



Prenatal and postnatal exposures to ambient air pollutants associated with allergies and airway diseases in childhood: A retrospective observational study

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ABSTRACT

It's inconsistent about associations of early exposures to outdoor air pollutants with allergies and airway diseases in childhood. Here, we investigated associations of prenatal and postnatal exposures to outdoor nitrogen dioxide (NO₂), sulphur dioxide (SO₂), and PM₁₀ (particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$) with asthma, wheeze, hay fever, rhinitis, pneumonia, and eczema in childhood. We surveyed 3,177 preschoolers who never change residences since birth in Shanghai, China. Parents reported information regarding children's health status. Daily-averaged concentrations of these pollutants in the children's gestation and in the first year of lifetime for district where children lived were collected by Shanghai Environmental Monitoring Center. After adjusting for covariates, exposures to higher level of NO₂ during different trimesters of gestation and of the first year of lifetime had significant associations with the increased odds of asthma, hay fever, rhinitis, pneumonia, and eczema in childhood. Associations of NO₂ exposures in the early trimesters of gestation and of the first year of lifetime with pneumonia were stronger than in the later trimesters, whereas associations of NO₂ exposures in the early trimesters with hay fever and eczema were weaker than in the later trimesters. Our results indicated that prenatal and postnatal exposures to outdoor NO₂ could be risk factors for allergies and airway diseases in childhood. Both dose and duration were related with the influence degree of early NO₂ exposure on childhood allergies and airway diseases.

1. Introduction

Childhood prevalences of asthma and allergies have sharply increased in the recent 30 years in China (Zhang et al., 2013; Huang et al., 2015). Several studies have evaluated associations of outdoor air pollutants and these diseases, but their findings were not consistent (Brauer et al. 2016; Cai et al., 2017a,b; Cohen et al. 2017; Guarnieri and Balmes, 2014; Laborde et al., 2015; Liu et al., 2014, 2016a, 2016b; Lu et al., 2013; Kan et al., 2012; Kan and Shi 2019; Norback et al. 2019b).

Several systematic reviews concluded that exposure to high levels of outdoor NO₂, SO₂, and PM₁₀ could exacerbate symptoms or induce onset of asthma in childhood (Brunekreef and Holgate, 2002; Gasana et al., 2012; Guarnieri et al., 2014; Kan and Shi 2019; Kim et al., 2013; Bowatte et al., 2015; Liu et al. 2016; Norback et al. 2019b; Weinmayr

et al., 2010; D'Amato et al., 2002). Herein, Bowatte et al. (2015) searched the related peer-reviewed articles during 1960–2014 and summarized associations of early childhood exposures to traffic-related air pollution with allergic or respiratory diseases/symptoms at later ages from the birth-cohort studies. They reported that exposure to these pollutants in the early lifetime was associated with induce of asthma among < 12-year-olds children, and found some significant associations between these pollutants and allergic rhinitis during lifetime (Bowatte et al., 2015). However, studies from USA (Parker et al., 2009) and Norway (Ofstedal et al., 2009) suggested that exposure to NO₂ in long-term had no significant association with new-onset asthma. In a global-scale study, Anderson et al. (2012) used satellite-based estimates and found that outdoor air pollutants did not associated with childhood prevalence of asthma at the community level. In Europe, a multi-center

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study also did not find significant association of outdoor air pollutants and prevalence of asthma in childhood (Mölter et al., 2015).

Besides, studies found that associations of outdoor air pollutants with asthma and allergies in childhood had to do with not only the exposure dose but also the exposure period (Kim et al., 2013; Guarnieri et al., 2014; Bowatte et al., 2015). Some studies reported that exposure to outdoor air pollutants in the early lifetime were associated with respiratory tract infections among infants (Aguilera et al., 2013) or asthma in childhood (Clark et al., 2010; Deng et al., 2015, 2016). However, few studies investigated and compared associations of prenatal (during gestation) and postnatal (during the first year) exposures to outdoor air pollutants in various trimesters with asthma and allergies in childhood (Norback et al., 2018, 2019a).

Here we collected data for childhood health from phase one of the Shanghai CCHH (China, Children, Homes, Health) study (Huang et al., 2015; Liu et al., 2016a,b). Shanghai Environmental Monitoring Center provided daily-averaged SO_2 , NO_2 , and PM_{10} concentrations. We investigated associations between period-averaged concentrations of these pollutants in different periods of prenatal and postnatal exposures with prevalences of lifetime-ever asthma, wheeze, hay fever, rhinitis, pneumonia, and eczema in preschoolers. We hypothesized that the studied diseases were associated with exposures to these pollutants in different periods.

2. Methods

2.1. Study subjects

From April 2011 to April 2012, we conducted a cross-sectional study and multi-stage hierarchically sampled preschool children from five districts of Shanghai city. At teacher-parent meeting, a questionnaire was distributed to the children's parents or was sent by post to the children's teachers, who distributed and collected questionnaires from parents. Questions for health information were translated from the ISAAC (International Study of Asthma and Allergies in Childhood) (Asher et al., 1995). When answer was "Yes" to the question, we defined children as having the disease. Besides, questions about household environment and life styles were modified and translated from the DBH (Dampness in Building and Health) study (Bornehag et al., 2004). A total of 2,426 and 3,177 four to six years-old children was selected to be analyzed the target associations. These children were born during 2006–2008 in Shanghai, were reported as term births (gestation duration > 8.5 months (≥ 37 weeks)), had detailed birth date, and did not change residence since pregnancy. These children were distributed in Jing-An district, Bao-Shan district, and Feng-Xian district of Shanghai (Liu et al., 2016a,b). Our questionnaire and proposal were approved by the ethical committee for the School of Public Health in Fudan University. More information for this study and questionnaire was provided in our previous article (Huang et al., 2015).

2.2. Ambient air pollutants

The Shanghai Environmental Monitoring Center provided data for 24 h-averaged concentrations of outdoor SO_2 , NO_2 , and PM_{10} , as well as 24 h-averaged values of outdoor air temperature, for each districts of Shanghai city during 2006–2012. Daily measurements of these pollutants were made in each district by local monitoring station. The exposure periods were classified by trimester during gestation and during first year of lifetime. Period-averaged concentrations of these pollutants in various periods in the residence-located district were calculated as the exposure levels for these pollutants. For gestation, since the gestation duration was impossibly estimated in the exact day resolution in the present study, we assumed that the gestation durations for all studied children were 9.0 months. If a boy was born in January 1, 2007 and his residence was in Bao-Shan district, we considered the mean concentration of SO_2 from October 1, 2006 to December 31, 2006 for

Bao-Shan district as his SO_2 exposure level in the third trimester of gestation, and so on. And we considered the mean concentration of SO_2 for Bao-Shan district from January 1, 2007 to March 31, 2008 as his SO_2 exposure level in the first trimester of lifetime, and so on.

2.3. Health outcomes

We studied six health outcomes, including asthma, wheeze, hay fever, rhinitis, pneumonia, and eczema. These outcomes appeared during the child's lifetime ever from birth to the survey day. Herein asthma, hay fever, and pneumonia were diagnosed by a doctor and reported by parents. Questions for these diseases were derived from the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 1995). The supplemental Table S1 provided the detailed questions for these diseases. A pilot study among preschoolers in Chongqing, China had confirmed the questionnaire validity (Zhang et al., 2013). Children were defined as having the disease when answer was responded as "yes" in the question for the disease.

2.4. Statistical analyses

According to prior literature (Kanchongkittiphon et al., 2015; Hu et al., 2014; Wang et al., 2015; Cai et al., 2017a,b, 2019, 2020; Norback et al., 2018, 2019a) and our valid data, we considered these factors as covariates: age, sex, ownership of residence, duration of breastfeeding, family history of atopy, distance of residence close to main traffic road, home dampness-related exposures, early residential renovation, environmental tobacco smoke (ETS), usage of heating during winter, birth month, and ambient air temperature (mean air temperature during the same period as ambient air pollutants). Here, family history of atopy was defined as at least one family members having had at least one of asthma, eczema, and allergic nose or eye problems. ETS was defined as at least one family members smoking in the current residence. Ownership of residence was considered as a proxy of socioeconomic status. Home dampness-related exposures was defined as that at least one indicator was found in the residence: visible mold spots, visible damp stains, water damage, damp clothing/bedding, moldy odor, and condensation on windows during winter.

The statistical analyses were performed by SPSS 19.0 (SPSS Ltd., USA) and STATA 11.0 (STATA Corp., Texas, USA). Logistic regression analysis was applied to evaluate associations of the increased odds of diseases with increments in the interquartile range (IQR) in each air pollutant. We used two-level (district-child) mixed-effects logistic regression model to analyze the target associations. Two regression models were used to adjust these associations. First, the crude associations were adjusted for all above-mentioned covariates. Second, since correlations between pairs of the studied pollutants in different periods were not high (all correlation coefficients < 0.7) in the Pearson's correlation analyses (Table S2 and Table S3), these associations were further adjusted with mutually adjusting for other two air pollutants in the same periods. We indicated these associations using adjusted odds ratios (AOR) with 95% confidence intervals (CIs), with significance as p -value < 0.05.

3. Results

Among the 3,177 selected children (Table 1), the average age was 5.1-year-olds. Most children's residences were located in Jing-An district, Bao-Shan district, and Feng-Xian district. Here 57.7% children were breastfed ≤ 6 months and 57.8% exposed to ETS. More than 72% had home dampness-related exposures; 42.6% children's residences closed to a high traffic road within 200 m; 32.3% of families had early renovation. The prevalence of asthma was 8.4%, wheeze 28.1%, hay fever 12.0%, rhinitis 51.3%, pneumonia 33.3%, and eczema 20.4%, respectively.

With respect to outdoor air pollutants (Table 2), the averaged

Table 1
Demographic information (N = 3177).

Items	Mean $\pm$ SD or n (%)
Current age (year-olds)	5.1 $\pm$ 0.8
Sex	
males	1615 (51.0)
females	1551 (49.0)
Residence-located district	
Jing-An	802 (25.2)
Bao-Shan	939 (29.6)
Feng-Xian	1093 (34.4)
Others	343 (10.8)
Ownership of residence	
Owner	2085 (66.7)
Renter	1042 (33.3)
Family history of atopy	
Yes	670 (21.6)
No	2439 (78.4)
Duration of breastfeeding (months)	
≤ 6	1805 (57.7)
> 6	1321 (42.3)
Home damp exposures	
Yes	2285 (72.2)
No	882 (27.8)
Environmental tobacco smoke (ETS)	
Yes	1799 (57.8)
No	1316 (42.4)
Distance of residence close to main traffic road	
< 200 m	1224 (42.6)
≥ 200 m	1650 (51.9)
Use of heating during winter	
Yes	2712 (85.8)
No	447 (14.2)
Renovated the residence during early lifetime	
Yes	1025 (32.3)
No	2152 (67.7)

SD, standard deviation.

concentrations in different trimesters of gestational period had small differences and were about 46 $\mu\text{g}/\text{m}^3$ for SO_2 , 56 $\mu\text{g}/\text{m}^3$ for NO_2 , and 83 $\mu\text{g}/\text{m}^3$ for PM_{10} , respectively. The interquartile range (IQR) for concentrations during different durations of gestational period also had small differences and were about 13 $\mu\text{g}/\text{m}^3$ for SO_2 and 22 $\mu\text{g}/\text{m}^3$ for NO_2 , respectively; the IQR for concentration of PM_{10} was about 20 $\mu\text{g}/\text{m}^3$ in different trimesters of gestational period. The averaged concentrations in different trimesters of the first year of lifetime also had small differences and were about 45 $\mu\text{g}/\text{m}^3$, 55 $\mu\text{g}/\text{m}^3$, and 83 $\mu\text{g}/\text{m}^3$ of SO_2 , NO_2 , and PM_{10} , respectively (Table S2). The interquartile range (IQR) for concentrations during different durations of the first year of lifetime were about 12 $\mu\text{g}/\text{m}^3$ and 22 $\mu\text{g}/\text{m}^3$ of SO_2 and NO_2 , respectively; the IQR for concentration of PM_{10} was about 15 $\mu\text{g}/\text{m}^3$ in different trimesters of the first year of lifetime.

Fig. 1 shows the adjusted associations of three pollutants during different durations of gestational period with the studied diseases in single-pollutant model. Most associations of the studied diseases with SO_2 and PM_{10} were not statistically significant. Most associations of NO_2 with hay fever, pneumonia, and eczema were significant and adjusted ORs for these associations had small differences within different trimesters. Herein, with respect to NO_2 exposure in different trimesters of gestational period, the strongest associations were found for hay fever and the adjusted odds ratios (95%CI) for the first (IQR: 21.4 $\mu\text{g}/\text{m}^3$), second (22.4 $\mu\text{g}/\text{m}^3$), and third (21.2 $\mu\text{g}/\text{m}^3$) trimester, and the entire gestational period () were 1.59 (1.16–2.18), 1.59 (1.14–2.21), 1.65 (1.21–2.25), and 1.68 (1.19–2.37) respectively.

For different durations of the first year of lifetime (Fig. 2), most associations of NO_2 with asthma, hay fever, rhinitis, pneumonia, and

Table 2
Mean concentration ($\mu\text{g}/\text{m}^3$) of ambient air pollutants in different durations.

Pollutants	Mean ± SD	Min	Percentile			Max	IQR
			25%	50%	75%		
1. Gestational period (N = 2426)							
(1) The first trimester							
SO ₂	45.7 ± 7.6	22.6	39.4	44.2	51.8	71.1	12.4
NO ₂	56.0 ± 10.8	33.6	43.4	59.8	64.8	74.1	21.4
PM ₁₀	83.1 ± 13.8	51.9	72.4	82.2	94.7	118.9	22.3
(2) The second trimester							
SO ₂	45.8 ± 8.0	26.0	38.9	44.3	51.9	84.5	13.0
NO ₂	56.2 ± 11.3	33.8	43.3	60.3	65.7	74.1	22.4
PM ₁₀	82.5 ± 13.6	54.5	72.0	81.7	92.6	121.6	20.6
(3) The third trimester							
SO ₂	45.8 ± 7.8	23.6	39.3	44.3	52.0	83.7	12.7
NO ₂	55.9 ± 11.1	33.6	43.5	60.1	64.7	77.0	21.2
PM ₁₀	83.2 ± 12.8	48.8	73.3	82.4	92.3	130.1	19.0
(4) Entire pregnancy							
SO ₂	45.7 ± 7.1	28.0	39.8	44.2	53.4	60.3	13.6
NO ₂	56.0 ± 10.5	36.0	42.4	62.2	64.4	67.5	22.0
PM ₁₀	83.0 ± 7.7	67.1	76.7	83.0	87.7	104.6	11.0
2. The first year of life after birth (N = 3177)							
(1) The first trimester							
SO ₂	44.8 ± 7.5	25.6	39.2	43.2	50.2	81.4	11.0
NO ₂	55.6 ± 11.2	32.1	43.0	59.4	65.1	74.1	22.1
PM ₁₀	82.3 ± 12.5	51.4	72.6	81.4	91.1	120.8	18.5
(2) The second trimester							
SO ₂	44.8 ± 7.5	22.2	38.8	43.0	50.5	81.9	11.7
NO ₂	55.7 ± 11.2	33.3	42.9	59.9	64.9	74.1	22.0
PM ₁₀	82.7 ± 12.3	51.5	73.4	81.5	92.3	122.4	18.9
(3) The third trimester							
SO ₂	44.9 ± 7.5	22.1	38.9	43.1	51.2	81.3	12.3
NO ₂	55.3 ± 11.2	34.3	42.7	59.5	64.6	74.5	21.9
PM ₁₀	83.3 ± 11.8	54.5	75.1	82.4	91.5	118.9	16.4
(4) The fourth trimester							
SO ₂	44.9 ± 7.6	22.5	38.8	42.8	51.4	65.5	12.6
NO ₂	54.9 ± 11.4	33.9	42.6	58.9	64.3	74.1	21.7
PM ₁₀	83.2 ± 11.2	48.1	75.5	82.1	91.1	119.3	15.6
(5) Entire first year of life after birth							
SO ₂	44.9 ± 6.7	27.2	39.2	43.5	51.2	57.9	12.0
NO ₂	55.4 ± 10.7	36.0	41.8	62.4	64.1	67.1	22.3
PM ₁₀	82.9 ± 6.0	69.2	77.1	84.3	87.3	96.6	10.2

SD, standard deviation; IQR, interquartile range.

eczema were statistically significant, but most associations of SO_2 and PM_{10} and the studied diseases were not significant. With respect to NO_2 exposure in different trimesters, the strongest associations were found for hay fever and the adjusted odds ratios (95%CI) for the first (IQR: 22.1 $\mu\text{g}/\text{m}^3$), second (22.0 $\mu\text{g}/\text{m}^3$), third (21.9 $\mu\text{g}/\text{m}^3$), and fourth (21.7 $\mu\text{g}/\text{m}^3$) trimester, and the entire first year of lifetime () were 1.58 (1.19–2.05), 1.65 (1.24–2.13), 1.72 (1.30–2.22), 1.57 (1.21–2.02), and 1.73 (1.30–2.35) respectively.

Furthermore, for the gestation period (Fig. 3), when associations of NO_2 with the studied diseases were further adjusted to SO_2 and PM_{10} in the same duration in the multi-pollutant model, most of these associations were still significant for hay fever, pneumonia, and eczema. Associations of NO_2 exposures in different trimesters with hay fever, and eczema were stronger than in the single-pollutant model. Association of exposure to NO_2 in the 2nd trimesters with hay fever, pneumonia, rhinitis and eczema was stronger than in the first trimester, whereas association of exposure to NO_2 in the 2nd and 3rd trimester with asthma was weaker than in the first trimester. None significant association of SO_2 and PM_{10} exposures during gestational period with the studied diseases were found in the multi-pollutant model.

For the first year of lifetime (Fig. 4), when associations of NO_2 with the studied diseases were further adjusted to SO_2 and PM_{10} in the same

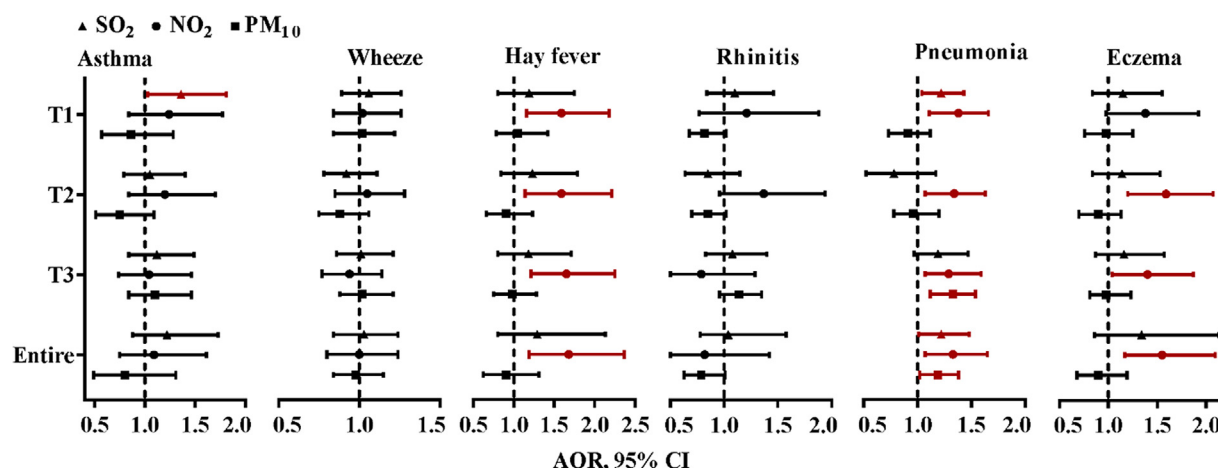


Fig. 1. Adjusted associations of air pollutants (increment of IQR) during different durations of gestational period with health outcomes in single-pollutant model. The red bars indicate statistical significance. The detailed values were presented in Table S4. T1, the 1st trimester. T2, the 2nd trimester. T3, the 3rd trimester. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

duration in the multi-pollutant model, most of these associations also were still significant for hay fever, rhinitis, and pneumonia. Associations of NO₂ exposures in different trimesters with hay fever, rhinitis, pneumonia, and eczema were stronger than in the single-pollutant model. Association of NO₂ exposure in the fourth trimester with asthma was stronger than in the other trimesters. Association of NO₂ exposure in the first trimester with hay fever was weaker than in other trimesters, whereas association of NO₂ exposure in the first trimester with pneumonia was stronger than in other trimesters. None significant associations of SO₂ and PM₁₀ with the studied diseases were found in the multi-pollutant model.

4. Discussion

In this retrospective cohort study, prenatal and postnatal exposures to higher level of outdoor NO₂ in different trimesters had significant associations with the higher odds of asthma, hay fever, rhinitis, pneumonia, and eczema in childhood. For prenatal exposure, associations of NO₂ in the early trimesters of gestation with asthma and pneumonia were stronger than in the later trimesters, whereas associations of NO₂ exposures in the early trimesters with hay fever and eczema were weaker than in the later trimesters. For postnatal exposure, associations of NO₂ in the early trimesters of gestation with pneumonia were

stronger than in the later trimesters, whereas associations of NO₂ exposures in the early trimesters with asthma, hay fever, and eczema were weaker than in the later trimesters. In the multi-pollutant model, no significant associations were found between SO₂ and PM₁₀ exposures and the studied diseases.

Our findings of NO₂ exposures were consistent with several previous studies (Aguilera et al., 2013; Bowatte et al., 2015; Clark et al., 2010; D'Amato et al., 2015; Deng et al., 2015; Gasana et al., 2012; Gehring et al., 2015; Hasunuma et al., 2014; Kan and Shi, 2019; Kim et al., 2013; Lee et al., 2003, 2008; Liu et al., 2014, 2016a, 2016b; Lu et al., 2013; MacIntyre et al., 2014; Norback et al., 2018; Sbihi et al., 2015; Weinmayr et al., 2010; Weir et al., 2013). In a meta-analysis of the related studies which were published during 1996–2010 with respect to asthma, Gasana et al. (2012) found higher level of outdoor NO₂ exposure was positively associated with higher asthma prevalence in childhood (OR, 95% CI: 1.05, 1.00–1.11). Another meta-analysis for 19 birth-cohort studies in 1960–2014 also suggested that of outdoor NO₂ exposure was significantly associated with the increased odds of asthma in childhood (OR, 95% CI: 1.09, 0.96–1.23 for increment of 10 µg/m³) (Bowatte et al., 2015). For children up to 14–16-year-olds, a combined birth-cohort study in Sweden, Germany, and the Netherlands found that NO₂ concentration increasing in 10 µg/m³ at the birth address associated with the asthma odd increased in 13% (OR, 95% CI: 1.13,

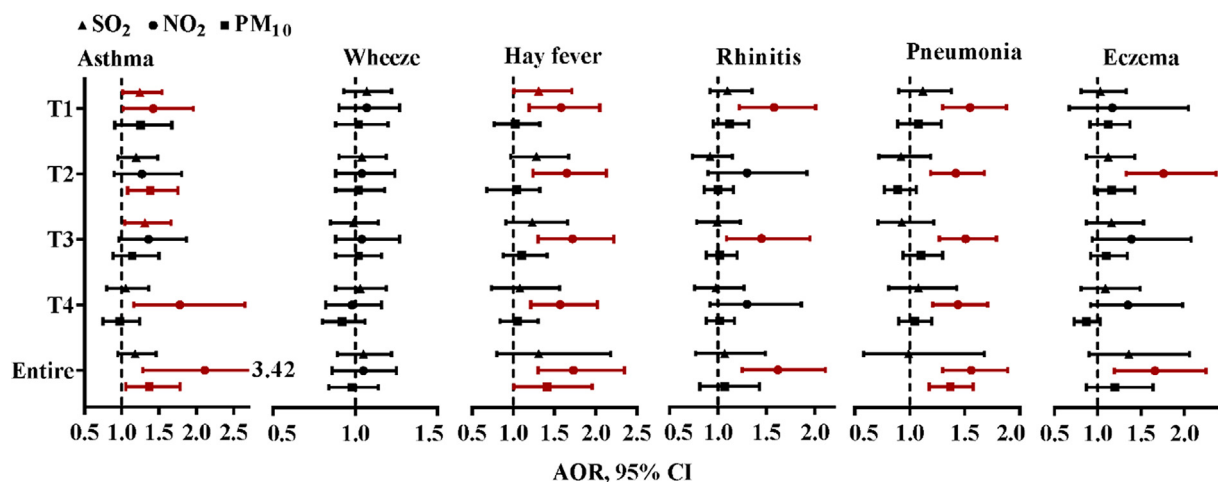


Fig. 2. Adjusted associations of air pollutants (increment of IQR) during different durations of the first year of lifetime with health outcomes in single-pollutant model. The red bars indicate statistical significance. The detailed values were presented in Table S5. T1, the 1st trimester. T2, the 2nd trimester. T3, the 3rd trimester. T4, the 4th trimester. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

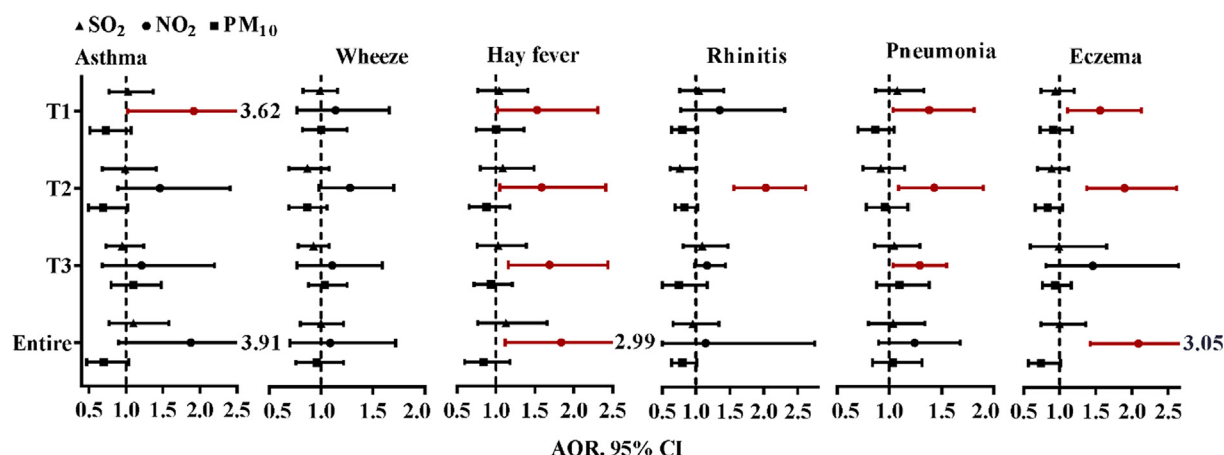


Fig. 3. Adjusted associations of NO_2 exposures (increment of IQR) during different durations of gestational period with health outcomes in multi-pollutant model. The red bars indicate statistical significance. The detailed values were presented in Table S6. T1, the 1st trimester. T2, the 2nd trimester. T3, the 3rd trimester. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.02–1.25) (Gehring et al., 2015). Deng et al. found that a $15\text{-}\mu\text{g}/\text{m}^3$ increase in NO_2 during the gestation (OR, 95% CI: 1.74, 1.15–2.62) and during the first year (OR, 95% CI: 1.90, 1.20–3.00) had significant associations with lifetime-ever doctor-diagnosed asthma among 3–6-year-olds children in Northeast China (Deng et al. 2015). With respect to hay fever and rhinitis, the study of 3–6-year-olds children in Northeast China also found that childhood allergic rhinitis was associated with exposure to NO_2 in lifetime (OR, 95% CI: 1.04, 1.01–1.07 for $10\text{ }\mu\text{g}/\text{m}^3$ increment) (Lu et al., 2013). With respect to pneumonia, exposure to NO_2 in gestation period was associated with the increased odd of lower respiratory tract infections in infants in Spain (OR, 95% CI: 1.05, 0.98–1.12) (Aguilera et al., 2013). A multicenter study in Europe found that exposure to NO_2 in long-term had significant associations with the higher odds of doctor-diagnosed pneumonia (OR, 95% CI: 1.30, 1.02–1.65 for increment of $10\text{ }\mu\text{g}/\text{m}^3$) (MacIntyre et al., 2014). With respect to eczema, a population-based cohort study for about 619 thousand preschoolers from 28 regions of Japan during 1997–2009 found that exposure to outdoor NO_2 in lifetime could increase prevalence of atopic dermatitis in 0.39% for an increment of 1 ppb (Hasunuma et al., 2014). A study identified 2,477 one-year-old infants in four Canadian cities and reported that exposure to outdoor NO_2 in the first year of lifetime was significantly associated with atopic development (Sbihi et al., 2015). In the National Health and Nutrition Examination Survey (NHANES) in 2005–2006, Weir et al. (2013) also

found that outdoor NO_2 in high annually-averaged level was associated with the increased odd of lifetime allergic sensitization. These findings further suggested that early exposure to ambient NO_2 could be a risk factor for asthma, hay fever, rhinitis, pneumonia, and eczema in childhood.

Besides, no significant associations with respect to PM_{10} is consistent with some previous studies (Anderson et al., 2010; Mölter et al., 2015). Anderson et al. (2010) reported that exposure to outdoor PM_{10} in the child's lifetime was not associated with the prevalence of eczema in childhood in the phase one of the ISAAC study. The Europe multicenter study found that PM_{10} exposure in long-term was not associated with asthma in childhood (OR, 95% CI: 0.88, 0.63–1.24, per $10\text{ }\mu\text{g}/\text{m}^3$ increases) (Mölter et al., 2015).

Outdoor air pollutants in China were generally worse than in the USA and in the European countries (Anderson et al., 2012; Brauer et al., 2016; Cohen et al., 2017; Zhang et al., 2012). The proportional differences in concentrations of air pollutants between health and sick children in the United States (Wilhelm et al., 2008; Parker et al., 2009; Mann et al., 2010; McConnell et al., 2010) and in the European countries (Jerrett et al., 2008; Oftedal et al., 2009; Aguilera et al., 2013; MacIntyre et al., 2014; Mölter et al., 2015) were generally greater than in our study and in the similar studies in China (Cai et al., 2014; Deng et al., 2015; Kan et al., 2012; Liu et al., 2014, 2016a, 2016b, 2020, Lu et al., 2013, 2020). Therefore, most ORs in our study for increased risk

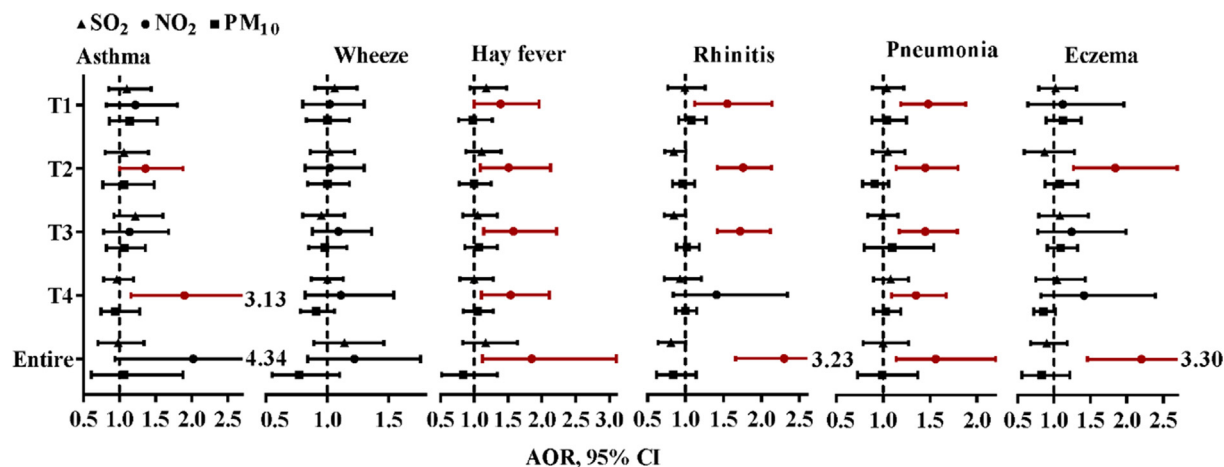


Fig. 4. Adjusted associations of NO_2 exposures (increment of IQR) during different durations of the first year of lifetime with health outcomes in multi-pollutant model. The red bars indicate statistical significance. The detailed values were presented in Table S7. T1, the 1st trimester. T2, the 2nd trimester. T3, the 3rd trimester. T4, the 4th trimester. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of asthma, hay fever, rhinitis, pneumonia, and eczema are generally higher than in the similar studies in Europe and USA.

In this study, both gestational and the first year of lifetime exposures on outdoor NO₂ could increase the odds of asthma, hay fever, rhinitis, pneumonia, and eczema in childhood. Interestingly, our results also indicated that associations of NO₂ exposures in the early trimesters of gestation and the first year of lifetime with pneumonia were stronger than in the later trimesters, whereas associations of NO₂ exposures in the early trimesters with hay fever and eczema were weaker than in the later trimesters. Several studies have suggested that outdoor air pollutants could have long-term effect on health outcomes in lifetime via transferring by mothers in gestation (Clark et al., 2010; Aguilera et al., 2013; Jedrychowski et al., 2013; Brunst et al., 2015). However, few studies reported the trimester-differences in the associations of NO₂ exposures and asthma, pneumonia, hay fever and eczema (Clark et al., 2010). It still is not clear for the mechanism for that prenatal exposure to outdoor NO₂ is a risk factor for postnatal respiratory and allergic diseases. NO₂ could induce inflammation and permeability among human epithelial cell cultures (Devalia et al., 1997; Bayram et al., 1999; Ezratty et al., 2014).

This study has limitations. First, we built this retrospective study from a cross-sectional study. We cannot provide causal inferences for the studied associations. Second, data for the health information and covariates were from parents-responded questionnaires and thus were subject to reporting error. Third, duration-averaged concentrations of outdoor air pollutants for the residence-located district were used to represent exposure level. Our assumption, that the gestation durations for all studied children were 9.0 months, could influence the precision of pollutant exposure level during the first trimester of gestation. Besides, we did not include exposure from indoor-originated pollutants. Fourth, although some residential factors were considered as covariates, there possibly are other factors also could confound effect of the studied pollutants on respiratory health in childhood (Kanchongkittiphon et al., 2015; Norback et al. 2018, 2019a).

Nevertheless, this study has several strengths. First, The ISAAC questionnaire was validated via physician assessment (Jenkins et al., 1996) and we provided guidance for answering questionnaire during the survey. Second, children did not change their residences since gestation. Therefore, district-averaged concentrations could reflect the child's exposure levels. Third, population densities and industrial factories were different in the studied districts, and thus differed in concentrations of outdoor air pollutants were different in these districts. This is an excellent chance to investigate associations of outdoor air pollutants with childhood health outcomes.

5. Conclusions

Prenatal and postnatal exposures to outdoor NO₂ could be risk factors for allergies and airway diseases in childhood. Both exposure dose and exposure duration were related with the influence degree of outdoor NO₂ on allergies and airway diseases in childhood. Exposures to high level of NO₂ in the early trimesters of gestation and the first year of lifetime had larger influence on childhood pneumonia than in the later trimesters, but exposures to high level of NO₂ in the early trimesters had smaller influence on childhood hay fever and eczema than in the later trimesters.

CRedit authorship contribution statement

Wei Liu: Conceptualization, Methodology, Software, Investigation, Visualization, Data curation, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition. **Chen Huang:** Conceptualization, Methodology, Software, Writing - review & editing, Supervision, Funding acquisition. **Jiao Cai:** Investigation, Visualization, Data curation, Writing - original draft. **Qingyan Fu:** Conceptualization, Methodology, Software, Investigation,

Visualization, Data curation, Writing - original draft. **Zhijun Zou:** Investigation, Visualization, Data curation, Writing - original draft. **Chanjuan Sun:** Investigation, Visualization, Data curation, Writing - original draft. **Jialing Zhang:** Investigation, Visualization, Data curation, Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105853>.

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