



Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children



Qihong Deng^{a, b, c, *}, Chan Lu^a, Cuiyun Ou^a, Lv Chen^b, Hong Yuan^{c, d}

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

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

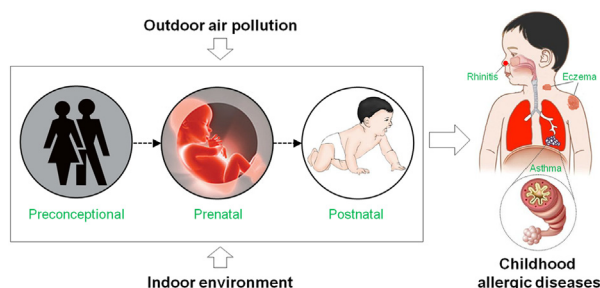
^c Institute of Environmental Health, Central South University, Changsha, Hunan, China

^d The Third Xiangya Hospital, Central South University, Changsha, Hunan, China

HIGHLIGHTS

- We studied allergy risk of some environmental factors during children's whole life exposure.
- Both outdoor air pollution and indoor environment can be associated with childhood allergy.
- The risk of environmental factor is determined by its timing of exposure.
- Early life exposure before birth can play an important role in the incidence of allergic diseases.
- Allergic symptoms are associated with indoor environment only.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Environmental factors have been found to be associated with allergic diseases, but it is unclear which environmental factor during which exposure window causes what kind of allergic diseases.

Objectives: We investigated association between exposure to some predominant outdoor and indoor environmental factors during preconceptional, prenatal, and postnatal periods and allergic diseases/symptoms in 2598 children in China.

Methods: Children's lifetime incidence of allergic diseases and current prevalence of allergic symptoms and exposure to indoor new furniture/redecoration and mold/dampness was surveyed by a questionnaire. Exposure to outdoor air pollutants was estimated by the concentrations measured at air quality monitoring stations. Multiple logistic regression model was used to evaluate the associations between outdoor air pollutants and indoor environmental factors and allergic diseases (asthma, allergic rhinitis, and eczema) and symptoms (wheezing, night cough, and rhinitis-like).

Results: We found that preconceptional, prenatal, and postnatal exposure to outdoor industrial and traffic air pollutants were significantly associated with increase in the risk of childhood asthma, and also positively associated with allergic rhinitis and eczema. However, we cannot distinguish the effect of outdoor air pollutants and exposure windows because of their high correlations. New furniture was associated with eczema and allergic rhinitis during postnatal exposure, but redecoration associated with asthma and eczema during prenatal exposure. Indoor visible mold/damp stains was significant for

* Corresponding author. School of Energy Science and Engineering, Central South University, Changsha, 410083, Hunan, China.

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

eczema during prenatal exposure and asthma during postnatal exposure respectively, but window condensation was significant for all childhood allergic diseases during both prenatal and postnatal exposures. Allergic symptoms in children were found to be associated with exposure to indoor factors only. *Conclusions:* Associations between outdoor air pollutants and indoor environmental factors and childhood allergic diseases/symptoms were divergent and related to the timing of exposure.

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1. Introduction

Asthma and allergy have become the most common chronic disease in children and the leading cause of pediatric hospitalization worldwide (Eder et al., 2006). The prevalence of childhood asthma and allergic diseases has been found to be increasingly rapidly, especially in developing countries such as China (Asher et al., 2006; Eder et al., 2006; Zhang et al., 2013). Apart from well known genetic factors, environmental factors have been found to be important contributors to the manifestations of allergic diseases (London, 2007). However, some fundamental issues about the role of environmental factors in the etiology of allergic diseases are still unclear:

- Outdoor or indoor? Although outdoor air pollution has long been suggested as a trigger for asthma or allergic diseases in children (Brauer et al., 2007), concern has arisen in recent years about indoor environment as a risk factor for the increased incidence of allergic disease because people spend more than 80% of their time indoors globally (Heinrich, 2011; Mendell, 2007).
- Which environmental risk factor? An array of environmental risk factors have been investigated, such as outdoor air pollutants and indoor environmental tobacco smoke (ETS), mold and dampness, allergens, and “new” chemicals (von Mutius, 2000; Bornehag et al., 2001, 2003, 2004; Kasznia-Kocot et al., 2010; Kim et al., 2013; Guarnieri and Balmes, 2014). However, which environmental factors is the main cause for the increase in prevalence of allergic disease is not well understood.
- Which timing of exposure: early life or late life? Adult or childhood chronic disease development proposes the importance of exposures throughout life or late life exposure (Gunnell et al., 1999; Yazdanbakhsh et al., 2002). However, there is recently increasing evidence pointing to the influence of prenatal and early life exposures on the development of allergic disease (Gluckman et al., 2008; Duijts, 2012). It remains largely unclear whether a time window exists within which the organism may be especially sensitive to the specific environmental influences.
- What kind of allergic disease and symptom? So far, there is a large difference and lack of consistency in the association between allergic diseases and symptoms and outdoor and indoor environmental factors (Penard-Morand et al., 2005; Heinrich, 2011), maybe due to different exposure level and metrics.

To address these issues, we aim to investigate the relation of asthma and allergy to some predominant outdoor and indoor environmental factors in China that, includes: (1) Serious outdoor Outdoor air pollution. With the rapid economic development, China is now facing one of the world worst industrial air pollution and also the worsening traffic air pollution due to the rapidly growing number of motor vehicles in the urban (Kan et al., 2012);

(2) Compelling indoor Indoor new furniture and redecoration. Due to the rapid urbanization progress, a huge number of people, especially the new couples and expected parents, migrated into new buildings in urban areas during the past decade. New building materials, and decoration materials, and new furniture caused high indoor level chemicals, such as volatile and semi volatile organ compounds (VOCs and SVOCs) (Bornehag et al., 2004; Schlink et al., 2010); (3) Mold and dampness in the home. Due to lack of central air conditioning and heating systems, mold and dampness in dwellings is very serious in the southern China with subtropical climate (Mendell et al., 2011).

We hypothesized that different developmental stages of environmental exposure can result in dissimilar impact on childhood allergic diseases and symptoms. We divided the child's whole life exposure into preconceptional, prenatal, and postnatal stages, and then evaluated the risk of exposure to outdoor air pollutants and indoor environmental factors during these stages on childhood allergic diseases/symptoms. Although the importance of exposure timing and how this affects the children's health outcomes were observed (Selevan et al., 2000), no one has systematically compiled the preconceptional, prenatal, postnatal developmental exposures and childhood allergy.

2. Materials and methods

2.1. Study population

Our work is a part of nationwide cross-sectional China-Children-Homes-Health (CCHH) epidemiology study (Zhang et al., 2013). Between September 2011 and January 2012, we conducted a survey for respiratory disease and symptoms in children in the kindergartens in Changsha, the capital city of Hunan Province in south-central China, having a population of 7.22 million inhabitants and covering an area of 1909 km². The study protocol were reviewed and approved by the Ethics Committee of the Central South University and also by the health department and school board 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 distributed to the children at 36 randomly chosen kindergartens throughout the city. 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 the overall response rate 78%. We first excluded 745 children from kindergartens having response rate lower than 50%. These excluded kindergartens were basically distributed in the outer suburbs where the children are mainly from the far rural areas and their parents are mainly rural migrant workers. For these children, the early life

exposure cannot be estimated by using the urban data. Then, we 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 and allergy (Brauer et al., 2008; Clark et al., 2010). 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 outcome were finally excluded. Totally, the 2598 complete data sets were entered into a database.

2.2. Health outcomes

The target variables were lifetime incidence of physician-diagnosed allergic diseases (asthma, allergic rhinitis, and eczema) and current prevalence of allergic symptoms (wheezing, night cough, and rhinitis-like). Asthma, allergic rhinitis, and eczema were respectively estimated based on positive answers to the questions: “Has a doctor ever diagnosed asthma/allergic rhinitis/eczema in your child?” Wheezing, night cough, and rhinitis-like symptoms were estimated on the basis of positive responses to the questions: “Has your child had wheezing or whistling in the chest/a dry cough at night/rhinitis-like symptoms without cold during the past 12 months?”

2.3. Confounding variables

Potential confounding variables obtained from the parent administered questionnaires included child's sex, age, breastfeeding, environmental tobacco smoke (ETS) at home, household furry pets, and parental atopy. Parental atopy is a measure of genetic predisposition to allergy and was defined as the father or mother of the index child ever having been diagnosed as having asthma or other allergic diseases.

2.4. Exposure

2.4.1. Timing of exposure

Child's whole life exposure was divided into three windows: preconceptional (exposure during 1 year before conception), prenatal (exposure during the whole pregnancy), and postnatal (exposure from birth to the current).

2.4.2. Outdoor air pollution

Concentrations of particulate matters with diameter less than 10 μm (PM_{10}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) obtained from 7 municipal air pollution monitoring stations were used to represent ambient air pollution in Changsha, because these regulated pollutants are continuously routinely measured. SO_2 could be used as an indicator of industry-related air pollution, NO_2 as traffic-related air pollution, and PM_{10} as a surrogate of complex mixture of air pollutants (Kan et al., 2012). Measurements at the monitoring stations strictly followed the standard methods set by the State Environmental Protection Agency of China: PM_{10} by a tapered element oscillating microbalance (TEOM1400, Rupprecht & Patashnick, USA), SO_2 by ultraviolet fluorescent method (ML/EC9850, Ecotech, Australia) and NO_2 by the chemiluminescent method (ML/EC9841B, Ecotech, Australia). We collected daily 24-h average concentrations of PM_{10} , SO_2 and NO_2 obtained from 7 monitoring stations during the period 2004–2012 that spanned the whole life exposure for all the children aged 3–6 years in the present study.

Children's exposure was calculated in terms of the air pollutant

concentrations at their kindergartens, because the parents usually enrolled their children in the kindergarten nearest to their homes. We first estimated the daily average air pollutant concentrations at 36 kindergartens from the data at 7 monitoring stations by using an inverse distance weighted (IDW) method (Deng et al., 2015a). The monthly mean concentrations of PM_{10} , SO_2 and NO_2 at each kindergarten were then calculated by averaging the daily average concentrations during each month. The preconceptional, prenatal, and postnatal exposures were respectively defined as the averages of the monthly mean concentrations of PM_{10} , SO_2 , and NO_2 during 1 year before conception, the full gestational months, and the past years since birth.

2.4.3. Indoor renovation

Indoor renovation was assessed based on questionnaire-based information about new furniture and redecoration. Exposure to indoor redecoration was estimated by two questions: “Did you redecorate your apartment (Yes/No/Don't know)?” and if yes, “When did you redecorate: Before conception/During pregnancy/After the child was born?” Exposure to indoor new furniture was assessed by another two questions: “Did you get new furniture in your home (Yes/No)?” and if yes: “When did you get new furniture: Before conception/During pregnancy/After the child was born?” In present study, we considered 82, 68, and 60 “Don't know” answers to redecoration respectively in preconceptional, prenatal, and postnatal periods as missing data.

2.4.4. Indoor mold and dampness

Indoor mold and dampness was also assessed based on questionnaire-based information about visible mold/damp stains and condensation on windows. Exposure to indoor visible mold/damp stains was estimated by the question: “Have you had visible mold growth/damp stains on the floor, walls, or ceilings in any of your dwellings during pregnancy/in the room the child sleeps after birth (Yes/No)?” Exposure to condensation on windows was based on the question: “Have you had condensation on the inside of the window during wintertime in any of your dwellings during pregnancy/in the room the child sleeps after birth (Yes/No/Don't know)?” We also considered 242 “Don't know” answers to window condensation as missing data in the present study.

2.5. Statistical analysis

We used multiple logistic regression model to evaluate the association between outdoor and indoor environmental factors and childhood allergic diseases and symptoms during different time windows by adjusting for confounding variables. On the other hand, effects of outdoor and indoor environmental factors were mutually adjusted so as to separate their effects. Results of the logistic regression analyses were interpreted by odds ratios (OR) with 95% confidence interval (95% CI) where p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 16.0, SPSS Inc, Chicago, USA).

Outdoor air pollutants were entered into the logistic regression model as continuous variables and their associations with health outcomes were estimated by unit increases of two standard deviations (SD) in their exposure levels. Indoor renovation and mold/dampness were entered into the logistic regression model as categorical variables, and their associations with health outcomes were estimated by setting none exposure cases as the reference, i.e. $\text{OR} = 1$.

3. Results

Of 2598 respondents, 175 (6.7%), 187 (7.2%), and 737 (28.4%) respectively reported a history of asthma, allergic rhinitis, and eczema, and 509 (19.6%), 430 (16.6%), and 1060 (40.8%) respectively had wheezing, night cough, and rhinitis-like symptoms during the past year. Table 1 shows the prevalence of asthma and allergic diseases and symptoms stratified by the potential covariates. Higher prevalence of allergic diseases and symptoms was found in boys than girls. Higher prevalence of allergic diseases but lower prevalence of allergic symptoms was found in older children than in the younger. Breastfeeding decreased the prevalence of allergic diseases and symptoms, except eczema. Prevalences of allergic diseases and symptoms were higher in children with parental atopy than those without. We found the allergic diseases were not related to the household pets and ETS at home, maybe due to few families raised pets and very few parents smoked when the child at home in China.

Table 2 shows statistics of children's exposure to outdoor air pollution, indoor renovation activities and mold/dampness during preconceptional, prenatal, and postnatal periods. The outdoor PM₁₀ and SO₂ were high up to 119 ± 13 and 91 ± 25 µg/m³ before conception and 110 ± 11 and 82 ± 26 µg/m³ during pregnancy, but substantially decreased to 93 ± 4 and 51 ± 11 µg/m³ during postnatal years, indicating that effective measures had been taken in the past years to reduce the classic air pollution in the city. However, the levels of traffic air pollution (NO₂) were gradually increased from 43 ± 7 µg/m³ before conception to 46 ± 8 µg/m³ during pregnancy and 49 ± 6 µg/m³ during postnatal years. For indoor environmental factors, 14% and 25% families redecorated their houses and installed new furniture before conception; the percentages decreased to 5% and 13% during pregnancy but increased up to 19% and 38% during postnatal years. On the other hand, 17% and 47% families observed visible mold/damp stains and condensation on windows in winter during pregnancy but the

Table 2

Statistics of exposure to outdoor air pollution, indoor renovation activities and mold/dampness (n = 2598).

(1) Outdoor air pollution	Mean (µg/m ³)	SD (µg/m ³)
Preconceptional (one year before pregnancy)		
PM ₁₀	119	13
SO ₂	91	25
NO ₂	43	7
Prenatal (during the whole pregnancy)		
PM ₁₀	110	11
SO ₂	82	26
NO ₂	46	8
Postnatal (from birth to the current)		
PM ₁₀	93	4
SO ₂	51	11
NO ₂	49	6
(2) Indoor renovation	Number (n)	Percentage (%)
Preconceptional		
New furniture	647	25
Redecoration	370	14
Prenatal		
New furniture	338	13
Redecoration	139	5
Postnatal		
New furniture	980	38
Redecoration	499	19
(3) Indoor mold or dampness	Number (n)	Percentage (%)
Prenatal		
Visible mold/damp stains	435	17
Condensation on windows	1222	47
Postnatal		
Visible mold/damp stains	308	12
Condensation on windows	869	33

PM₁₀ = particulate matter ≤ 10 µm in aerodynamic diameter; SO₂ = sulfur dioxide; NO₂ = nitrogen dioxide; SD = Standard deviation.

percentages were decreased to 12% and 33% in postnatal years.

Table 3 shows the associations between outdoor air pollutants and allergic diseases and symptoms during three time windows. In

Table 1

Demographics and prevalence of allergic diseases and symptoms in children stratified by covariates (n = 2598).

	n	Lifetime prevalence of diseases, n (%)			Current prevalence of symptoms, n (%)		
		Asthma	Allergic rhinitis	Eczema	Wheezing	Night cough	Rhinitis-like
Total	2598	175 (6.7)	187 (7.2)	737 (28.4)	509 (19.6)	430 (16.6)	1060 (40.8)
Sex							
Male	1399	117 (8.4)	116 (8.3)	429 (30.7)	299 (21.4)	237 (16.9)	601 (43.0)
Female	1199	58 (4.8)	71 (5.9)	308 (25.7)	210 (17.5)	193 (16.1)	459 (38.3)
p-value		<0.001	0.020	0.005	0.014	0.557	0.018
Age (years)							
3	665	26 (3.9)	28 (4.2)	202 (30.4)	146 (22.0)	113 (17.0)	276 (41.5)
4	952	77 (8.1)	80 (8.4)	263 (27.6)	177 (18.6)	180 (18.9)	398 (41.8)
5	815	59 (7.2)	64 (7.9)	220 (27.0)	157 (19.3)	120 (14.7)	323 (39.6)
6	166	13 (7.8)	15 (9.0)	52 (31.3)	29 (17.5)	17 (10.2)	63 (38.0)
p-value		0.007	0.006	0.410	0.323	0.019	0.729
Breast-feeding							
No	222	24 (10.8)	20 (9.0)	58 (26.1)	49 (22.1)	40 (18.0)	100 (45.0)
Yes	2376	151 (6.4)	167 (7.0)	679 (28.6)	460 (19.4)	390 (16.4)	960 (40.4)
p-value		0.009	0.260	0.506	0.297	0.478	0.187
Parental atopy							
No	2332	120 (5.1)	115 (4.9)	642 (27.5)	412 (17.7)	363 (15.6)	910 (39.0)
Yes	266	55 (20.7)	72 (27.1)	95 (35.7)	97 (36.5)	67 (25.2)	150 (56.4)
p-value		<0.001	<0.001	0.005	<0.001	<0.001	<0.001
Environmental tobacco smoke (ETS) at home							
No	864	60 (6.9)	56 (6.5)	235 (27.2)	149 (17.2)	136 (15.7)	320 (37.0)
Yes	1734	115 (6.6)	131 (7.6)	502 (29.0)	360 (20.8)	294 (17.0)	740 (42.7)
p-value		0.762	0.310	0.316	0.033	0.429	0.004
Household pets (cats or dogs)							
No	2394	165 (6.9)	174 (7.3)	674 (28.2)	464 (19.4)	392 (16.4)	977 (40.8)
Yes	204	10 (4.9)	13 (6.4)	63 (30.9)	45 (22.1)	38 (18.6)	83 (40.7)
p-value		0.321	0.687	0.292	0.245	0.333	0.849

Table 3

Associations between exposure to outdoor air pollution and childhood allergic diseases in terms of adjusted odds ratio (OR) with 95% confidence interval (CI).

	Basic model ^a			Indoor adjusted model ^b		
	Asthma	Allergic rhinitis	Eczema	Asthma	Allergic rhinitis	Eczema
Preconceptional						
PM ₁₀	1.09 (0.64, 1.85)	0.86 (0.51, 1.45)	0.80 (0.59, 1.08)	0.91 (0.51, 1.62)	0.87 (0.49, 1.53)	0.70 (0.50, 0.98)*
SO ₂	1.56 (1.13, 2.14)**	1.33 (0.97, 1.83)	1.16 (0.97, 1.38)	1.44 (1.01, 2.05)*	1.42 (1.01, 2.00)*	1.15 (0.95, 1.39)
NO ₂	1.51 (1.09, 2.09)*	1.25 (0.91, 1.72)	1.16 (0.97, 1.38)	1.43 (1.00, 2.05)(*)	1.27 (0.90, 1.80)	1.20 (0.99, 1.46)
Prenatal						
PM ₁₀	1.04 (0.66, 1.64)	1.05 (0.68, 1.64)	0.95 (0.74, 1.23)	1.04 (0.61, 1.75)	1.00 (0.60, 1.65)	0.89 (0.67, 1.19)
SO ₂	1.58 (1.14, 2.19)**	1.22 (0.88, 1.69)	0.99 (0.81, 1.19)	1.58 (1.07, 2.32)*	1.27 (0.87, 1.85)	1.01 (0.81, 1.26)
NO ₂	1.75 (1.23, 2.48)**	1.47 (1.04, 2.07)*	1.10 (0.91, 1.33)	1.87 (1.24, 2.83)**	1.59 (1.07, 2.37)*	1.17 (0.94, 1.45)
Postnatal						
PM ₁₀	1.66 (1.07, 2.58)*	1.58 (1.03, 2.44)*	1.07 (0.86, 1.34)	1.47 (0.82, 2.64)	1.78 (1.00, 3.19)(*)	1.09 (0.81, 1.47)
SO ₂	1.56 (1.09, 2.24)*	1.27 (0.89, 1.81)	1.20 (0.98, 1.47)	1.47 (0.90, 2.42)	1.44 (0.90, 2.31)	1.27 (0.96, 1.67)
NO ₂	1.56 (1.14, 2.14)**	1.34 (0.98, 1.82)	1.13 (0.95, 1.34)	1.54 (1.01, 2.34)*	1.51 (1.01, 2.27)*	1.10 (0.88, 1.38)

OR (95%CI) was estimated for 2SD increase in PM₁₀, SO₂, and NO₂. *p < 0.05, (*) p = 0.05, **p ≤ 0.01.^a Basic model was adjusted for the basic covariates in Table 1 i.e. child's sex, age, breast-feeding, parental atopy, ETS at home, and household pets.^b Indoor adjusted model was further adjusted for the indoor environmental factors including new furniture, redecoration, mold or damp stains, and window condensation, besides the basic covariates adjusted in the basic model.

the basic model, we found that exposure to industrial and traffic air pollutants (SO₂ and NO₂) was significantly associated with asthma with ORs (95% CIs) = 1.56 (1.13–2.14) and 1.51 (1.09–2.09), 1.58 (1.14–2.19) and 1.75 (1.23–2.48), and 1.56 (1.09–2.24) and 1.56 (1.14–2.14) respectively during preconceptional, prenatal, and postnatal periods. SO₂ and NO₂ had also positive effects on childhood allergic rhinitis and eczema at significant or borderline significant levels. However, the industrial and traffic air pollutants (SO₂ and NO₂) were moderately correlated with each other (0.68, 0.48, and 0.63 respectively in preconceptional, prenatal, and postnatal periods) and highly correlated between exposure windows (>0.8) (please see Table S1 in Supplementary Material), and therefore we cannot distinguish the effects of the specific air pollutants and time windows. For particulate air pollutant PM₁₀, we found it was not associated with childhood asthma, allergic rhinitis, and eczema during preconceptional and prenatal periods, but it was significantly associated with asthma and allergic rhinitis during postnatal period maybe due to close correlation with SO₂ and NO₂ (please see Table S1 in Supplementary Material). In addition, we found that the association between exposure to outdoor air pollutants and childhood allergic diseases was robust and consistent when it was adjusted for the indoor environmental factor. However, our results indicated that exposure to outdoor air pollutants was not associated with the current allergic symptoms in children (please see Table S2 in Supplementary Material).

Table 4 shows the association between exposure to indoor new furniture and redecoration and allergic diseases and symptoms. We found that new furniture was not associated with allergic diseases

during preconceptional and prenatal periods, but during postnatal period it was significant associated with eczema with OR = 1.34 (1.06–1.69) and associated with rhinitis at marginally significant level with OR = 1.48 (0.97–2.25). Redeclaration was not found association with allergic diseases during preconceptional and postnatal period, but significantly associated with asthma (OR = 2.23; 95% CI: 1.29–3.88) and eczema (OR = 1.52; 95% CI: 1.05–2.20) during pregnancy. On the other hand, we found that current night cough and rhinitis-like symptoms in children were strong significantly associated with postnatal exposure to new furniture [OR = 1.44 (1.10–1.90) and 1.37 (1.10–1.69)] and redecoration [OR = 1.62 (1.18–2.23) and 1.57 (1.21–2.03)] and also associated with preconceptional exposure to new furniture and redecoration at marginal significance.

Table 5 shows the association between exposure to indoor mold/dampness and allergic diseases and symptoms in children. We found that both prenatal and postnatal exposure to window condensation was significantly associated with childhood diseases with adjusted ORs respectively 1.49 (1.04, 2.15) and 1.62 (1.05, 2.51) for asthma, 1.76 (1.24, 2.52) and 2.09 (1.35, 3.25) for allergic rhinitis, and 1.37 (1.12, 1.66) and 1.44 (1.14, 1.80) for eczema. The allergic risk of exposure to visible mold/damp stains was different, only significant for eczema during prenatal period with adjusted OR = 1.40 (1.09–1.80) and asthma during postnatal period with adjusted OR = 1.80 (1.15–2.83). However, we observed that current allergic symptoms in children were all strongly associated with mold and dampness at home.

Table 4

Associations between exposure to indoor renovation and childhood allergic diseases/symptoms in terms of adjusted odds ratio (OR) with 95% confidence interval (CI).

	Allergic diseases			Current symptoms		
	Asthma	Allergic rhinitis	Eczema	Wheezing	Night cough	Rhinitis-like
Preconceptional						
New furniture	0.72 (0.48, 1.08)	1.20 (0.84, 1.72)	1.11 (0.90, 1.37)	0.95 (0.75, 1.21)	1.27 (0.99, 1.62)	1.20 (0.99, 1.45)
Redecoration	0.68 (0.40, 1.16)	1.38 (0.91, 2.08)	1.09 (0.85, 1.40)	1.03 (0.77, 1.37)	1.33 (0.99, 1.77)	1.27 (1.01, 1.60)*
Prenatal						
New furniture	1.08 (0.67, 1.73)	0.74 (0.44, 1.24)	1.13 (0.87, 1.47)	1.00 (0.74, 1.36)	1.02 (0.74, 1.41)	1.22 (0.96, 1.56)
Redecoration	2.23 (1.29, 3.88)**	0.76 (0.37, 1.58)	1.52 (1.05, 2.20)*	1.45 (0.96, 2.19)	1.14 (0.72, 1.81)	1.31 (0.91, 1.87)
Postnatal						
New furniture	1.08 (0.71, 1.66)	1.48 (0.97, 2.25)	1.34 (1.06, 1.69)*	1.27 (0.97, 1.65)	1.44 (1.10, 1.90)**	1.37 (1.10, 1.69)**
Redecoration	1.31 (0.79, 2.18)	1.15 (0.69, 1.92)	1.21 (0.92, 1.59)	1.18 (0.85, 1.63)	1.62 (1.18, 2.23)**	1.57 (1.21, 2.03)***

No indoor renovation was set as reference. *p < 0.05, **p < 0.01, ***p < 0.001.

Adjusted for the basic covariates in Table 1 (child's sex, age, breast-feeding, parental atopy, ETS at home, household pets), indoor mold or dampness, and outdoor air pollutants (PM₁₀, SO₂, and NO₂).

Table 5
Associations between exposure to indoor mold or dampness and childhood allergic diseases/symptoms in terms of adjusted odds ratio (OR) with 95% confidence interval (CI).

	Allergic diseases			Current symptoms		
	Asthma	Allergic rhinitis	Eczema	Wheezing	Night cough	Rhinitis-like
Prenatal						
Visible mold/damp stains	1.27 (0.82, 1.97)	0.65 (0.40, 1.07)	1.40 (1.09, 1.80)**	1.51 (1.14, 1.99)**	1.62 (1.21, 2.18)***	1.46 (1.15, 1.85)**
Condensation on window	1.49 (1.04, 2.15)*	1.76 (1.24, 2.52)**	1.37 (1.12, 1.66)**	1.47 (1.17, 1.84)***	1.40 (1.10, 1.78)**	1.51 (1.26, 1.81)***
Postnatal						
Visible mold/damp stains	1.80 (1.15, 2.83)**	1.01 (0.61, 1.66)	1.23 (0.93, 1.63)	1.69 (1.25, 2.27)***	1.91 (1.41, 2.59)***	2.11 (1.62, 2.75)***
Condensation on window	1.62 (1.05, 2.51)*	2.09 (1.35, 3.25)***	1.44 (1.14, 1.80)**	1.42 (1.09, 1.85)**	1.70 (1.29, 2.24)***	1.58 (1.28, 1.94)***

No indoor mold or dampness was set as reference. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Adjusted for the basic covariates in Table 1 (child's sex, age, breast-feeding, parental atopy, ETS at home, household pets), indoor renovation, and outdoor air pollutants (PM_{10} , SO_2 , and NO_2).

4. Discussion

We examined the association between preconceptional, prenatal, postnatal exposure to outdoor air pollution and some indoor environmental factors in China and childhood allergic diseases/symptoms. We found that the level of outdoor air pollution in China is much higher than that in developed countries and the international air quality guidelines, new buildings and house renovation have become popular during the past decade in China, and indoor mold and dampness is very serious in the south central China without heating in winter. These outdoor and indoor environmental factors were found to be associated with childhood asthma, allergic rhinitis and eczema during different timings of exposure.

The strength of our work is that we comprehensively investigated the effect of both outdoor and indoor environmental factors on the childhood allergic diseases and symptoms during different timings of exposure. We found that both outdoor air pollution and indoor mold/dampness and renovation were risk factors for childhood allergic diseases and symptoms, which are consistent with the available studies. Outdoor air pollution has long been linked to exacerbations but not incidence of asthma, and thus the role of ambient air pollution exposure in the development of asthma and allergies remains unclear (Brauer et al., 2002, 2007; Gehring et al., 2002; Morgenstern et al., 2008; Clark et al., 2010). Recently, a growing body of epidemiologic studies have shown associations between home mold and dampness and indoor materials or their emissions and allergic health effects (Bornehag et al., 2001; Heinrich, 2011; Le Cann et al., 2011). Mold and dampness in the home could stimulate growth of various fungi, bacteria, dust mites, and other biological agents and hence increase the risk for allergic diseases and symptoms in children (Garret et al., 1998; Dharmage et al., 2002; Jaakkola et al., 2005; Fisk et al., 2007; Tham et al., 2007). Meanwhile, redecoration activities and new surface materials could emit many VOCs and SVOCs and hence have been identified as risk factors for allergic sensitization and diseases (Oie et al., 1997; Diez et al., 2003; Bornehag et al., 2004; Franck et al., 2014; Herbarth et al., 2006; Mendell, 2007). The potential interaction between outdoor air pollution and indoor allergens has been recently suggested but received little attentions (Gilmour et al., 2006). Very few studies investigated the effect of exposure to both outdoor and indoor environmental factors on children's allergy (von Mutius, 2000; Lee et al., 2003; Kasznia-Kocot et al., 2010; Kim et al., 2013; Liu et al., 2014). Our recent work (Deng et al., 2015b) observed that the exposures to both outdoor air pollution and indoor air pollution during pregnancy and the first year of life were associated with childhood asthma.

We found the risk of outdoor and indoor environmental factors for childhood allergic diseases was ubiquitous during the whole developmental stages. Many epidemiological studies have shown the importance of exposure throughout life or late life in the

chronic development of childhood allergic diseases, i.e. life course model (Gauderman et al., 2005; Jaakkola et al., 2005; Brauer et al., 2007; Morgenstern et al., 2008; Iossifova et al., 2009; Heinrich, 2011; Mendell et al., 2011). However, it was surmised that prenatal and early life exposures to air pollution are of greater significance than late life exposure due to the susceptibility of target organs and systems during developmental periods of life, i.e. early life model (Mortimer et al., 2008). Some recent studies observed the effect of early life exposure to air pollution on the incidence of allergic diseases including asthma in children (Gehring et al., 2002; Clark et al., 2010; Aguilera et al., 2013; Gruziova et al., 2013; Nishimura et al., 2013; Deng et al., 2015a). Early life exposure to indoor mold/dampness and redecoration during pregnancy and/or during the first year of life increased the risk for childhood respiratory diseases (Diez et al., 2003; Herbarth et al., 2006; Iossifova et al., 2009; Franck et al., 2014).

Our results show that the effects of outdoor and indoor air pollution on allergic diseases are not the same in different timings of exposure. Firstly, asthma is the most common chronic disease in children and the leading cause of pediatric hospitalization worldwide (Eder et al., 2006). In our study, the lifetime prevalence of childhood asthma is 6.7% and was significantly associated with the outdoor industry- and traffic-related air pollutants and indoor mold/dampness during all life exposures, but only significantly associated with indoor renovation during early life exposure, i.e. during pregnancy. Recent epidemiological studies in developed countries have demonstrated the asthmatic risk of traffic-related air pollution for school children during current exposure (Zmirou et al., 2004; Gauderman et al., 2005; Hwang et al., 2005; Brauer et al., 2007; Morgenstern et al., 2008) and for pre-school children during early life exposure (Brauer et al., 2002; Gehring et al., 2002; Clark et al., 2010; Gruziova et al., 2013; Nishimura et al., 2013). We confirmed the asthmatic risk of exposure to traffic-related air pollution in China and further demonstrated the risk of exposure to industry-related air pollution that was overlooked in developed countries due to its low concentration (Deng et al., 2015a). Exposure to home mold and dampness has been suggested to be a strong and consistent indicator for the risk of asthma (Dharmage et al., 2002; Jaakkola et al., 2005; Tham et al., 2007; Heinrich, 2011; Tischer et al., 2011), but the asthmatic risk of early life exposure to indoor mold received less attention (Iossifova et al., 2009). On the other hand, although asthma has been reported to be associated with home renovation (Jaakkola et al., 2004; Dong et al., 2008; Heinrich, 2011; Liu et al., 2014), the effect of early life exposure has not yet been reported. However, several studies showed that redecoration during pregnancy or the first year of life increased the risk for childhood respiratory diseases such as obstructive bronchitis (Diez et al., 2003), wheezing (Franck et al., 2014), eczema and other allergic symptoms (Herbarth et al., 2006).

Secondly, allergic rhinitis or hay fever is the most common

respiratory disorder that affects the greatest number of people (Greiner et al., 2011). In our study, the lifetime prevalence of childhood allergic rhinitis is 7.2%, which was not only associated with the indoor mold/dampness but also associated with the traffic air pollutant (NO_2) and indoor new furniture. Allergic rhinitis occurs when the immune system overreacts to environmental allergens, such as molds and dust mites. Therefore, dampness and mold exposures at home are determinants of allergic rhinitis (Engvall et al., 2001; Kilpeläinen et al., 2001; Jaakkola et al., 2010, 2013; Wang et al., 2015). The associations between traffic-related air pollution and allergic rhinitis were also reported (Weiland et al., 1994; Duhme et al., 1996; Lee et al., 2003; Morgenstern et al., 2008). However, very few studies indicated the association between indoor furniture and allergic rhinitis (Wang et al., 2015).

Thirdly, eczema or atopic dermatitis is the most common inflammatory skin disease in childhood (Leung and Bieber, 2003). Exposure to air pollution may induce oxidative stress in the skin, leading to skin barrier dysfunction or immune dysregulation (Ahn, 2014), which may play an important role in the development of eczema. However, there is relatively little evidence in the association between long-term exposure to ambient air pollution and the development of eczema (Heinrich and Wichmann, 2004; Bowatte et al., 2015), and therefore warrant further studies. Our study found that eczema in preschool children was positively associated with the traffic-related pollutant NO_2 exposure during pre-conceptional, prenatal, and postnatal periods. Although many indoor environmental factors were proven to be associated with childhood eczema (McNally et al., 2001; Herbarth et al., 2006; Langan et al., 2006; Miyake et al., 2007; Bieber, 2008; Schäfer et al., 2008), only a few studies have focused on outdoor environmental factors and eczema (Weiland et al., 2004; Morgenstern et al., 2008; Ahn, 2014). In Taiwan, a nation-wide survey demonstrated that traffic-related air pollutants (CO and NO_x) were positively associated with childhood flexural eczema (Lee et al., 2008). Consistent with these evidences, our finding also suggest that outdoor air pollution, especially for traffic-related pollution, is one of potent risk factors for the development of childhood eczema.

In addition, we found that the current prevalence of asthma and allergic symptoms was only associated with the indoor renovation and mold/dampness. This finding is in agreement with the findings of other studies. Recently, the national cross-sectional CCHH studies have demonstrated the impact of housing characteristics and home environmental factors on asthma and asthma-related symptoms in Chinese children (Zhang et al., 2013). Home dampness and presence of molds, as well as window pane condensation in the winter season were consistently and positively associated with wheezing, dry cough, allergic rhinitis, and eczema symptoms in the last 12 months (Garret et al., 1998; Fisk et al., 2007; Tham et al., 2007; Dong et al., 2008; Wang et al., 2015).

There are some limitations of this study that should be acknowledged. 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, i.e. 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 and thus the parents are not active in participating 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 preconceptional and prenatal periods cannot be estimated by using the urban data. Secondly, another 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 allergic diseases are likely to remember the child's allergic symptoms and also the related indoor environmental factors such as mold/dampness and new furniture/redecoration. The third limitation is the potential misclassification of exposure. 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. Our assessment of background air pollution exposure might also have led to misclassification as children spend a fraction of their time at home or in transit. Fourthly, 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. Fifthly, we only considered three criteria air pollutants, PM_{10} , SO_2 and NO_2 , 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 $\text{PM}_{2.5}$, which was a better proxy for traffic air pollution (Gehring et al., 2002). Sixthly, we haven't measured the indoor VOCs concentrations and mold/dampness components. The associations between asthma and allergy and indoor renovation and mold/dampness were indirectly assessed by using questionnaire in the present study. The direct evidence by measuring indoor VOCs concentrations and mold/dampness components and their association with the childhood allergy is necessary (Mendell, 2007; Heinrich, 2011). At last, as the first step of the nationwide project (CCHH), our study only included one city. Additional research in other cities is needed to confirm the persistence and generalizability of the results.

5. Conclusions

We systematically investigated the association between childhood asthma and allergy and exposure to some predominant outdoor and indoor environmental factors in China. We found that outdoor air pollution and indoor renovation and mold/dampness were associated with allergic diseases and symptoms, but the associations were different during different timings of exposure. Our results indicates that public education programs or policies to reduce exposure to outdoor air pollution for expected parents, pregnant women and infants would be helpful to effectively decrease the risk of childhood allergic diseases. On the other hand, initiatives to diminish children's exposure to new furniture and house redecoration and measures to increase home ventilation to prevent indoor mold/dampness are useful to lower the prevalence of childhood allergic diseases and symptoms. Our study also provides a guide to prevent asthma and allergy in children by taking effective measures to reduce the exposure for target environmental factors at critical time windows. However, further investigations are needed to examine the role of different environmental factors in the pathogenesis of different allergic diseases to confirm the findings.

Competing financial interests

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.chemosphere.2016.03.032>.

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Supplementary Material

Table S1. Pearson correlations between exposures to outdoor air pollutants and between different timings of exposure (n=2,598).

Air pollutants	Between air pollutants			Between exposure windows
	PM ₁₀	SO ₂	NO ₂	
Preconceptional				Prenatal
PM ₁₀	1	0.33**	-0.23**	0.64**
SO ₂		1	0.68**	0.85**
NO ₂			1	0.90**
Prenatal				Postnatal
PM ₁₀	1	0.27**	-0.32**	0.54**
SO ₂		1	0.48**	0.83**
NO ₂			1	0.84**
Postnatal				Preconceptional
PM ₁₀	1	0.84**	0.37**	0.61**
SO ₂		1	0.63**	0.81**
NO ₂			1	0.86**

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

Supplementary Material

Table S2. Associations between exposure to outdoor air pollution and current allergic symptoms in terms of adjusted odds ratio (OR) with 95% confidence interval (CI).

	Basic model #			Adjusted model †		
	Wheezing	Night cough	Rhinitis-like	Wheezing	Night cough	Rhinitis-like
Preconceptional						
PM ₁₀	0.79 (0.56, 1.13)	0.97 (0.67, 1.41)	0.79 (0.60, 1.05)	0.73 (0.49, 1.08)	0.87 (0.57, 1.33)	0.76 (0.56, 1.04)
SO ₂	0.92 (0.75, 1.12)	0.94 (0.76, 1.17)	1.06 (0.90, 1.25)	0.91 (0.73, 1.15)	0.96 (0.75, 1.22)	1.11 (0.92, 1.32)
NO ₂	0.95 (0.77, 1.16)	0.89 (0.72, 1.10)	1.10 (0.93, 1.29)	0.97 (0.77, 1.21)	0.93 (0.73, 1.19)	1.14 (0.95, 1.37)
Prenatal						
PM ₁₀	1.13 (0.84, 1.52)	0.78 (0.57, 1.07)	0.92 (0.73, 1.17)	1.10 (0.79, 1.53)	0.89 (0.62, 1.28)	0.93 (0.71, 1.22)
SO ₂	0.86 (0.69, 1.08)	0.93 (0.73, 1.18)	0.99 (0.83, 1.18)	0.91 (0.70, 1.17)	0.98 (0.74, 1.29)	1.01 (0.83, 1.24)
NO ₂	0.95 (0.77, 1.19)	0.99 (0.79, 1.25)	1.05 (0.88, 1.25)	1.01 (0.79, 1.30)	1.05 (0.80, 1.38)	1.08 (0.88, 1.32)
Postnatal						
PM ₁₀	0.80 (0.62, 1.03)	0.75 (0.58, 0.98)*	1.11 (0.90, 1.37)	0.72 (0.52, 1.01)	0.81 (0.57, 1.16)	1.25 (0.95, 1.66)
SO ₂	0.89 (0.70, 1.12)	0.87 (0.68, 1.11)	1.06 (0.88, 1.27)	0.74 (0.54, 1.02)	0.83 (0.59, 1.15)	1.07 (0.83, 1.38)
NO ₂	0.95 (0.78, 1.16)	0.96 (0.78, 1.19)	1.08 (0.92, 1.27)	0.81 (0.62, 1.05)	0.91 (0.69, 1.20)	1.12 (0.90, 1.38)

Basic model was adjusted for the basic covariates in Table 1, i.e. child's sex, age, breast-feeding, parental atopy, ETS at home, and household pets.

† Adjusted model was further adjusted for the indoor environmental factors including new furniture, redecoration, mold or damp stains, and window condensation on the base of basic model.

* p<0.05