77), and 1.37 (1.04–1.80). After adjustment for other pollutants and trimesters, we found the association was significant only in specific trimester: the first trimester for eczema (1.54, 1.14–2.09), the second trimester for asthma (1.72, 1.02–2.97), and the third trimester for allergic rhinitis (1.77, 1.09–2.89). Sensitivity analysis indicated that the trimester sensitive to the development of allergic diseases was stable.

Conclusion: Maternal exposure to traffic-related air pollutant NO₂ during pregnancy, especially in specific trimesters, is associated with an increased risk of developing asthma, rhinitis, and eczema in children. Our results support the hypothesis that childhood allergic diseases originate in fetal life and are triggered by traffic-related air pollution in sensitive trimesters.

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1. Introduction

Asthma and allergy are the most common diseases and major health issues in children worldwide because they lead to a heavy economic burden and poor quality of life (Asher, 2006; Eder et al., 2006). During past decades, most developing countries such as China witnessed a rapid increase in the prevalence of childhood

asthma and allergies that deserves more attention (Ait-Khaled et al., 2007; Zhang et al., 2013). Although it is largely accepted that gene-environment interactions contribute to the development of asthma and allergies, the changing environment is likely responsible for the rapid increase in the prevalence (London, 2007).

Mounting evidence suggests that long-term exposure to ambient air pollution is associated with the development of asthma and allergies in children (Guarnieri and Balmes, 2014; Kim et al., 2013), and a distinct need is then to find out the key component of air pollution and the critical exposure window so as to develop more effective measures of prevention and intervention. Many recent epidemiological studies in developed countries have

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demonstrated that the traffic-related air pollution has been linked with childhood asthma and allergies (Brauer et al., 2002; Brunekreef and Sunyer, 2003; Gauderman et al., 2005; Gehring et al., 2010; Jerrett et al., 2008; Morgenstern et al., 2007). With the rapid urbanization and economic development during the past decade, China has recently witnessed a substantial increase in the amount of motor vehicles in larger cities that causes heavy traffic-related air pollution. However, there is a lack of studies in China whether the strikingly increased traffic-related air pollution is associated with the rapid increase of childhood asthma and allergies.

Early-life exposure to air pollution has recently been considered as an important determinant in the later development of allergic diseases in children (Warner, 2004). According to Barker hypothesis (Barker and Osmond, 1986), prenatal and early post-natal exposures influence developmental plasticity and result in altered programming which leads to development of a broad spectrum of diseases in childhood and adulthood (Gluckman et al., 2008). Emerging evidences show that exposure to air pollution during pregnancy is associated with elevated risk of adverse birth outcomes (Fleisch et al., 2015; Lakshmanan et al., 2015; de Medeiros et al., 2009; Srám et al., 2005) that have long-term health implications, including increased susceptibility to diseases in the later life (Kajekar, 2007). Some recent studies highlighted that exposure to air pollution during pregnancy is a potential stimulus for the early programming of asthma and allergy (Clark et al., 2010; Kozyrskyj et al., 2011; Sbihi et al., 2015), and our recent work also indicated that prenatal exposure to air pollution was significantly associated with asthma and allergic diseases in preschool children in China (Deng et al., 2015a, 2016, 2015b). Furthermore, some studies found that early childhood allergic diseases were associated with trimester-specific exposure during pregnancy (Aguilera et al., 2013; Esplugues et al., 2011; Hsu et al., 2015; Huang et al., 2015). Despite the importance of early-life exposure in the development of allergy, information on the effect of air pollution exposure, particularly during pregnancy, on allergic diseases early in life has rarely been assessed. The scarce epidemiological evidence on the effect of prenatal exposure to air pollution on the risk of childhood asthma and allergic diseases warrants further investigation.

In this study, we endorse the hypothesis on the fetal origins of childhood allergic diseases and further speculate that disease originates in specific trimester of pregnancy and is triggered by traffic-related air pollution. To test the hypothesis, the objective of our present work is to investigate the association between maternal exposure to air pollution during trimesters of pregnancy and lifetime incidence of asthma, allergic rhinitis, and eczema in preschool children. We carried out the investigation in a prospective cohort study in Changsha, a part of nationwide multicenter “China-Children-Homes-Health (CCHH)” study (Zhang et al., 2013).

2. Materials and methods

2.1. Study population

Between September 2011 and January 2012, we conducted a survey for childhood asthma and allergies in the kindergartens in Changsha, the capital city of Hunan Province in south-central China, having a population of 7.22 million and covering an area of 1909 km². The study protocol was approved by the Ethics Committee of the Central South University and also by the health department of each kindergarten. We used a self-administered Chinese questionnaire that combined the standard questionnaire designed by the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 2006) and a Swedish

questionnaire about dampness in buildings and health (DBH) (Bornehag et al., 2004) to collect information on health status, possible exposures to chemical substances in the immediate environment, and lifestyles of the children and their family members. A total of 4988 questionnaires were randomly distributed to the children at 36 participating kindergartens. Children were instructed to have the questionnaire completed by parents and to return it to kindergartens within one week.

We received 3897 completed questionnaires and the overall response rate was 78%. We first excluded 745 children from kindergartens having a response rate lower than 50%, as these excluded kindergartens were mostly distributed in the suburban areas where the children are mainly from the far rural areas and their parents are mainly rural migrant workers, and thus the children's exposure during pregnancy cannot be estimated by using the urban data. Then, we also excluded 162 children with low birth weight (<2.5 kg) and preterm birth (<37 weeks of gestation), and 10 children with multiple births, as these conditions may confound the association between air pollution and asthma (Brauer et al., 2008). We further excluded 80 children aged younger than 3 and older than 6, i.e. the children aged 3–6 were chosen in our study because there are few children >6 years in kindergartens and diagnosis of asthma among children <3 years is often confused. The 302 children without information on the health outcomes were finally excluded. Totally, the 2598 responses of valid questionnaires were used.

2.2. Exposure assessment

2.2.1. Exposure time window

We divided the entire pregnancy into three trimesters. The entire pregnancy was defined as the period from the first month to the last month of pregnancy. The first, second and third trimesters were respectively the periods from the first to third month, the fourth to sixth month, and the seventh to the last month of pregnancy.

2.2.2. Exposure to ambient air pollutants

We selected three pollutants, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and particulate matter ≤ 10 μm in diameter (PM₁₀) to represent ambient air pollution in Changsha where SO₂ was used as an indicator of industry-related air pollution, NO₂ as traffic-related air pollution, and PM₁₀ as a surrogate of complex mixture of air pollutants (Kan et al., 2012). Daily 24-hour average concentrations of PM₁₀, SO₂ and NO₂ were obtained from 7 municipal air quality monitoring stations during 2005–2008 that included the period of maternal pregnancy for all the children aged 3–6 in the present study. Measurements at the monitoring stations followed the standard methods set by the State Environmental Protection Agency of China: PM₁₀ by a tapered element oscillating microbalance (TEOM1400, Rupprecht & Patashnick, USA), SO₂ by ultraviolet fluorescent method (ML/EC9850, Ecotech, Australia) and NO₂ by the chemiluminescent method (ML/EC9841B, Ecotech, Australia). The detailed information on the monitoring stations and surveyed kindergartens was provided in our previous study (Deng et al., 2015a).

Individual exposure to air pollution was estimated by an inverse distance weighted (IDW) method described elsewhere (Deng et al., 2015a). Briefly, maternal exposure during pregnancy was calculated in terms of air pollutant concentrations at the kindergarten, because parents usually enrolled their children in the kindergarten nearest to their homes and worked near homes. At first, the average daily concentration at each kindergarten was calculated by the obtained daily concentrations from the nearest 4 monitoring stations. Then, the monthly mean concentrations of air pollutants at each kindergarten were computed as the averages

of the daily concentrations at the kindergarten within each month.

Maternal exposure during entire pregnancy was calculated as average of the monthly mean concentrations of PM₁₀, SO₂, and NO₂ during the full gestational months. Exposure during the first, second and third trimesters was respectively calculated as the average of the monthly mean concentrations of PM₁₀, SO₂, and NO₂ during the first to third month, the fourth to sixth month, and the seventh to the last month of pregnancy.

2.3. Health outcome

Health outcomes are lifetime prevalence of doctor-diagnosed allergy diseases. Occurrences of asthma, allergic rhinitis, and eczema were respectively defined as an affirmative answer to the questions: "Has a doctor ever diagnosed asthma/allergic rhinitis or hay fever/eczema in your child? ".

2.4. Confounding covariates

Potential confounding variables are obtained from the parent administered questionnaires including child's, parental, and residential factors: the child-related covariates included sex, age, birth season, and breastfeeding; parent-related covariates included parental atopy, maternal productive age, and parental socioeconomic status (SES); residential-related covariates included environmental tobacco smoke (ETS), new furniture, house redecoration, visible mold/damp stains, condensation on windows, mosquito repellent use, and pets keeping during pregnancy and the past years. It was identified in previous studies that these confounders were related to the reporting of childhood allergies and may affect estimated association between exposure to air pollution and allergic diseases. Children's birth season was classified into spring (March to May), summer (June to August), autumn (September to November), and winter (December to February) according to the climate characteristics in the city. Parental atopy was defined as a history of maternal or paternal asthma and allergic rhinitis. We used house size to indicate parental SES.

2.5. Statistical analysis

We used multiple logistic regression models to evaluate the association between exposure to each air pollutant during different trimesters and childhood asthma, allergic rhinitis, and eczema by adjusting for potential confounding covariates. Multi-pollutant and multi-pollutant/trimester models were further performed to adjust the effects of other air pollutants and trimesters. Associations in the regression analysis were calculated as odds ratio (OR) with 95% confidence interval (95% CI). A p value less than 0.05 was considered statistically significant. OR was estimated by an inter-quartile range (IQR) increase in the exposure level for each air pollutant. To investigate the robust of the link between exposure to air pollutants and childhood allergic diseases, we carried out sensitivity analysis for the parental and residential covariates. All statistical analyses were performed by SPSS software (version 16.0, SPSS Inc, Chicago, USA).

3. Results

Of 2598 children, 175 (6.8%), 187 (7.3%), and 737 (28.6%) respectively had a history of doctor diagnosed asthma, allergic rhinitis, and eczema. Table 1 shows the prevalence stratified by covariates. We observed that child's sex, parental atopy, and window condensation at residential environment were significantly associated with three allergic diseases ($p < 0.05$), i.e. the prevalences of asthma, rhinitis and eczema were higher in

Table 1

Demographics and prevalence of asthma, allergic rhinitis and eczema in children stratified by covariates (n=2598).

	Number (%)	Cases (Prevalence, %)		
		Asthma	Allergic rhinitis	Eczema
Total	2598 (100)	175 (6.8)	187 (7.3)	737 (28.6)
Child's				
Sex				
Boys	1399 (54)	117 (8.4)	116 (8.4)	429 (30.8)
Girls	1199 (46)	58 (4.9)	71 (6.0)	308 (25.9)
p-value		< 0.001	0.020	0.005
Age (year)				
3	665 (26)	26 (3.9)	28 (4.2)	202 (30.5)
4	952 (37)	77 (8.1)	80 (8.5)	263 (27.7)
5	815 (31)	59 (7.3)	64 (8.0)	220 (27.3)
6	166 (6)	13 (7.9)	15 (9.1)	52 (31.5)
p-value		0.017	0.007	0.513
Birth season				
Spring	598 (23)	41 (6.9)	49 (8.3)	137 (23.0)
Summer	744 (29)	50 (6.8)	56 (7.6)	213 (28.9)
Autumn	666 (26)	46 (6.9)	41 (6.2)	216 (32.6)
Winter	590 (22)	38 (6.5)	41 (7.0)	171 (29.2)
p-value		0.989	0.550	0.002
Breast-feeding				
No	222 (9)	24 (11.0)	20 (9.2)	58 (26.6)
Yes	2376 (91)	151 (6.4)	167 (7.1)	679 (28.7)
p-value		0.009	0.260	0.506
Parental				
Parental atopy				
No	2258 (87)	108 (4.9)	103 (4.7)	601 (26.8)
Yes	340 (13)	65 (19.4)	84 (24.9)	136 (40.4)
p-value		< 0.001	< 0.001	< 0.001
Maternal productive age (years) *				
≤ 30	1863 (72)	122 (6.6)	128 (6.9)	530 (28.6)
> 30	710 (28)	51 (7.2)	58 (8.3)	200 (28.4)
p-value		0.571	0.238	0.917
Parental socioeconomic status (SES) by house size (m²) *				
≤ 100	1531 (60)	113 (7.4)	108 (7.1)	410 (27.0)
> 100	1037 (40)	61 (5.9)	78 (7.6)	321 (31.1)
p-value		0.147	0.640	0.023
Residential				
Environmental tobacco smoke (ETS)				
No	864 (33)	60 (7.0)	56 (6.5)	235 (27.3)
Yes	1734 (67)	115 (6.7)	131 (7.6)	502 (29.2)
p-value		0.762	0.310	0.316
New furniture *				
No	1248 (52)	77 (6.2)	82 (6.6)	332 (26.7)
Yes	1156 (48)	87 (7.6)	94 (8.2)	358 (31.0)
p-value		0.178	0.127	0.020
House redecoration *				
No	1689 (73)	103 (6.1)	120 (7.2)	447 (26.6)
Yes	620 (27)	57 (9.2)	51 (8.3)	195 (31.5)
p-value		0.009	0.341	0.019
Visible mold/damp stains *				
No	1985 (77)	126 (6.4)	144 (7.3)	535 (27.1)
Yes	606 (23)	48 (8.0)	41 (6.9)	201 (33.3)
p-value		0.174	0.701	0.003
Condensation on windows*				
No	1175 (46)	63 (5.4)	59 (5.1)	294 (25.1)
Yes	1369 (54)	108 (8.0)	123 (9.1)	428 (31.4)
p-value		0.010	< 0.001	< 0.001
Mosquito repellent used*				
No	764 (30)	49 (6.5)	60 (7.9)	199 (26.2)
Yes	1811 (70)	122 (6.8)	127 (7.1)	529 (29.4)
p-value		0.775	0.455	0.099

* Sum of the number is not 2598 due to missing data. The values $p < 0.05$ were in bold.

children who are male, with parental atopy, and lived in houses with window condensation. Older children had more asthma and rhinitis and children born in autumn had more eczema. A total of 91% children were breast fed and they had less asthma ($p=0.009$). Maternal productive age was not significantly associated with children's diseases. Parental SES indicated by house size was also

Table 2
Statistics of the children's exposure to air pollutants (n=2598).

	Mean	SD	25th Percentile	50th Percentile	75th Percentile	IQR
Entire pregnancy						
PM ₁₀	110	11	103	108	115	12
SO ₂	82	26	62	75	98	36
NO ₂	46	8	40	45	52	12
1st trimester						
PM ₁₀	113	16	102	111	121	19
SO ₂	86	38	60	77	103	43
NO ₂	45	11	37	44	53	16
2nd trimester						
PM ₁₀	110	15	101	109	118	17
SO ₂	82	36	60	73	95	35
NO ₂	46	11	39	46	54	15
3rd trimester						
PM ₁₀	108	18	97	107	116	19
SO ₂	79	38	52	71	94	42
NO ₂	46	10	38	45	53	15

PM₁₀ (μg/m³)= particulate matter ≤ 10 μm in aerodynamic diameter; SO₂ (μg/m³)= sulfur dioxide; NO₂ (μg/m³)= nitrogen dioxide; SD = standard deviation, IQR = interquartile range.

not significantly related to the children's asthma and allergic rhinitis, but was significant to children's eczema ($p=0.023$). More than a half of the children were exposed to ETS but not associated with children's allergic diseases. Nearly half families had been installed new furniture that was found significant effect on children's eczema ($p=0.02$). A total of 27% families reported redecoration that significantly increased the risk of asthma ($p=0.009$) and eczema ($p=0.019$). Visible mold/damp stains observed in 23% families that increased the risk of eczema in children ($p=0.003$). A total of 70% families used mosquito repellent and only 6% families kept pets (dogs in our study) that were also not significantly associated with childhood allergic diseases.

Table 2 summarizes the statistics of children's exposure to air pollutants during entire pregnancy and three trimesters. The average individual exposure (mean ± SD) to PM₁₀, SO₂ and NO₂ were respectively 110 ± 11 μg/m³, 82 ± 26 μg/m³, and 46 ± 8 μg/m³ during entire pregnancy. Average exposure levels did not vary greatly across three trimesters, but the classic air pollutants (PM₁₀ and SO₂) were decreased and the traffic air pollutant (NO₂) was slightly increased from the first to the third trimesters.

Table 3 shows exposure correlations between air pollutants during each trimester and between trimesters for each air pollutant. The pollutants during each trimester were weakly or moderately correlated with each other, ranged from 0.15 to 0.66. Each pollutant was also weakly or moderately correlated between

Table 3
Pearson correlation between exposures to air pollutants and between trimesters (n=2598).

Air pollutants	Between air pollutants			Between trimesters
	PM ₁₀	SO ₂	NO ₂	
1st trimester				2nd trimester
PM ₁₀	1	0.41**	0.15**	0.14**
SO ₂		1	0.66**	0.40**
NO ₂			1	0.55**
2nd trimester				3rd trimester
PM ₁₀	1	0.38**	0.15**	0.24**
SO ₂		1	0.59**	0.39**
NO ₂			1	0.42**
3rd trimester				1st trimester
PM ₁₀	1	0.52**	0.29**	0.16**
SO ₂		1	0.62**	−0.05**
NO ₂			1	0.06**

** Correlation is significant at the 0.01 level (2-tailed).

different trimesters, ranged from −0.05 to 0.55. Therefore, the allergic risk of each pollutant could be further evaluated by using multi-pollutant model to adjust the effects of other pollutants and using multi-pollutant/trimester model to further adjust its effect in other trimesters.

Table 4 shows the association between exposure to outdoor air pollutants during pregnancy and childhood asthma. We found that exposure to particulate air pollutant PM₁₀ during both entire pregnancy and three trimesters was not associated with childhood asthma. Although exposure to industry-related air pollutant SO₂ was significantly associated with asthma in single-pollutant model, it was not significant in multi-pollutant model and the subsequent multi-pollutant/trimester model. However, the association between asthma and exposure to traffic-related air pollutant NO₂ during entire pregnancy was significant in single-pollutant model with adjusted OR (95% CI)=1.64 (1.20–2.21) and marginally significant in multi-pollutant model with adjusted OR (95% CI)=1.63 (0.99–2.70) after adjustment for PM₁₀ and SO₂. Furthermore, we found that the association in the second trimester was consistently significant, with adjusted OR (95% CI) respectively 1.70 (1.26–2.30) in single-pollutant model, 1.74 (1.15–2.62) in multi-pollutant model, and 1.72 (1.02–2.97) in multi-pollutant/trimester model, indicating that NO₂ exposure in the second trimester may increase the risk of developing asthma in preschool children.

Table 5 shows the association between exposure to outdoor air pollutants and allergic rhinitis. We found that both PM₁₀ and SO₂ were not associated with childhood allergic rhinitis during either entire pregnancy or three trimesters. However, the risk of childhood allergic rhinitis was associated with traffic-related air pollutant NO₂ during entire pregnancy with OR (95% CI)=1.38 (1.03–1.84) in single-pollutant model and 1.69 (1.03–2.77) in multi-pollutant model. On the other hand, the association between exposure to NO₂ and allergic rhinitis was significant only in the third trimester with adjusted OR (95% CI) respectively 1.36 (1.06–1.75) in single-pollutant model, 1.84 (1.19–2.85) in multi-pollutants model, and 1.77 (1.09–2.89) in multi-pollutant/trimester model, indicating that NO₂ exposure in the third trimester may increase the risk of developing allergic rhinitis in preschool children.

Table 6 shows the association between exposure to outdoor air pollutants and eczema. We also found that neither PM₁₀ nor SO₂ was associated with childhood eczema. However, the risk of eczema was associated with exposure to NO₂ during entire pregnancy and the first trimester. Adjusted OR (95% CI) was 1.20 (1.02–1.41) in single-pollutant model and 1.37 (1.04–1.80) in multi-pollutant model during entire pregnancy, and was 1.29 (1.11–1.49), 1.61 (1.25–2.09), and 1.54 (1.14–2.09) respectively in single-pollutant model, multi-pollutant model, and multi-pollutant/trimester model during the first trimester, indicating that NO₂ exposure in the first trimester may increase the risk of developing eczema in preschool children.

The association between exposure to traffic-related air pollutant NO₂ during trimesters of pregnancy and incidence of childhood allergic diseases was further investigated by sensitivity analysis for the presence of parental and residential covariates. We found that parental and residential factors had significant effect modification to the association only in sensitive trimesters (Table 7), i.e. the second trimester for asthma, the third trimester for allergic rhinitis, and the first trimester for eczema, but no significant modification in non-sensitive trimesters (please see the detailed effect modification in Table S1–S3 in Supplementary materials). The results indicated that the trimester sensitive to the development of allergic diseases was stable.

Table 4

Associations between exposure to outdoor air pollutants during pregnancy and childhood asthma in terms of odds ratio (OR) and 95% CI (n=2598).

Single-pollutant model			Multi-pollutant model †				Multi- pollutant and trimester model ‡
Crude	Adjusted #	+PM ₁₀	+ SO ₂	+ NO ₂	+ PM ₁₀ + SO ₂ + NO ₂		
Entire pregnancy							
PM ₁₀	1.16 (0.99, 1.37)	0.89 (0.68, 1.16)	—	0.92 (0.71, 1.19)	0.90 (0.70, 1.16)	0.90 (0.70, 1.17)	—
SO ₂	1.46 (1.20, 1.77)***	1.43 (1.10, 1.85)**	1.41 (1.09, 1.83)**	—	1.03 (0.66, 1.60)	1.00 (0.65, 1.56)	—
NO ₂	1.29 (1.02, 1.63)*	1.64 (1.22, 2.21)***	1.64 (1.21, 2.21)***	1.60 (0.97, 2.64)	—	1.63 (0.99, 2.70)	—
1st trimester							
PM ₁₀	1.30 (1.09, 1.55)**	1.07 (0.84, 1.38)	—	0.95 (0.73, 1.24)	0.91 (0.69, 1.19)	0.91 (0.69, 1.19)	0.91 (0.69, 1.19)
SO ₂	1.29 (1.10, 1.50)***	1.29 (1.08, 1.55)**	1.31 (1.08, 1.60)**	—	1.08 (0.78, 1.49)	1.08 (0.78, 1.50)	1.08 (0.78, 1.49)
NO ₂	1.27 (1.02, 1.58)*	1.50 (1.15, 1.96)**	1.56 (1.17, 2.08)**	1.38 (0.87, 2.18)	—	1.43 (0.89, 2.28)	1.02 (0.57, 1.80)
2nd trimester							
PM ₁₀	1.06 (0.89, 1.27)	0.96 (0.76, 1.20)	—	0.91 (0.72, 1.14)	0.86 (0.69, 1.09)	0.86 (0.69, 1.09)	0.89 (0.70, 1.13)
SO ₂	1.23 (1.08, 1.40)**	1.26 (1.05, 1.52)*	1.28 (1.07, 1.55)**	—	1.03 (0.80, 1.32)	1.03 (0.80, 1.33)	1.03 (0.78, 1.36)
NO ₂	1.22 (0.99, 1.50)	1.70 (1.26, 2.30)***	1.79 (1.31, 2.44)***	1.66 (1.10, 2.49)*	—	1.74 (1.15, 2.62)**	1.72 (1.02, 2.97)*
3rd trimester							
PM ₁₀	1.02 (0.86, 1.20)	0.85 (0.69, 1.05)	—	0.80 (0.63, 1.01)	0.76 (0.59, 0.97)*	0.76 (0.60, 0.97)*	0.76 (0.59, 0.97)*
SO ₂	1.13 (0.97, 1.33)	1.04 (0.85, 1.26)	1.13 (0.91, 1.41)	—	0.93 (0.67, 1.28)	0.95 (0.68, 1.31)	0.94 (0.66, 1.34)
NO ₂	1.11 (0.89, 1.38)	1.12 (0.86, 1.45)	1.32 (0.98, 1.78)	1.21 (0.79, 1.85)	—	1.40 (0.90, 2.19)	1.05 (0.65, 1.71)

ORs (95% CIs) were estimated for per IQR increase in PM₁₀, SO₂, and NO₂.

Single-pollutant model: adjustment for all the potential covariates in Table 1 (child's sex, age, birth season, breast-feeding, parental atopy, maternal productive age, parental SES by house size, ETS, new furniture, house redecoration, visible mold/damp stains, window condensation in winter, and mosquito repellent use).

† Multi- pollutant model: further adjustment for the effects of other air pollutants in the same time window on the base of single pollutant model.

‡ Multi- pollutant and trimester model: further adjustment for the effects of the air pollutant in other time windows on the base of multi-pollutant model.

*** p < 0.001.

** p < 0.01.

* p < 0.05.

(***) p = 0.001.

Table 5

Associations between exposure to outdoor air pollutants during pregnancy and childhood allergic rhinitis in terms of odds ratio (OR) and 95% CI (n=2598).

Single-pollutant model			Multi-pollutant model †				Multi- pollutant and trimester model ‡
Crude	Adjusted #		+PM ₁₀	+ SO ₂	+ NO ₂	+ PM ₁₀ + SO ₂ + NO ₂	
Entire pregnancy							
PM ₁₀	1.16 (0.99, 1.36)	0.99 (0.76, 1.29)	—	1.01 (0.78, 1.31)	1.00 (0.78, 1.29)	0.98 (0.76, 1.27)	—
SO ₂	1.27 (1.04, 1.55)*	1.17 (0.90, 1.50)	1.17 (0.90, 1.51)	—	0.80 (0.52, 1.25)	0.80 (0.51, 1.25)	—
NO ₂	1.15 (0.92, 1.44)	1.38 (1.03, 1.84)*	1.38 (1.03, 1.84)*	1.68 (1.03, 2.76)*	—	1.69 (1.03, 2.77)*	—
1st trimester							
PM ₁₀	1.09 (0.91, 1.30)	0.85 (0.67, 1.09)	—	0.81 (0.63, 1.05)	0.79 (0.61, 1.03)	0.79 (0.61, 1.03)	0.78 (0.60, 1.01)
SO ₂	1.10 (0.94, 1.30)	1.06 (0.88, 1.27)	1.20 (0.92, 1.36)	—	1.00 (0.72, 1.38)	1.00 (0.72, 1.39)	1.00 (0.72, 1.39)
NO ₂	1.01 (0.81, 1.26)	1.10 (0.85, 1.43)	1.22 (0.92, 1.62)	1.11 (0.71, 1.74)	—	1.22 (0.77, 1.93)	1.25 (0.72, 2.16)
2nd trimester							
PM ₁₀	1.15 (0.97, 1.36)	1.02 (0.81, 1.28)	—	1.00 (0.80, 1.26)	0.99 (0.79, 1.25)	0.99 (0.79, 1.25)	0.93 (0.73, 1.18)
SO ₂	1.16 (1.01, 1.32)*	1.09 (0.91, 1.31)	1.09 (0.91, 1.32)	—	1.00 (0.78, 1.30)	1.00 (0.78, 1.30)	0.99 (0.75, 1.30)
NO ₂	1.10 (0.90, 1.35)	1.22 (0.91, 1.64)	1.23 (0.90, 1.66)	1.22 (0.81, 1.84)	—	1.22 (0.81, 1.85)	0.92 (0.53, 1.60)
3rd trimester							
PM ₁₀	1.13 (0.97, 1.31)	1.10 (0.90, 1.35)	—	1.08 (0.86, 1.35)	0.96 (0.76, 1.22)	0.97 (0.77, 1.23)	0.96 (0.75, 1.22)
SO ₂	1.14 (0.98, 1.33)	1.09 (0.90, 1.32)	1.05 (0.85, 1.31)	—	0.76 (0.55, 1.05)	0.76 (0.55, 1.05)	0.76 (0.54, 1.09)
NO ₂	1.18 (0.96, 1.46)	1.36 (1.06, 1.75)*	1.39 (1.04, 1.86)*	1.81 (1.20, 2.75)**	—	1.84 (1.19, 2.85)**	1.77 (1.09, 2.89)*

ORs (95% CIs) were estimated for per IQR increase in PM₁₀, SO₂, and NO₂. *** p < 0.001, (**) p = 0.001.

Single-pollutant model: adjustment for all the potential covariates in Table 1 (child's sex, age, birth season, breast-feeding, parental atopy, maternal productive age, parental SES by house size, ETS, new furniture, house redecoration, visible mold/damp stains, window condensation in winter, and mosquito repellent use).

† Multi-pollutant model: further adjustment for the effects of other air pollutants in the same time window on the base of single pollutant model.

‡ Multi- pollutant and trimester model: further adjustment for the effects of the air pollutant in other time windows on the base of multi-pollutant model.

* p < 0.05.

** p < 0.01.

4. Discussion

Our prospective cohort study showed that maternal exposure to traffic-related air pollutant NO₂ during pregnancy was associated with incidence of allergic diseases in preschool children. We further found the trimester in utero sensitive to the development of allergic diseases, i.e. NO₂ exposure in the first, second, and third trimesters increased the risk of eczema, asthma, and allergic

rhinitis respectively. Although several recent studies found that early childhood allergic diseases were associated with trimester-specific exposure during pregnancy (Hsu et al., 2015; Huang et al., 2015), the present study, to our knowledge, is the first to systematically investigate the effect of prenatal exposure to outdoor air pollution during different trimesters on childhood allergy.

We found that asthma in preschool children was associated with the NO₂ exposure in utero. The result is consistent with

Table 6

Associations between exposure to outdoor air pollutants during pregnancy and childhood eczema in terms of odds ratio (OR) and 95% CI (n=2598).

Single-pollutant model			Multi-pollutant model †				Multi- pollutant and trimester model ‡
Crude	Adjusted #		+PM ₁₀	+ SO ₂	+ NO ₂	+ PM ₁₀ + SO ₂ + NO ₂	
Entire pregnancy							
PM ₁₀	0.96 (0.87, 1.06)	1.01 (0.87, 1.17)	—	1.02 (0.87, 1.19)	1.02 (0.88, 1.18)	1.01 (0.87, 1.17)	—
SO ₂	0.97 (0.86, 1.10)	1.08 (0.93, 1.26)	1.09 (0.93, 1.26)	—	0.86 (0.67, 1.10)	0.86 (0.67, 1.11)	—
NO ₂	1.08 (0.95, 1.23)	1.20 (1.02, 1.41)*	1.20 (1.02, 1.42)*	1.37 (1.05, 1.80)*	—	1.37 (1.04, 1.80)*	—
1st trimester							
PM ₁₀	0.97 (0.87, 1.08)	1.03 (0.89, 1.18)	—	0.99 (0.86, 1.15)	0.93 (0.80, 1.08)	0.93 (0.80, 1.08)	0.93 (0.80, 1.08)
SO ₂	1.06 (0.96, 1.17)	1.09 (0.98, 1.22)	1.10 (0.98, 1.23)	—	0.83 (0.68, 1.00) ^(*)	0.83 (0.68, 1.00) ^(*)	0.84 (0.70, 1.02)
NO ₂	1.22 (1.08, 1.38) ^(**)	1.29 (1.11, 1.49) ^(***)	1.32 (1.13, 1.55) ^(***)	1.57 (1.22, 2.02) ^(***)	—	1.61 (1.25, 2.09) ^(***)	1.54 (1.14, 2.09) ^(**)
2nd trimester							
PM ₁₀	0.94 (0.85, 1.04)	1.04 (0.92, 1.18)	—	1.03 (0.91, 1.17)	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)	1.01 (0.88, 1.16)
SO ₂	0.94 (0.87, 1.03)	1.05 (0.94, 1.17)	1.04 (0.93, 1.17)	—	0.91 (0.78, 1.06)	0.91 (0.78, 1.06)	0.91 (0.76, 1.08)
NO ₂	1.04 (0.92, 1.17)	1.24 (1.05, 1.46)*	1.24 (1.04, 1.46)*	1.36 (1.08, 1.70) ^(**)	—	1.36 (1.08, 1.70) ^(**)	1.11 (0.83, 1.50)
3rd trimester							
PM ₁₀	1.00 (0.91, 1.09)	0.98 (0.87, 1.10)	—	0.98 (0.86, 1.11)	1.00 (0.87, 1.14)	0.99 (0.87, 1.14)	0.99 (0.86, 1.14)
SO ₂	0.97 (0.88, 1.07)	1.00 (0.89, 1.12)	1.01 (0.89, 1.14)	—	1.07 (0.89, 1.29)	1.07 (0.89, 1.29)	1.10 (0.90, 1.34)
NO ₂	0.95 (0.83, 1.07)	0.96 (0.83, 1.10)	0.96 (0.82, 1.13)	0.89 (0.71, 1.13)	—	0.90 (0.70, 1.14)	0.71 (0.54, 0.92)*

ORs (95% CIs) were estimated for per IQR increase in PM₁₀, SO₂, and NO₂.

Single-pollutant model: adjustment for all the potential covariates in Table 1 (child's sex, age, birth season, breast-feeding, parental atopy, maternal productive age, parental SES by house size, ETS, new furniture, house redecoration, visible mold/damp stains, window condensation in winter, and mosquito repellent use).

† Multi-pollutant model: further adjustment for the effects of other air pollutants in the same time window on the base of single pollutant model.

‡ Multi-pollutant and trimester model: further adjustment for the effects of the air pollutant in other two trimesters on the base of multi-pollutant model.

* p < 0.05.

(*) p = 0.05.

** p < 0.01.

(***) p = 0.001.

*** p < 0.001.

Table 7Odds ratios of childhood eczema, asthma, and allergic rhinitis respectively for NO₂ exposure in the first, second, and third trimesters stratified by covariates (n=2598).

	Eczema in 1st trimester	Asthma in 2nd trimester	Allergic rhinitis in 3rd trimester
Parental atopy			
No	1.32 (0.95, 1.83)	1.14 (0.62, 2.11)	1.37 (0.74, 2.53)
Yes	3.85 (1.69, 8.77) ^(***)	2.65 (1.01, 6.94)*	2.63 (1.14, 6.11)*
Maternal productive age (years)			
≤ 30	1.85 (1.28, 2.66) ^(***)	1.98 (1.01, 3.87)*	1.66 (0.94, 2.95)
> 30	1.01 (0.57, 1.79)	1.03 (0.34, 3.13)	2.18 (0.79, 6.01)
Parental socioeconomic status (SES) by house size			
≤ 100	0.80 (0.55, 1.15)	1.58 (0.78, 3.21)	1.43 (0.73, 2.82)
> 100	0.57 (0.38, 0.86)**	1.99 (0.82, 4.81)	2.29 (1.05, 5.00)*
Environmental tobacco smoke (ETS)			
No	1.68 (0.97, 2.92)	2.91 (1.11, 7.64)*	1.90 (0.77, 4.66)
Yes	1.53 (1.06, 2.20)*	1.33 (0.67, 2.62)	1.68 (0.93, 3.01)
New furniture			
No	1.46 (0.98, 2.17)	2.23 (1.03, 4.84)*	1.69 (0.82, 3.50)
Yes	1.61 (1.01, 2.56)*	1.11 (0.50, 2.44)	1.87 (0.94, 3.72)
House redecoration			
No	1.36 (0.95, 1.95)	1.81 (0.92, 3.55)	1.40 (0.78, 2.49)
Yes	1.44 (0.76, 2.72)	1.50 (0.56, 3.97)	2.93 (1.06, 8.10)*
Visible mold/damp stains			
No	1.60 (1.13, 2.27)**	2.10 (1.10, 4.01)*	1.48 (0.84, 2.60)
Yes	1.44 (0.76, 2.75)	1.05 (0.36, 3.03)	4.05 (1.32, 12.43)*
Condensation on windows			
No	1.94 (1.21, 3.11)**	2.10 (0.83, 5.33)	0.98 (0.42, 2.26)
Yes	1.35 (0.90, 2.01)	1.55 (0.78, 3.07)	2.42 (1.30, 4.49)**
Mosquito repellent use			
No	2.66 (1.49, 4.76) ^(***)	1.00 (0.33, 3.01)	2.86 (1.15, 7.08)*
Yes	1.27 (0.88, 1.81)	2.08 (1.09, 3.98)*	1.49 (0.82, 2.71)

ORs (95% CIs) were estimated for per IQR increase in PM₁₀, SO₂, and NO₂ by multi-pollutant and trimester model.

(***) p = 0.001.

* p < 0.05.

** p < 0.01.

several limited studies. A cohort study in Canada found that the asthmatic risk for children aged 3–4 years was 1.10 (95% CI: 1.05–1.15) for 10 µg/m³ increase in NO₂ exposure in utero (Clark et al., 2010). Our previous work showed a higher asthmatic risk for children aged 3–6 years in China, i.e. 1.74 (95% CI: 1.15–2.62) for 15 µg/m³ increase in NO₂ exposure in utero (Deng et al., 2015a). A prospective cohort study in Japan found that the distance between the residence and the nearest main road, a surrogate for traffic-related pollution, during pregnancy was associated with an increased risk of doctor-diagnosed asthma (Miyake et al., 2010). Most early-life studies on the risk of childhood asthma focused on postnatal exposure and some recent studies reported that NO₂ exposure during the first year of life was associated with physician-diagnosed asthma in pre-school children (Brauer et al., 2002; Clark et al., 2010; Deng et al., 2015a, 2015b; Gruziova et al., 2013; Morgenstern et al., 2007; Nishimura et al., 2013).

We observed association between childhood rhinitis and NO₂ exposure in utero. Although it has been extensively reported that postnatal exposure to traffic-related air pollution was related to allergic rhinitis in preschool children (Morgenstern et al., 2008), school-age children (Weiland et al., 2004; Gehring et al., 2010), middle-school students (Lee et al., 2003), and adolescents (Duhme et al., 1996), no studies have so far been available to report the association between childhood rhinitis and prenatal exposure to traffic-related air pollution.

We found that childhood eczema was associated with NO₂ exposure during pregnancy. Although many indoor factors were proven to be associated with childhood eczema (Bieber, 2008; Langan et al., 2006, 2009; McNally et al., 1998; Zutavern et al., 2005), few studies have evaluated the relationship between outdoor environmental factors and eczema (Ahn, 2014; Lee et al., 2008a, 2008b; Morgenstern et al., 2008; Weiland et al., 2004) and even less studies have examined the associations between early-life exposure to air pollution and risk of childhood eczema (Brauer

et al., 2002; Gehring et al., 2010). A recent birth cohort study in Spain found the risk of eczema in infants during the first 12–18 months of age was positively associated with traffic-related pollutant NO₂ exposure during pregnancy (Aguilera et al., 2013). Another recent birth cohort study in Taiwan found that occurrence of eczema in infants of 6 months of age was significantly associated with exposure to carbon monoxide (CO), another proxy measure of traffic-related pollution, during the whole gestational period with OR = 1.37 (95% CI: 1.06–1.78) (Huang et al., 2015). A prospective cohort study in Japan found that an increased risk of atopic eczema was associated with a shorter distance between the residence and the nearest main road, another surrogate for traffic-related pollution, during pregnancy (Miyake et al., 2010). Another prospective cohort study indicated that higher prenatal exposure to fine particulate matter, another surrogate for traffic-related pollution, may increase the risk of infant eczema (Jedrychowski et al., 2011).

We found that association between childhood asthma and allergy and NO₂ exposures during pregnancy was trimester specific: asthma in the second trimester, rhinitis in the third trimester, and eczema in the first trimester. Very little work has so far examined the risk effect of air pollution exposure in specific trimesters of pregnancy on childhood respiratory infection and diseases. A recent cross-sectional study in USA demonstrated that higher prenatal PM_{2.5} exposure at the second trimester (mid-gestation in 16–25 weeks) was associated with asthma development by age 6 years in boys (Hsu et al., 2015). Two recent birth cohort studies reported associations between childhood eczema and specific trimester exposure to air pollution: One in Spain found the risk of eczema in infants during the first 12–18 months of age was positively associated with traffic-related pollutant NO₂ exposure during the 2nd and 3rd trimesters (Aguilera et al., 2013) and another in Taiwan found that the risk of eczema in infants of 6 months of age was significantly associated with exposure to carbon monoxide (CO) during the 1st trimester (Huang et al., 2015). The study in Spain also found that the association between lower respiratory tract infections (LRTI) and NO₂ exposure during the 2nd trimester was slightly stronger compared with the 1st and 3rd trimesters (Aguilera et al., 2013). An INMA cohort study also found the association with LRTI, bronchiolitis, bronchitis, wheezing and persistent cough varied in different prenatal periods, although it was not statistically significant (Esplugues et al., 2011). The recent INMA cohort study found that in utero exposures, more specifically during the second trimester of pregnancy, may be more relevant for long-term adverse consequences for lung function than exposures later in life (Morales et al., 2015). A USA cohort study of 232 asthmatic children indicated that the association between allergic sensitization at 6–11 years of age and exposure to air pollution during pregnancy was stronger in the first and second trimesters (Mortimer et al., 2008). Another USA cohort study also found deficits in offspring lung function at preschool age in relation to maternal short-term exposure to traffic-related air pollutants (PM_{2.5}) in the second trimester of pregnancy (Jedrychowski et al., 2010).

Sensitivity analysis indicated that the association between exposure to traffic-related air pollutant NO₂ during trimesters of pregnancy and childhood allergic diseases was stable, parental and residential factors had only significant effect modification in sensitive trimesters. The effect of parental and indoor environmental factors on the association between postnatal exposure to air pollution and childhood asthma and allergy has been investigated by many epidemiological studies. It is becoming clear that family history of allergic diseases or parental atopy was associated with an increased risk of atopic diseases in the offspring, suggesting that some genetic markers could impose susceptibility to the effect of environmental factors in childhood (de Planell-Saguer et al.,

2014; Jaakkola et al., 2001; Zutavern et al., 2005). A growing body of research has associated chemical emissions from common indoor materials with risk of asthma, allergies, and pulmonary infections (Diez et al., 2000; Franck et al., 2014; Jaakkola and Knight, 2008). However, the interaction during pregnancy has been rarely investigated. Our recent work demonstrated that exposure to indoor new furniture/redecoration and mold/dampness during pregnancy was associated with childhood asthma and allergy (Deng et al., 2015b and 2016).

Our observed association between childhood asthma, allergic rhinitis, and eczema and prenatal exposure to traffic-related air pollutant is biologically plausible. First, the period of in utero is critical in the development of dermal and respiratory systems, as the fetal skin structures develop rapidly in the first trimester (Huang et al., 2015) and the respiratory airways develop rapidly during the second and third trimesters of pregnancy (Hislop, 2002; Shi et al., 2007). Therefore, potential harmful effects of toxic pollutants during pregnancy might result in long-lasting impaired capacity to fight infections and increased risk of allergic manifestations later in life (Bieber, 2008; Kajekar, 2007; Turnovska and Marinov, 2009). Second, allergic diseases are inflammatory disorders. Possible mechanism underlying association between in utero exposure to air pollution and postnatal respiratory diseases includes oxidative stress and inflammation that results in decreased placental blood flow and reduced transfer of nutrients to the fetus (Kannan et al., 2006), and the possible mechanism underlying the risk of eczema includes damage to the skin barrier by reactive oxygen species and reactive nitrogen species elicited by air pollution (Ahn, 2014; Bowler and Crapo, 2002). Thirdly, epigenetic regulation provides another mechanistic explanation for linking early-life exposure with subsequent development of allergic diseases. According to the Barker hypothesis that organs undergo developmental programming in utero that predetermines subsequent physiologic and metabolic adaptations during adult life (Miller and Ho, 2008), the prenatal environmental exposures influence developmental plasticity and result in altered programming, which is responsible for lasting functional changes of organs that lead to the development of a variety of complex diseases. In addition, the prenatal window represents a critical period in which the developing immune system may be primed toward an allergic phenotype (Prescott, 2010; Wright and Brunst, 2013). Allergic diseases were characterized by dominant T helper 2 (Th2) mechanisms (Farooqi and Hopkin, 1998). Recent evidences indicated that exposure to air pollution during pregnancy could lead to a shift of the Th1/Th2 balance in the immune system toward increased Th2 responses during fetal development and after birth (Prescott et al., 2013).

We note several strengths of this study. We suggested a multi-pollutant/trimester regression model to assess the association between maternal exposure to air pollutants during trimesters of pregnancy and allergic diseases in preschool children. The method could disentangle the effect of air pollutant in specific trimester by adjusting the effect of other air pollutants and its effect in other trimesters. We then, for the first time, identified the specific trimester sensitive to the effect of exposure to traffic-related air pollutant on the development of asthma, allergic rhinitis, and eczema.

We also acknowledge several limitations of this study. First, a limitation of questionnaire-based studies is the selection bias. In our study, we excluded children from kindergartens having a response rate lower than 50% due to a special situation in China. These excluded kindergartens were basically distributed in the suburban areas where the children are mainly from the far rural areas and their parents are mainly rural migrant workers. Generally, the prevalence of allergic diseases in these migrant children exposed to farming in early life is lower (Riedler et al., 2001), and

thus the parents are not active to participate in the questionnaire survey that causes a much lower response rate in these migrant children. On the other hand, the migrant children's exposure during pregnancy cannot be estimated by using the urban data. However, we found that there is no significant difference in the prevalence between all the population and the selected population (please see Table S4 in Supplementary materials). Secondly, we only considered three criteria air pollutants, PM₁₀, SO₂ and NO₂, to represent the ambient air pollution. In China, these pollutants have been paid great attention and have been routinely monitored and the levels have been published to the public (Kan et al., 2012). However, it is important to further investigate the roles of other pollutants, particularly PM_{2.5} and carbon monoxide (CO), which were better proxies for traffic air pollution (Gehring et al., 2010). The third limitation is the potential misclassification of exposure. We estimated maternal exposure to air pollution during pregnancy according to children's exposure in kindergarten. We assumed that mother worked near home or kindergartens and also that the air pollution exposure is the same between kindergarten and the home by considering the situation in China that the parents usually enrolled their children in kindergarten nearest to their home. In addition, exposure to air pollution was modeled by using an inverse distance weighted (IDW) method based on the data from ambient air quality monitoring stations. This modeling method may also lead to bias of exposure because the number of monitoring stations was few and the sources of the air pollution and the land use conditions were ignored. Finally, we found that the incidence of childhood allergic diseases was associated with maternal exposure to air pollution during specific trimester of pregnancy, but the results must be interpreted carefully because of the moderate correlation between the exposures in trimesters of pregnancy. On the other hand, we were unable to confidentially distinguish between prenatal and postnatal exposures because of their close correlation (Deng et al., 2016), which is a common disadvantage in epidemiologic studies.

5. Conclusions

Our prospective cohort study showed that maternal exposure to traffic-related air pollutant NO₂ during pregnancy was associated with the incidence of allergic diseases in preschool children. We found sensitive trimester in utero for developing allergic diseases, i.e. NO₂ exposure in the first, second, and third trimesters may increase the risk of developing eczema, asthma, and allergic rhinitis respectively. Our results may support the hypothesis that childhood allergic diseases originate in fetal life and are triggered by traffic-related air pollution in sensitive trimesters, but we cannot separate the effects of prenatal and postnatal exposure. Our results indicated that the rapid increase of childhood allergic diseases in Changsha may be partially due to the rapid increase of traffic-related air pollution, although the classic industry-related air pollutants such as PM₁₀ and SO₂ were greatly decreased. Our findings could be also used to develop more effective measures of prevention and intervention of allergic diseases in children with regard to the key component of air pollution and the critical exposure window. However, further investigations are required to identify the relevant mechanism(s) underlying the association between exposure to air pollution during specific trimester in utero and childhood allergic diseases.

Conflicts of interests

We declare that we have no conflicts of interest.

Acknowledgments

The research was supported by the National Natural Science Foundation of China (Nos. 51178466 and 51576214) and the Doctoral Program of Higher Education of China (No. 20120162110011). The authors gratefully acknowledge all the children, their parents/guardians and the kindergartens for their time and enthusiastic participation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2016.05.050>.

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Supplemental Materials

Table S1

Association between NO₂ exposure during different trimesters of pregnancy and childhood asthma stratified by covariates by using multi- pollutant and trimester model (n = 2,598).

	1 st trimester	2 nd trimester	3 rd trimester
Parental atopy			
No	0.78 (0.39, 1.57)	1.14 (0.62, 2.11)	1.10 (0.61, 1.98)
Yes	2.17 (0.69, 6.86)	2.65 (1.01, 6.94)*	0.84 (0.34, 2.09)
Maternal productive age (years)			
≤30	0.73 (0.37, 1.44)	1.98 (1.01, 3.87)*	1.12 (0.63, 2.02)
>30	2.36 (0.76, 7.35)	1.03 (0.34, 3.13)	0.80 (0.31, 2.05)
Parental socioeconomic status (SES) by house size			
≤100	0.80 (0.38, 1.69)	1.58 (0.78, 3.21)	1.21 (0.65, 2.24)
>100	1.41 (0.56, 3.50)	1.99 (0.82, 4.81)	0.86 (0.38, 1.98)
Environmental tobacco smoke (ETS)			
No	0.68 (0.24, 1.96)	2.91 (1.11, 7.64)*	0.79 (0.35, 1.78)
Yes	1.23 (0.61, 2.45)	1.33 (0.67, 2.62)	1.23 (0.66, 2.28)
New furniture			
No	0.77 (0.35, 1.70)	2.23 (1.03, 4.84)*	1.14 (0.57, 2.29)
Yes	1.02 (0.44, 2.39)	1.11 (0.50, 2.44)	0.89 (0.45, 1.77)
House redecoration			
No	0.85 (0.42, 1.72)	1.81 (0.92, 3.55)	1.05 (0.58, 1.89)
Yes	1.69 (0.61, 4.65)	1.50 (0.56, 3.97)	0.90 (0.37, 2.21)
Visible mold/damp stains			
No	0.91 (0.47, 1.76)	2.10 (1.10, 4.01)*	0.97 (0.54, 1.74)
Yes	1.49 (0.45, 4.98)	1.05 (0.36, 3.03)	1.44 (0.56, 3.69)
Condensation on windows			

No	1.02 (0.38, 2.72)	2.10 (0.83, 5.33)	0.65 (0.28, 1.50)
Yes	0.98 (0.48, 2.01)	1.55 (0.78, 3.07)	1.33 (0.72, 2.44)

Mosquito repellent use

No	0.65 (0.21, 1.93)	1.00 (0.33, 3.01)	1.74 (0.63, 4.82)
Yes	1.19 (0.60, 2.37)	2.08 (1.09, 3.98)*	0.91 (0.51, 1.60)

* p<0.05.

ORs (95% CIs) were calculated by multiple pollutants and trimesters model that were adjusted for all the potential covariates in Table 1 except for the considered covariates and further adjusted for the effects of PM₁₀ and SO₂ in the same trimester and the effects of NO₂ in other two trimesters.

Table S2

Association between NO₂ exposure during different trimesters of pregnancy and childhood allergic rhinitis stratified by covariates by using multi- pollutant and trimester model (n = 2,598).

	1 st trimester	2 nd trimester	3 rd trimester
Parental atopy			
No	1.05 (0.51, 2.16)	0.73 (0.36, 1.50)	1.37 (0.74, 2.53)
Yes	1.72 (0.69, 4.27)	1.22 (0.49, 3.04)	2.63 (1.14, 6.11)*
Maternal productive age			
≤30	1.25 (0.65, 2.39)	0.87 (0.45, 1.68)	1.66 (0.94, 2.95)
>30	1.26 (0.42, 3.81)	0.73 (0.25, 2.16)	2.18 (0.79, 6.01)
Parental socioeconomic status (SES) by house size			
≤100	2.04 (0.99, 3.00)	1.12 (0.53, 2.36)	1.43 (0.73, 2.82)
>100	0.57 (0.22, 1.48)	0.78 (0.33, 1.85)	2.29 (1.05, 5.00)*
Environmental tobacco smoke (ETS)			
No	0.81 (0.28, 2.30)	1.31 (0.46, 3.67)	1.90 (0.77, 4.66)
Yes	1.40 (0.74, 2.67)	0.86 (0.44, 1.67)	1.68 (0.93, 3.01)
New furniture			
No	1.13 (0.52, 2.44)	1.12 (0.50, 2.48)	1.69 (0.82, 3.50)
Yes	1.36 (0.60, 3.04)	0.73 (0.33, 1.63)	1.87 (0.94, 3.72)
House redecoration			
No	1.00 (0.51, 1.95)	1.25 (0.64, 2.47)	1.40 (0.78, 2.49)
Yes	2.38 (0.81, 7.01)	0.51 (0.17, 1.48)	2.93 (1.06, 8.10)*
Visible mold/damp stains			
No	1.21 (0.65, 2.26)	1.16 (0.61, 2.19)	1.48 (0.84, 2.60)
Yes	1.83 (0.51, 6.55)	0.39 (0.12, 1.27)	4.05 (1.32, 12.43)*
Condensation on windows			
No	0.70 (0.26, 1.88)	0.96 (0.35, 2.61)	0.98 (0.42, 2.26)
Yes	1.59 (0.81, 3.11)	0.96 (0.49, 1.88)	2.42 (1.30, 4.49)**
Mosquito repellent use			
No	2.39 (0.97, 5.90)	0.79 (0.30, 2.08)	2.86 (1.15, 7.08)*

Yes	0.81 (0.40, 1.66)	1.06 (0.54, 2.12)	1.49 (0.82, 2.71)
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* p<0.05, ** p<0.01.

ORs (95% CIs) were calculated by multiple pollutants and trimesters model that were adjusted for all the potential covariates in Table 1 except for the considered covariates and further adjusted for the effects of PM₁₀ and SO₂ in the same trimester and the effects of NO₂ in other two trimesters.

Table S3

Association between NO₂ exposure during different trimesters of pregnancy and childhood eczema stratified by covariates by using multi- pollutant and trimester model (n = 2,598).

	1 st trimester	2 nd trimester	3 rd trimester
Parental atopy			
No	1.32 (0.95, 1.83)	1.07 (0.77, 1.48)	0.66 (0.49, 0.88)**
Yes	3.85 (1.69, 8.77)(***)	1.24 (0.57, 2.71)	0.93 (0.47, 1.86)
Maternal productive age			
≤30	1.85 (1.28, 2.66)(***)	1.00 (0.71, 1.43)	0.68 (0.50, 0.92)*
>30	1.01 (0.57, 1.79)	1.19 (0.67, 2.12)	0.81 (0.48, 1.39)
Parental socioeconomic status (SES) by house size			
≤100	1.56 (1.04, 2.32)*	1.05 (0.70, 1.57)	0.80 (0.55, 1.15)
>100	1.52 (0.95, 2.43)	1.18 (0.75, 1.84)	0.57 (0.38, 0.86)**
Environmental tobacco smoke (ETS)			
No	1.68 (0.97, 2.92)	0.81 (0.47, 1.40)	0.90 (0.56, 1.44)
Yes	1.53 (1.06, 2.20)*	1.26 (0.88, 1.80)	0.65 (0.47, 0.90)**
New furniture			
No	1.46 (0.98, 2.17)	1.08 (0.72, 1.63)	0.71 (0.49, 1.03)
Yes	1.61 (1.01, 2.56)*	1.12 (0.72, 1.74)	0.71 (0.49, 1.04)
House redecoration			
No	1.36 (0.95, 1.95)	1.09 (0.77, 1.57)	0.73 (0.53, 1.00)(*)
Yes	1.44 (0.76, 2.72)	1.13 (0.62, 2.07)	0.55 (0.32, 0.96)*
Visible mold/damp stains			
No	1.60 (1.13, 2.27)**	1.13 (0.80, 1.59)	0.68 (0.50, 0.93)*
Yes	1.44 (0.76, 2.75)	1.01 (0.55, 1.85)	0.83 (0.48, 1.42)
Condensation on windows			
No	1.94 (1.21, 3.11)**	1.20 (0.76, 1.89)	0.71 (0.47, 1.06)
Yes	1.35 (0.90, 2.01)	1.03 (0.70, 1.53)	0.71 (0.50, 1.01)

Mosquito repellent use			
No	2.66 (1.49, 4.76)(***)	0.97 (0.54, 1.73)	0.65 (0.39, 1.08)
Yes	1.27 (0.88, 1.81)	1.14 (0.80, 1.62)	0.73 (0.54, 1.01)

* p<0.05, (*) p=0.05, ** p<0.01, (***) p=0.001.

ORs (95% CIs) were calculated by multiple pollutants and trimesters model that were adjusted for all the potential covariates in Table 1 except for the considered covariates and further adjusted for the effects of PM₁₀ and SO₂ in the same trimester and the effects of NO₂ in other two trimesters.

Table S4

Prevalence of asthma, allergic rhinitis and eczema in children among different populations.

	n	Cases (prevalence, %)		
		Asthma	Allergic rhinitis	Eczema
All population	3,897	270 (6.9)	294 (7.5)	1,137 (29.2)
Selected population	2,598	175 (6.8)	187 (7.3)	737 (28.6)
Population with low response rate (<50%)	745	54 (7.2)	62 (8.3)	238 (31.9)