



Early life exposure to traffic-related air pollution and allergic rhinitis in preschool children



Qihong Deng ^{a, b, *}, Chan Lu ^a, Yichen Yu ^a, Yuguo Li ^c, Jan Sundell ^{a, d}, Dan Norbäck ^{a, e}

^a School of Energy Science and Engineering, Central South University, Changsha, Hunan, China

^b XiangYa School of Public Health, Central South University, Changsha, Hunan, China

^c Department of Mechanical Engineering, The University of Hong Kong, Hong Kong, China

^d School of Architecture, Tsinghua University, Beijing, China

^e Department of Medical Sciences, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Article history:

Received 3 August 2016

Received in revised form

18 October 2016

Accepted 24 October 2016

Available online 26 October 2016

Keywords:

Allergic disease

Air pollution

Children health

First-year of life

Pregnancy

Rhinitis

ABSTRACT

Background: Evidence linking long-term exposure to outdoor air pollution with allergic rhinitis (AR) in children is scarce, and the role of components of air pollution and timing of exposure remains unclear.

Objective: To assess the association of pre- and post-natal exposure to air pollution with life-time prevalence of AR in preschool children.

Methods: We conducted a cohort study of 2598 children aged 3–6 years in Changsha, China. The lifetime prevalence of AR was assessed by a questionnaire administered by parents. Children's exposures to di-oxide nitrogen (NO₂), sulfur dioxide (SO₂) and particulate matter with an aerodynamic diameter ≤ 10 μm (PM₁₀) during different pre- and post-natal timing windows were estimated using the measured concentrations at monitoring stations. The odds ratio (OR) and 95% confidence interval (CI) of childhood AR for exposure to different air pollutants during different timing windows were assessed by logistic regression model in terms of an interquartile range (IQR) increase in exposure level.

Results: Life-time prevalence of AR in preschool children (7.3%) was associated with both pre- and post-natal exposure to traffic-related air pollution (TRAP), but only significant during the third trimester of pregnancy with adjusted OR = 1.40 (95% CI: 1.08–1.82) for a 15 μg/m³ increase in NO₂ and during the first-year of life with adjusted OR = 1.36 (95% CI: 1.03–1.78) and 1.54 (95% CI: 1.07–2.21) respectively for 11 and 12 μg/m³ increase in NO₂ and PM₁₀. The association of early life exposure to TRAP with childhood AR was robust by adjusting for other air pollutants and timing windows. Sensitivity analysis indicated that the association was higher in the children who are male, young, with genetic predisposition by parental atopy, and living in damp houses.

Conclusion: Early life exposure to traffic-related air pollutant during pregnancy and first-year of life may contribute to childhood AR.

© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

Allergic rhinitis (AR) is the most common chronic allergic disease and now recognized as a global health problem that affects as many as 40% children [1]. The prevalence of childhood AR has continuously increased in recent decades worldwide, including China [2]. Due to the fact that AR is not a serious condition, it is frequently ignored and under-diagnosed, especially in developing

countries, leading to more serious complications in both upper and lower airways such as asthma, sinusitis, and otitis media [3]. Besides the significantly high morbidity and substantial health care costs, AR strongly affects children's mental health, quality of life, and learning at school [1]. The increasing trend and severity in AR deserve more attention. The major need lies in finding out the key causal factors and timing windows so as to develop more effective measures of prevention and intervention.

There is accumulating evidence that both genetic and environmental factors play important roles in the etiology of allergic diseases including AR. Genetic factors are unlikely to explain the rapid increase in prevalence and therefore environmental factors have

* Corresponding author. School of Energy Science and Engineering, Central South University, Changsha, Hunan, China.

E-mail address: qhdeng@csu.edu.cn (Q. Deng).

been found to be important contributors to the manifestations of allergic diseases. Mounting evidence suggests that long-term exposure to air pollution, particular the traffic-related air pollution, contributes to the development of allergic disease [4,5]. Surprisingly very few studies have addressed AR as an endpoint, although some recent short-term epidemiological studies have demonstrated a strong association between air pollution and outpatient visits for AR [6–8]. However, the limit evidences linking long-term exposure to air pollution and allergic rhinitis were equivocal [9–13], and hence warrant further studies.

Early-life exposure has recently been suggested to be an important determinant in the later development of allergic diseases throughout childhood and lifespan. Environmental challenges during pregnancy and early postnatal life have long been hypothesized to modulate the susceptibility to chronic diseases in later life, which is commonly referred to as “Barker hypothesis” or “theory of developmental programming” [14]. Due to the rapid development and immaturity of the immune and respiratory systems, the fetuses and infants are most vulnerable to the adverse effects of air pollution [10]. However, the effect of air pollution exposure during early life, particularly during pregnancy and the first year of life, on allergic diseases in later life has rarely been assessed [10,11,15–18].

Having in mind the inconsistent evidences linking AR with long-term exposure to air pollution and the scanty data on the effect of early life exposure, we engaged in a nationwide study “China-Children-Homes-Health” (CCHH) to examine the association between lifetime prevalence of AR in preschool children and early life exposure to air pollution during different time windows, with an objective to identify the key components of air pollution and time windows of exposure.

2. 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. A Chinese version questionnaire combining a standard one designed by the International Study of Asthma and Allergies in Childhood (ISAAC) and another Swedish one about dampness in buildings and health (DBH) [2,19], with some changes to address the housing and cultural characteristics in China, was administered to collect information on health status and possible exposure to the indoor environmental factors of children and 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 with overall response rate 78%. We first excluded 745 children from kindergartens having a response rate lower than 50%, as these kindergartens were mostly distributed in the suburban areas where the children are mainly from the far rural areas and thus the children's early-life exposure during pregnancy and first-year of life cannot be estimated using 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 allergic diseases. We further excluded 80 children aged younger than 3 and older than 6 because of few data.

The 302 children without information about health outcome were finally excluded. Therefore, in total 2598 responses of valid questionnaires were used.

2.2. Exposure assessment

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 [20]. Average daily concentrations of PM₁₀, SO₂ and NO₂ were obtained from 7 municipal air pollution monitoring stations. 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 distribution of monitoring stations and surveyed kindergartens was provided in our previous study [16].

Individual exposure to air pollution was estimated by an inverse distance weighted (IDW) method described elsewhere [16]. Briefly, children's exposure was calculated in terms of the air pollutant concentrations at their kindergartens. 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.

We divided the lifetime exposure into prenatal and postnatal periods. Prenatal period during pregnancy was further divided into three trimesters, and the postnatal period was further divided into first-year of life and thereafter or after first-year (from the second year to the last year). The monthly mean concentrations of PM₁₀, SO₂, and NO₂ were used to estimate the exposure during above different timing windows.

2.3. Health outcome

Health outcomes are lifetime prevalence of doctor-diagnosed allergic rhinitis, which was defined as an affirmative answer to the question: “Has your child ever been diagnosed having hay fever or allergic rhinitis (AR)?”

2.4. Confounding covariates

Information on potential confounders was obtained from the questionnaire. The confounding variables in the present analysis included personal factors (child's sex, age, birth season, breast-feeding, parental atopy, and socioeconomic status (SES) indicated by house size) and indoor factors including environmental tobacco smoke (ETS) at home, new furniture, house redecoration, visible mold/damp stains, condensation on windows in winter, cockroaches noted, and household pets (Table 1). These confounders were related to the reporting of childhood allergies and may affect estimated associations between AR and air pollution [21]. Parental atopy was a measure of genetic predisposition and defined as an affirmative answer to the question: “Have you ever been diagnosed having atopic diseases (asthma, allergic rhinitis, or eczema)?” ETS was defined as an affirmative answer to the question: “Is there a family member smoking at home (Yes/No)?” and if yes: “Who is smoking?” In the present work, the family SES was estimated by using house size, as we haven't the information about parental education and occupation.

Table 1

Demographic information and lifetime prevalence of allergic rhinitis among children (n = 2598).

	Number	(%)	Allergic rhinitis		p-value
			Case (n)	Prevalence (%)	
Total	2598	(100)	187	7.3	—
Sex					
Boys	1399	(54)	116	8.4	0.020
Girls	1199	(46)	71	6.0	
Age (year)					
3	665	(26)	28	4.2	0.006
4	952	(37)	80	8.5	
5	815	(31)	64	8.0	
6	166	(6)	15	9.1	
Birth season					
Warm (May–September)	1152	(44)	84	7.4	0.850
Cold (October–April)	1446	(56)	103	7.2	
Breast-feeding					
No	222	(9)	20	9.2	0.260
Yes	2376	(91)	167	7.1	
Parental atopy					
No	2258	(87)	103	4.6	<0.001
Yes	340	(13)	84	24.9	
Socioeconomic status (SES) by house size (m²)					
≤75	836	(33)	49	5.9	0.054
>75	1732	(67)	137	8.0	
Environmental tobacco smoke (ETS) at home					
No	864	(33)	56	6.5	0.310
Yes	1734	(67)	131	7.6	
New furniture					
No	1248	(52)	82	6.6	0.127
Yes	1156	(48)	94	8.2	
House redecoration					
No	1689	(73)	120	7.2	0.341
Yes	620	(27)	51	8.3	
Visible mold/damp stains					
No	1985	(77)	144	7.3	0.701
Yes	606	(23)	41	6.9	
Window condensation in winter					
No	1175	(46)	59	5.1	<0.001
Yes	1369	(54)	123	9.1	
Household pets (dogs)					
No	2427	(94)	176	7.3	0.882
Yes	167	(6)	11	6.6	
Cockroaches noted					
No	827	(33)	59	7.2	0.737
Yes	1653	(67)	121	7.4	

The sum of number is not 2598 due to the missing data.

The values p < 0.05 were in bold.

2.5. Statistical analysis

We used multiple logistic regression models to evaluate the associations between outdoor air pollution and childhood allergic rhinitis during different exposure windows adjusting for potential confounding covariates. Associations in the regression analysis were calculated as odds ratios (ORs) with 95% confidence interval (CI). A p value less than 0.05 was considered statistically significant. Air pollutants were entered into the models as continuous variables. ORs were estimated by per interquartile range (IQR) increase in the exposure level of each pollutant. All statistical analyses were performed by SPSS software (version 16.0, SPSS Inc, Chicago, USA).

The robustness of the effect estimate of air pollutant was further explored by multi-pollutant model by controlling the effects of other air pollutants in the same time window and multi-window model by controlling the effects of the air pollutant in other time windows. We also performed sensitivity analysis to examine whether associations between AR and air pollution were modified by the potential confounding factors by including an interaction term (products of these factors and the pollutants) in the regression models.

3. Results

Of 2598 children, 187 (7.3%) had a history of doctor-diagnosed AR. Table 1 shows the lifetime prevalence of AR stratified by covariates. Totally, the prevalence is significantly higher in the children who are male, old, with genetic predisposition indicated by parental atopy, and living in damp houses indicated by window condensation than in the children who are female, young, without genetic predisposition, and living in houses without window condensation ($p < 0.05$). Children with higher SES had higher AR prevalence at marginal significance. Birth season and breast-feeding had not impact on AR prevalence in children. Higher prevalence, but not significant, was observed in houses with ETS (67%), cockroaches (67%), new furniture (48%) and redecoration (27%). Indoor visible mold/damp stains and keeping pets (dogs) had insignificant impact on childhood AR.

Table 2 provides the distributions of average air pollution exposure during different timing windows. The mean individual exposures to PM₁₀ and SO₂ were respectively 110 and 82 µg/m³ during the entire pregnancy, decreased to 103 and 68 µg/m³ during first-year and further decreased to 90 and 46 µg/m³ during past years of life. By contrast, NO₂ was slightly increased from 46 µg/m³ during pregnancy to 48 µg/m³ during first-year and 50 µg/m³ during past years of life. Similar trend was observed in three trimesters of pregnancy.

Table 3 shows the correlations between pollutants (PM₁₀, SO₂, and NO₂) in different time windows and the correlations of pollutants between time windows. The pollutants were weakly or moderately correlated with each other in all time windows, and thus we can use multi-pollutant model to estimate the effect of the pollutant by controlling for other pollutants. Correlations of the pollutants between different trimesters of pregnancy were also weak or moderate, ranging from −0.05 to 0.55, and thus we can use multi-window model to discriminate the effects of air pollutant between trimesters. However, correlations of the pollutants between entire pregnancy, first-year, and after first-year are strong

Table 2

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

	Mean	Percentiles			IQR
		25 th	50 th	75 th	
1st trimester					
PM ₁₀	113	102	111	121	19
SO ₂	86	60	77	103	43
NO ₂	45	37	44	53	16
2nd trimester					
PM ₁₀	110	101	109	118	17
SO ₂	82	60	73	95	35
NO ₂	46	39	46	54	15
3rd trimester					
PM ₁₀	108	97	107	116	19
SO ₂	79	52	71	94	42
NO ₂	46	38	45	53	15
Entire pregnancy					
PM ₁₀	110	103	108	115	12
SO ₂	82	62	75	98	36
NO ₂	46	40	45	52	12
First year					
PM ₁₀	103	96	103	108	12
SO ₂	68	51	64	80	29
NO ₂	48	42	47	53	11
After first year (from the second to the last year)					
PM ₁₀	90	87	90	93	6
SO ₂	46	39	45	51	12
NO ₂	50	44	49	56	12

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

Table 3

Pearson correlations between air pollutants and between different time windows (n = 2598).

Air pollutants	Between air pollutants			Between time windows
	PM ₁₀	SO ₂	NO ₂	
1st trimester				2nd trimester
PM ₁₀	1	0.41 ^a	0.15 ^a	0.14 ^a
SO ₂		1	0.66 ^a	0.40 ^a
NO ₂			1	0.55 ^a
2nd trimester				3rd trimester
PM ₁₀	1	0.38 ^a	0.15 ^a	0.24 ^a
SO ₂		1	0.59 ^a	0.39 ^a
NO ₂			1	0.42 ^a
3rd trimester				1st trimester
PM ₁₀	1	0.52 ^a	0.29 ^a	0.16 ^a
SO ₂		1	0.62 ^a	−0.05 ^a
NO ₂			1	0.06 ^a
Entire pregnancy				First-year
PM ₁₀	1	0.27 ^a	−0.32 ^a	0.53 ^a
SO ₂		1	0.48 ^a	0.82 ^a
NO ₂			1	0.86 ^a
First year				After first-year
PM ₁₀	1	0.50 ^a	−0.10 ^a	0.50 ^a
SO ₂		1	0.42 ^a	0.85 ^a
NO ₂			1	0.92 ^a
After first year				Entire pregnancy
PM ₁₀	1	0.87 ^a	0.45 ^a	0.51 ^a
SO ₂		1	0.66 ^a	0.77 ^a
NO ₂			1	0.83 ^a

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

that we cannot use multi-window model to distinguish their effects.

Table 4 provides effect estimates of childhood AR for an IQR increase in PM₁₀, SO₂, and NO₂ exposures during the entire pregnancy and three trimesters. We found that childhood AR was significantly associated with traffic-related air pollutant NO₂ during entire pregnancy with adjusted OR = 1.41 (95% CI: 1.05–1.88), but only significant during 3rd trimester with adjusted OR = 1.40 (95% CI: 1.08–1.82). Single-pollutant model showed that the traffic-related air pollutant NO₂ was significantly associated with AR only during 3rd trimester with adjusted OR = 1.40 (95% CI:

1.08–1.82). The association between NO₂ and childhood AR was robust, as the multi-pollutant model by adjustment for other pollutants and multi-window model by further adjustment for exposures in other trimesters both yielded consistent patterns as single-pollutant model, except for variations in the effect estimates.

Table 5 provides effect estimates of childhood AR during entire pregnancy postnatal period, including first-year and thereafter past years of life. We found that postnatal exposure to traffic-related air pollutants NO₂ and PM₁₀ were both significantly associated with AR, but only significant during the first-year with adjusted OR = 1.36 (1.03–1.78) and 1.54 (1.07–2.21) respectively. All the air pollutants were not associated with AR during the past years of life. Multi-pollutant model obtained similar results as single-pollutant model.

Given the significant differences in lifetime prevalence of AR by child's sex, age, parental atopy, and window condensation (Table 1), we examined whether associations for the traffic-related air pollutant, PM₁₀ and NO₂, were differed in these susceptible children by stratified analysis. Table 6 showed that a consistent pattern that childhood AR was significantly associated with NO₂ during 3rd trimester and first-year and PM₁₀ during first-year in the susceptible children who are male, young (aged 3–4 years old), with genetic predisposition defined by parental atopy, and living in damp houses indicated by window condensation.

4. Discussion

In this population-based prospective cohort study, we found that AR in preschool children was significantly associated with both pre- and post-natal exposure to traffic-related air pollution (TRAP), which is consistent with the recent studies [10–12]. On the other hand, we newly found that the association was only significant during the third trimester of pregnancy and the first-year of life, and the association was robust after adjusting for potential confounding covariates, other air pollutants, and other exposure windows, which indicated that early life TRAP exposure during pregnancy and the first year of life may cause childhood AR. Sensitivity analysis further indicated that stronger association was observed in susceptible children who are male, young (aged 3–4

Table 4

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

Single-pollutant model			Multi-pollutant model ^b				Multi-pollutant and window model ^c
Crude	Adjusted ^a	+ PM ₁₀	+ SO ₂	+ NO ₂	+ PM ₁₀ + SO ₂ + NO ₂		
1st trimester							
PM ₁₀	1.09 (0.91, 1.30)	0.84 (0.64, 1.09)	—	0.81 (0.62, 1.07)	0.80 (0.61, 1.06)	0.80 (0.61, 1.06)	0.78 (0.59, 1.03)
SO ₂	1.10 (0.94, 1.30)	1.04 (0.86, 1.27)	1.08 (0.88, 1.33)	—	0.97 (0.70, 1.34)	0.98 (0.71, 1.36)	0.98 (0.71, 1.36)
NO ₂	1.01 (0.81, 1.26)	1.11 (0.82, 1.49)	1.19 (0.87, 1.61)	1.15 (0.71, 1.87)	—	1.21 (0.75, 1.97)	1.10 (0.65, 1.86)
2nd trimester							
PM ₁₀	1.15 (0.97, 1.36)	1.05 (0.85, 1.29)	—	1.01 (0.81, 1.26)	0.98 (0.78, 1.22)	0.98 (0.78, 1.22)	0.94 (0.75, 1.19)
SO ₂	1.16 (1.01, 1.32)*	1.10 (0.92, 1.30)	1.09 (0.91, 1.31)	—	0.98 (0.75, 1.26)	0.98 (0.76, 1.27)	0.98 (0.74, 1.28)
NO ₂	1.10 (0.90, 1.35)	1.25 (0.95, 1.64)	1.26 (0.94, 1.70)	1.28 (0.85, 1.93)	—	1.29 (0.85, 1.97)	1.04 (0.62, 1.72)
3rd trimester							
PM ₁₀	1.13 (0.97, 1.31)	1.08 (0.86, 1.34)	—	1.05 (0.83, 1.33)	0.95 (0.75, 1.21)	0.94 (0.74, 1.20)	0.96 (0.75, 1.23)
SO ₂	1.14 (0.98, 1.33)	1.09 (0.89, 1.34)	1.08 (0.87, 1.34)	—	0.75 (0.54, 1.05)	0.75 (0.53, 1.05)	0.74 (0.52, 1.06)
NO ₂	1.18 (0.96, 1.46)	1.40 (1.08, 1.82)*	1.44 (1.08, 1.91)*	1.86 (1.22, 2.83)**	—	1.92 (1.24, 2.97)**	1.87 (1.14, 3.07)*
Entire pregnancy							
PM ₁₀	1.16 (0.99, 1.36)	0.98 (0.75, 1.28)	—	0.99 (0.77, 1.29)	0.98 (0.76, 1.27)	0.96 (0.74, 1.24)	—
SO ₂	1.27 (1.04, 1.55)*	1.16 (0.90, 1.49)	1.16 (0.90, 1.49)	—	0.76 (0.49, 1.18)	0.75 (0.48, 1.17)	—
NO ₂	1.15 (0.92, 1.44)	1.41 (1.05, 1.88)*	1.41 (1.05, 1.88)*	1.82 (1.10, 3.01)*	—	1.84 (1.11, 3.05)*	—

OR (95%CI) was estimated for an IQR increase in PM₁₀, SO₂, and NO₂.

* p<0.05.

** p<0.01.

^a Single-pollutant model: adjustment for all the potential covariates in Table 1 including personal factors (child's sex, age, birth season, breast-feeding, and parental atopy, SES) and indoor factors (ETS, new furniture, visible mold/damp stains, window condensation, cockroach and household dogs).

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

^c Multi-pollutant and window model: further adjustment for the effects of the air pollutant in other windows (trimesters) on the base of multi-pollutant model.

Table 5

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

	Single-pollutant model		Multi-pollutant model ^b			
	Crude	Adjusted ^a	+ PM ₁₀	+ SO ₂	+ NO ₂	+ PM ₁₀ + SO ₂ + NO ₂
First year						
PM ₁₀	1.39 (1.14, 1.71)***	1.54 (1.07, 2.21)*	—	1.57 (1.10, 2.25)*	1.53 (1.07, 2.18)*	1.51 (1.05, 2.16)*
SO ₂	1.29 (1.09, 1.53)**	1.16 (0.88, 1.53)	1.22 (0.91, 1.62)	—	0.82 (0.54, 1.26)	0.89 (0.57, 1.38)
NO ₂	1.30 (1.02, 1.65)*	1.36 (1.03, 1.78)*	1.37 (1.04, 1.80)*	1.56 (1.03, 2.37)*	—	1.49 (0.98, 2.26)
After first year (from the second to the last year)						
PM ₁₀	1.35 (1.10, 1.66)**	1.27 (0.92, 1.75)	—	1.18 (0.67, 2.05)	1.08 (0.72, 1.62)	1.18 (0.67, 2.09)
SO ₂	1.30 (1.07, 1.58)**	1.20 (0.93, 1.55)	1.08 (0.69, 1.69)	—	0.98 (0.66, 1.46)	0.88 (0.50, 1.53)
NO ₂	1.40 (1.03, 1.90)*	1.39 (0.99, 1.96)	1.32 (0.85, 2.05)	1.42 (0.83, 2.42)	—	1.42 (0.83, 2.42)
Postnatal (from the first to the last year)						
PM ₁₀	1.46 (1.17, 1.82)***	1.58 (1.07, 2.33)*	—	1.78 (1.00, 3.16)*	1.42 (0.90, 2.25)	1.84 (1.04, 3.28)*
SO ₂	1.32 (1.09, 1.60)**	1.21 (0.93, 1.59)	0.90 (0.60, 1.34)	—	0.94 (0.60, 1.45)	0.66 (0.38, 1.14)
NO ₂	1.42 (1.05, 1.91)*	1.41 (1.01, 1.97)*	1.18 (0.79, 1.76)	1.50 (0.86, 2.62)	—	1.57 (0.91, 2.73)

OR (95%CI) was estimated for an IQR increase in PM₁₀, SO₂, and NO₂.

* p<0.05.

** p<0.01.

*** p<0.001.

^a Single-pollutant model: adjustment for all the potential covariates in Table 1 including personal factors (child's sex, age, birth season, breast-feeding, and parental atopy, SES) and indoor factors (ETS, new furniture, visible mold/damp stains, window condensation, cockroach and household dogs).^b Multi-pollutant model: further adjustment for the effects of the other air pollutants in the same time window on the base of single-pollutant model.**Table 6**

Adjusted odds ratio (95%CI) of allergic rhinitis for exposure to traffic-related air pollutants stratified by significant covariates (n = 2598).

	Child's sex ^a		Child's age ^a		Parental atopy ^a		Window condensation ^a	
	Boys	Girls	3–4 years old	5–6 years old	Yes	No	Yes	No
PM₁₀								
1st trimester	0.72 (0.52, 1.01)	1.10 (0.71, 1.70)	0.78 (0.50, 1.21)	1.11 (0.79, 1.57)	0.85 (0.54, 1.33)	0.85 (0.61, 1.18)	0.77 (0.55, 1.07)	0.98 (0.61, 1.55)
2nd trimester	1.11 (0.85, 1.45)	0.97 (0.69, 1.37)	1.06 (0.75, 1.50)	1.14 (0.87, 1.50)	0.85 (0.58, 1.25)	1.12 (0.87, 1.44)	0.93 (0.72, 1.20)	1.29 (0.90, 1.86)
3rd trimester	1.25 (0.94, 1.67)	0.83 (0.58, 1.20)	1.42 (0.94, 2.14)	1.18 (0.90, 1.53)	1.04 (0.71, 1.51)	1.07 (0.81, 1.41)	0.98 (0.74, 1.29)	1.30 (0.89, 1.91)
Entire pregnancy	1.09 (0.77, 1.55)	0.86 (0.56, 1.30)	1.19 (0.75, 1.88)	1.24 (0.91, 1.68)	0.82 (0.53, 1.28)	1.06 (0.76, 1.47)	0.79 (0.57, 1.10)	1.48 (0.94, 2.35)
First year	1.74 (1.10, 2.75)*	1.25 (0.68, 2.30)	1.94 (1.28, 2.94)**	1.48 (1.00, 2.19)*	1.88 (1.00, 3.53)*	1.30 (0.82, 2.05)	1.93 (1.23, 3.02)**	0.94 (0.50, 1.78)
After first year	1.56 (1.02, 2.39)*	0.98 (0.60, 1.61)	1.79 (1.21, 2.66)**	1.19 (0.69, 2.03)	1.37 (0.79, 2.38)	1.17 (0.78, 1.76)	1.36 (0.91, 2.02)	1.17 (0.66, 2.07)
Postnatal	2.06 (1.23, 3.44)**	1.14 (0.62, 2.07)	1.92 (1.30, 2.85)***	1.55 (0.70, 3.43)	1.87 (0.98, 3.57)	1.34 (0.82, 2.18)	1.91 (1.19, 3.08)**	1.12 (0.57, 2.20)
NO₂								
1st trimester	1.05 (0.71, 1.53)	1.24 (0.77, 2.00)	1.13 (0.79, 1.64)	0.91 (0.55, 1.49)	1.20 (0.75, 1.94)	1.06 (0.72, 1.55)	1.33 (0.93, 1.90)	0.76 (0.45, 1.30)
2nd trimester	1.37 (0.96, 1.95)	1.15 (0.74, 1.79)	1.39 (0.98, 1.98)	0.81 (0.51, 1.30)	1.36 (0.86, 2.15)	1.15 (0.81, 1.63)	1.30 (0.93, 1.81)	1.20 (0.73, 1.97)
3rd trimester	1.59 (1.12, 2.25)**	1.22 (0.81, 1.85)	1.49 (1.07, 2.08)*	1.06 (0.67, 1.68)	1.63 (1.05, 2.55)*	1.24 (0.89, 1.73)	1.43 (1.04, 1.96)*	1.41 (0.88, 2.26)
Entire pregnancy	1.55 (1.06, 2.27)*	1.31 (0.82, 2.08)	1.63 (1.11, 2.39)*	0.90 (0.56, 1.44)	1.61 (0.99, 2.62)	1.25 (0.87, 1.82)	1.54 (1.09, 2.20)*	1.20 (0.71, 2.04)
First year	1.43 (1.00, 2.04)*	1.32 (0.86, 2.04)	1.83 (1.26, 2.66)**	0.89 (0.58, 1.37)	1.60 (1.02, 2.52)*	1.22 (0.86, 1.73)	1.52 (1.09, 2.12)*	1.11 (0.67, 1.81)
After first year	1.57 (1.01, 2.45)*	1.24 (0.71, 2.16)	1.87 (1.18, 2.96)**	0.96 (0.57, 1.63)	1.57 (0.89, 2.76)	1.26 (0.81, 1.95)	1.50 (0.99, 2.27)	1.23 (0.66, 2.28)
Postnatal	1.57 (1.02, 2.42)*	1.28 (0.75, 2.20)	1.93 (1.23, 3.04)**	0.97 (0.58, 1.63)	1.62 (0.93, 2.82)	1.26 (0.82, 1.94)	1.55 (1.03, 2.33)*	1.19 (0.65, 2.19)

OR (95%CI) was estimated for an IQR increase in PM₁₀ and NO₂.

* p<0.05.

** p<0.01.

*** p<0.001.

^a Adjustment for all the potential covariates in Table 1 including personal factors (child's sex, age, birth season, breast-feeding, and parental atopy, SES) and indoor factors (ETS, new furniture, visible mold/damp stains, window condensation, cockroach and household dogs) except for the stratified covariate.

years old), with genetic predisposition defined by parental atopy, and living in damp houses with window condensation.

The strength of our study was that we identified the susceptible window of exposure and the key component of air pollution in the development of childhood AR by analyzing its association with different air pollutants during different exposure windows. We mutually adjusted the effects of other air pollutants and other exposure timing windows so as to estimate their independent associations by using multi-pollutant model and multi-pollutant/window model [17].

We found the prevalence of AR in preschool children in Changsha was 7.3% that was similar to several previous studies in China [21,22]. However, a recent cross-sectional survey that the prevalence was high up to 48% in preschool children in Beijing [23]. Our results showed a gender disparity in the associations between childhood AR and air pollution, i.e. higher prevalence and stronger effect in boys than those in girls, which was also consistent with

previous studies [21,22,24,25]. The gender disparity may be linked to the different lung function growth rates and differences in airway size. We also found a higher AR prevalence and stronger effect of air pollution on AR in children living in damp houses with window condensation as in our studies [26,27]. Dampness, especially the index of condensation on windowpane in winter, was a strong and significant risk factor for asthma and allergy. In addition, we found a higher AR prevalence and stronger effect of air pollution on AR in children whose parents with a history of atopic diseases. 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. Although many epidemiological studies addressed the interaction between postnatal exposure to air pollution and hereditary allergic predisposition on childhood asthma and allergy [24,28], the effect modification of environmental exposure by genetic constitution is believed to occur predominantly prenatally and shortly after birth [29]. We are the first one to investigate the

interaction during pregnancy and the early postnatal life.

It has been shown that children are particularly susceptible to the adverse effects of air pollution. Children may be a particularly vulnerable population because they spend more time outdoors, are generally more physically active, and have higher ventilation rates than adults. Furthermore, children's lungs are growing and their immune systems are still immature [30]. In addition, children have narrower airways, thus irritation caused by air pollution that would produce only a slight response in an adult can result in potentially significant obstruction in the airways of a young child. Early life exposure during pregnancy or infancy to ambient air pollution seems to be particularly important for respiratory effects in later life [16,17,31]. However, very few studies investigated the role of early life exposure to air pollution in the later development of AR in children. Our findings in present work provide further support that early life exposure to ambient air pollution has also impact on AR in preschool children.

We observed significant association between childhood rhinitis and early life exposure to traffic-related air pollution during pregnancy and the first year of life. Although some recent short-term epidemiological studies have demonstrated a strong association between air pollution and outpatient AR visits [6,7], the evidences linking long-term exposure to air pollution with AR were scarce and equivocal [9,10]. Few cross-sectional studies reported that current exposure to air pollution is associated with allergic rhinitis in preschool- and school-age children [28,32]. Several recent birth cohort studies also found a positive or marginally significant association between AR in young children and postnatal exposure to traffic-related air pollution during the first few years of life [4,11,12,33]. We further found that exposure to traffic-related air pollution (NO₂) in the third trimester of pregnancy was significant for the risk of childhood AR. The trimester-specific risk of exposure to air pollution for childhood AR has never been investigated. However, our work can be supported by some recent studies examining the risk of air pollution exposure in specific trimester of pregnancy for childhood respiratory infections or diseases [34–37]. Our recent work also demonstrated that maternal exposures to traffic-related air pollutant during the first, second, and third trimesters of pregnancy were respectively associated with increased risk of childhood eczema, asthma, and allergic rhinitis [17].

Our observed association between childhood AR and early life exposure to traffic-related air pollutant is biologically plausible. The period of in utero and the first year of life is critical in the development of the immune and respiratory systems [30], and potential harmful effects of toxic pollutants during this period might result in long-lasting impaired capacity to fight infections and increased risk of allergic manifestations later in life. Atopic diseases were characterised by dominant T helper 2 (Th2) mechanisms. 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 shortly after birth [38]. On the other hand, AR is an inflammation of the nasal airways. The traffic-related air pollutant NO₂ has a direct pro-inflammatory effect on the sensitive airways of children and PM₁₀ can produce a large quantity of reactive oxygen species which trigger the inflammatory processes in the respiratory tract [39]. Therefore, early life exposure to the traffic-related air pollutants could cause childhood allergic rhinitis. Recently, epigenetic regulation provides another mechanistic explanation for linking early-life exposure with subsequent development of allergic rhinitis [40].

There are several limitations of this study that should be acknowledged. Firstly, the potential limitation of our study is the recall bias. The questionnaires were completed by children's parents retrospectively. Generally, parents with family allergic history

or whose child had been doctor-diagnosed with AR are likely to remember the child's symptoms of allergic rhinitis and also the related indoor environmental factors such as mold/dampness, new furniture. Secondly, a potential misclassification of exposure is that we assumed the same exposure to air pollution between kindergarten and home by considering the situation in China that parents usually enrolled their children in the kindergarten nearest to their home. Thirdly, 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 lead to bias of exposure because the number of monitoring stations was sparse and the land use conditions were ignored. Finally, 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 [20]. However, it is important to further investigate the roles of other pollutants, particularly PM_{2.5}, which was a better proxy for traffic air pollution.

5. Conclusions

Our prospective cohort study found that AR in preschool children was associated with both pre- and post-natal exposure to traffic-related air pollution (TRAP), but only significant during the third trimester of pregnancy and the first-year of life, which indicated that early life TRAP exposure during pregnancy and the first year of life may lead to the later development of allergic rhinitis in preschool children. The result indicates that public education programs or policies to reduce exposure to traffic-related air pollution for pregnant women and/or early infants may reduce the risk of childhood allergic rhinitis, especially for susceptible children who are male, young, with genetic predisposition, and living in damp house. Our findings could be also used to develop more effective measures to prevent children from allergic rhinitis, such as improving automobile emission standards, setting strict regulation or limitation of traffic density around kindergartens, planning kindergartens far away from the main roads. However, further investigations to identify the relevant mechanism(s) underlying the association between early life exposure to air pollution and childhood allergic rhinitis are also required.

Conflict of interests

None.

Acknowledgements

The work was supported by the National Natural Science Foundation of China (No. 51576214). We are particularly indebted to the children, their parents and the kindergartens for their time and enthusiastic participation.

References

- [1] C.L. Ng, D. Wang, Latest developments in allergic rhinitis in allergy for clinicians and researchers, *Allergy* 70 (2015) 1521–1530.
- [2] M.I. Asher, S. Montefort, B. Björkstén, et al., Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys, *Lancet* 368 (2006) 733–743.
- [3] J. Bousquet, P.V. Cauwenberge, N. Khaltaev, J. Bousquet, P.V. Cauwenberge, N. Khaltaev, Allergic rhinitis and its impact on asthma, *J. Allergy Clin. Immunol.* 108 (2001) S147–S334.
- [4] M. Brauer, G. Hoek, H.A. Smit, et al., Air pollution and development of asthma, allergy and infections in a birth cohort, *Eur. Respir. J.* 29 (2007) 879–888.
- [5] U. Gehring, A.H. Wijga, M. Brauer, et al., Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life, *Am. J.*

- Respir. Crit. Care Med. 181 (2010) 596–603.
- [6] P. Villeneuve, M.S. Doiron, D. Stieb, R. Dales, R. Burnett, R. Dugandzic, Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? *Allergy* 61 (2006) 750–758.
 - [7] F. Zhang, W. Wang, J. Lv, T. Krafft, J. Xu, Time-series studies on air pollution and daily outpatient visits for allergic rhinitis in Beijing, China, *Sci. Total Environ.* 409 (2011) 2486–2492.
 - [8] C.-C. Chen, H.-F. Chiu, C.-Y. Yang, Air pollution exposure and daily clinical visits for allergic rhinitis in a subtropical city: Taipei, Taiwan, *J. Toxicol. Environ. Health A* 79 (2016) 494–501.
 - [9] J. Heinrich, H.-E. Wichmann, Traffic related pollutants in Europe and their effect on allergic disease, *Curr. Opin. Allergy Clin. Immunol.* 4 (2004) 341–348.
 - [10] G. Bowatte, C. Lodge, A.J. Lowe, et al., The influence of childhood traffic related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies, *Allergy* 70 (2015) 245–256.
 - [11] W. Liu, C. Huang, Y. Hu, Q. Fu, Z. Zou, C. Sun, et al., Associations of gestational and early life exposures to ambient air pollution with childhood respiratory diseases in Shanghai, China: a retrospective cohort study, *Environ. Int.* 92–93 (2016) 284–293.
 - [12] Q. Deng, C. Lu, C. Ou, L. Chen, H. Yuan, Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children, *Chemosphere* 152 (2016) 459–467.
 - [13] E. Fuertes, M. Standl, J. Cyrys, D. Berdel, A. von Berg, C.P. Bauer, et al., A longitudinal analysis of associations between traffic-related air pollution with asthma, allergies and sensitization in the GINIplus and LISAplus birth cohorts, *PeerJ* 1 (2013) e193.
 - [14] P.D. Gluckman, M.A. Hanson, C. Cooper, K.L. Thornburg, Effect of in utero and early-life conditions on adult health and disease, *N. Engl. J. Med.* 359 (2008) 61–73.
 - [15] I. Aguilera, M. Pedersen, R. García Esteban, et al., Early-life exposure to outdoor air pollution and respiratory health, ear infections, and eczema in infants from the INMA study, *Environ. Health Perspect.* 121 (2013) 387–392.
 - [16] Q. Deng, C. Lu, D. Norbäck, et al., Early life exposure to ambient air pollution and childhood asthma in China, *Environ. Res.* 143 (2015) 83–92.
 - [17] Q. Deng, C. Lu, Y. Li, et al., Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema, *Environ. Res.* 150 (2016) 119–127.
 - [18] F. Rancière, N. Bougas, M. Viola, I. Momas, Early exposure to traffic-related air pollution, respiratory symptoms at 4 years of age, and potential effect modification by parental allergy, stressful family events, and gender: a prospective follow-up study of the PARIS Birth Cohort, *Environ. Health Perspect.* (2016), <http://dx.doi.org/10.1289/EHP239>.
 - [19] C.-G. Bornehag, J. Sundell, C.J. Weschler, et al., The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study, *Environ. Health Perspect.* 112 (2004) 1393–1397.
 - [20] H. Kan, R. Chen, S. Tong, Ambient air pollution, climate change, and population health in China, *Environ. Int.* 42 (2012) 10–19.
 - [21] Y. Li, Y. Jiang, S. Li, X. Shen, J. Liu, F. Jiang, Pre- and postnatal risk factors in relation to allergic rhinitis in school-aged children in China, *PloS One* 10 (2015) e0114022.
 - [22] W.J. Kong, J.J. Chen, Z.Y. Zheng, Q.M. Shi, Y. Zhou, Prevalence of allergic rhinitis in 3–6-year-old children in Wuhan of China, *Clin. Exp. Allergy* 39 (2009) 869–874.
 - [23] Y.M. Zhang, J. Zhang, S.L. Liu, et al., Prevalence and associated risk factors of allergic rhinitis in preschool children in Beijing, *Laryngoscope* 123 (2013) 28–35.
 - [24] D.G. Peroni, G.L. Piacentini, L. Alfonsi, et al., Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors, *Clin. Exp. Allergy* 33 (2003) 1349–1354.
 - [25] H.Y. Chung, C.J. Hsieh, C.C. Tseng, L.M. Yiin, Association between the first occurrence of allergic rhinitis in preschool children and air pollution in Taiwan, *Int. J. Environ. Res. Public Health* 13 (2016) 268.
 - [26] J. Choi, Y. Sun, Y. Choi, et al., Associations between building characteristics and children's allergic symptoms – a cross-sectional study on child's health and home in Seoul, South Korea, *Build. Environ.* 75 (2014) 176–181.
 - [27] Y. Sun, Y. Zhang, J. Sundell, Z. Fan, L. Bao, Dampness at dorm and its associations with allergy and airways infection among college students in China: a cross-sectional study, *Indoor Air* 19 (2009) 174–182.
 - [28] Y.L. Lee, C.K. Shaw, H.J. Su, et al., Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan, *Eur. Respir. J.* 21 (2003) 964–970.
 - [29] R.L. Miller, Ho S-m, Environmental epigenetics and asthma: current concepts and call for studies, *Am. J. Respir. Crit. Care Med.* 177 (2008) 567–573.
 - [30] P.G. Holt, C.A. Jones, The development of the immune system during pregnancy and early life, *Allergy* 55 (2000) 688–697.
 - [31] T. Turnovska, B. Marinov, The influence of air pollution during intrauterine development and early childhood on respiratory functions at later age, *Int. J. Hyg. Environ. Health* 212 (2009) 519–532.
 - [32] M.-M. Liu, D. Wang, Y. Zhao, et al., Effects of outdoor and indoor air pollution on respiratory health of Chinese children from 50 kindergartens, *J. Epidemiol.* 23 (2013) 280–287.
 - [33] V. Morgenstern, A. Zutavern, J. Cyrys, et al., Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children, *Am. J. Respir. Crit. Care Med.* 177 (2008) 1331–1337.
 - [34] I. Aguilera, M. Pedersen, R. García-Esteban, F. Ballester, M. Basterrechea, A. Esplugues, et al., Early-life exposure to outdoor air pollution and respiratory health, ear infections, and eczema in infants from the inma study, *Environ. Health Perspect.* 121 (2013) 387–392.
 - [35] H.-H.L. Hsu, Y.-H.M. Chiu, B.A. Coull, I. Kloog, J. Schwartz, A. Lee, et al., Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences, *Am. J. Respir. Crit. Care Med.* 192 (2015) 1052–1059.
 - [36] C. Huang, H. Wen, P. Chen, T. Chiang, S. Lin, Y. Guo, Prenatal air pollutant exposure and occurrence of atopic dermatitis, *Br. J. Dermatol.* 173 (2015) 981–988.
 - [37] E. Morales, R. Garciaesteban, O.A.D.L. Cruz, M. Basterrechea, A. Lertxundi, C. Zabaleta, et al., Intrauterine and early postnatal exposure to outdoor air pollution and lung function at preschool age, *Thorax* 70 (2015) 64–73.
 - [38] R.J. Wright, K.J. Brunst, Programming of respiratory health in childhood: influence of outdoor air pollution, *Curr. Opin. Pediatr.* 25 (2013) 232–239.
 - [39] D. Peden, Mechanisms of pollution-induced airway disease: in vivo studies, *Allergy* 52 (1997) 37–44.
 - [40] M.M. Patel, R.L. Miller, Air pollution and childhood asthma: recent advances and future directions, *Curr. Opin. Pediatr.* 21 (2009) 235–242.