



Asthma and rhinitis among Chinese children — Indoor and outdoor air pollution and indicators of socioeconomic status (SES)



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ABSTRACT

Background: Few data exist on asthma and rhinitis across China in relation to indoor and outdoor air pollution, climate and socioeconomic factors. The main aim was to study associations between asthma, rhinitis and current respiratory symptoms among pre-school children across China and selected indoor and outdoor exposure and indicators of socio-economic status (SES) in mutually adjusted models.

Methods: Chinese children (3–6 yr.) (n = 39,782) were recruited from randomly selected day care centres in seven cities in China. Data on asthma, respiratory symptoms, rhinitis, indoor and outdoor exposure at home and SES were assessed by a parentally administered questionnaire. Lifetime mean ambient temperature, PM₁₀, NO₂, and GDP per capita on city level were calculated.

Results: Totally 7.4% had ever doctors' diagnosed (DD) asthma and 8.7% DD-rhinitis, 19.7% had current wheeze, 45.0% rhinitis and 16.9% cough. DD-asthma was associated with ambient temperature (OR = 1.15, 95% CI 1.11–1.20 per °C), NO₂ (OR = 1.16, 95% CI 1.02–1.33 per 10 µg/m³), indoor mould/dampness (OR = 1.25, 95% CI 1.13–1.39) and living near major roads (OR = 1.13, 95% CI 1.02–1.25). DD-rhinitis was associated with ambient temperature (OR = 1.07, 95% CI 1.05–1.10 per °C), NO₂ (OR = 1.20, 95% CI 1.09–1.32 per 10 µg/m³), GDP (OR = 1.03, 95% CI 1.01–1.06 per 10,000 RenMinBi/year), indoor mould/dampness (OR = 1.23, 95% CI 1.11–1.35), passive smoking (OR = 1.11, 95% CI 1.01–1.21), and living near major roads (OR = 1.14, 95% CI 1.03–1.25). Children in suburban or rural areas, in larger families (≥ 5 persons) and with prenatal farm exposure had less DD-asthma and DD-rhinitis.

Conclusions: Economic development level of the city, higher SES, ambient temperature, NO₂, PM₁₀, traffic air pollution and mould/dampness can be risk factors for asthma and rhinitis and respiratory symptoms among pre-school children in China. Breastfeeding, large family size and early-life farm exposure could be protective factors.

1. Introduction

There has been a global increase of asthma and allergies since the 1970s (Asher et al., 2006; Burr et al., 2006). The large ISAAC international study has demonstrated that the increase of asthma and

allergic diseases is most pronounced in middle-income countries, especially in the Asia Pacific region (Asher et al., 2006). China is one of the largest middle-income countries and there has been a considerable increase of asthma in China in the past decades (Huang et al., 2015; National Cooperation Group on Childhood Asthma of China, 1998; Sha

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et al., 2015; Zhang et al., 2013). Moreover, three national asthma surveys across China in 1990, 2000 and 2010 have demonstrated a considerable variation in asthma prevalence across China with the highest prevalence in Shanghai and the lowest in Lhasa (National Cooperation Group on Childhood Asthma of China, 1998; Sha et al., 2015).

We spend > 90% of our time indoors. Passive smoking (Heinrich, 2011; Ciaccio and Gentile, 2013) and mould and dampness (Heinrich, 2011; Tischer et al., 2011; WHO, 2009) are the most well-established indoor risk factors for childhood asthma, rhinitis and allergic diseases. Moreover, several studies have demonstrated that outdoor air pollution, including NO₂, SO₂ and particulate matter (PM) are risk factors for asthma (Jassal, 2015; Tzivian, 2011) and allergic diseases (Brandt et al., 2015), and children growing up in rural areas have a lower risk of allergies (Schröder et al., 2015; Jie et al., 2013). Recently, there has been a focus on traffic-related air pollution (TRAP) as a risk factor for asthma (Antó, 2012; Khreis et al., 2017).

Some protective factors have been identified. Early studies found that breastfeeding could protect against asthma and allergy development but recent larger reviews have not confirmed this finding (Victora et al., 2016). Several studies from western countries have demonstrated that prenatal or perinatal exposure to the farm environment is protective for allergic disease development (Campbell et al., 2015; Wlasiuk and Vercelli, 2012). It has been observed that a larger family size, especially older siblings, could protect against the development of allergies but the issue on family size is complex. Inverse association with older siblings is main phenomena of more affluent countries and a greater severity of symptoms of asthma and rhinitis in larger families is globally more widespread (Strachan et al., 2015).

A low socio-economic status plays a major role in the development of many types of diseases (Spencer et al., 2015) and there could be an interaction between social determinants and environmental exposure for early-life health outcomes (Appleton et al., 2016). China has a rapid economic development but we found few studies on associations between indicators of socio-economic status (SES) and asthma and rhinitis in China. One ecological analysis of data from 10 cities in China reported a strong correlation between GDP per capita on city level and prevalence of doctors' diagnosed asthma (Zhang et al., 2013).

There is a need for larger epidemiological studies on risk factors for childhood asthma and allergic diseases in China including both indoor and outdoor air pollution and SES. The CCHH study (China-Children-Homes-Health) is a multicentre study including pre-school children across China (Zhang et al., 2013). The main aim of this paper is to study associations between diagnosed asthma, diagnosed rhinitis and current respiratory symptoms among pre-school children across China and selected indoor and outdoor exposure and indicators of SES in mutually adjusted models. The following hypotheses were tested: lifetime-ever incidence of asthma and rhinitis diagnosed by a doctor, and prevalence of current wheeze, rhinitis symptoms and night-time cough are associated with the indoor and outdoor exposure and indicators of SES.

2. Methods

2.1. Study design

The study can be characterised as a retrospective cohort study based on a one-time questionnaire survey when the children were 3–6 y old. Data about doctor's diagnosed asthma and rhinitis covered the whole life (cumulative incidence). The recall period for wheeze, dry cough and rhinitis was the last 12 months. Exposures on city level (climate, air pollution and city GDP per capita) were calculated as average values over the whole life, from birth to the questionnaire survey. Individual exposure to passive smoking and dampness or mould was assessed from birth to the questionnaire survey. Data on home size, number of persons living in the home, residential area, and living near major roads with heavy traffic were for the current home. An additional sensitivity

analysis was performed restricted to children living in the same home since birth.

2.2. Study population

Pre-school children recruited from randomly selected areas and randomly selected day care centres in seven major cities including three northern cities (Urumqi, Beijing, Taiyuan) and four southern cities (Nanjing, Shanghai, Chongqing and Changsha) in China. All are megacities with populations ranging from 4 to 24 million. Shanghai and Beijing has over 20 million inhabitants. In China, the children start school at 6 yr. age and about 80% of all children aged 3–5 years attended a day care centre and in urban areas, the day care attendance is even higher (Norbäck et al., 2017a). The one child policy was still valid when CCHH was performed and thus most of the children had no siblings.

All children in the selected day care centres were invited to participate. A questionnaire was distributed to the parents or other guardians in the period from December 2010 to January 2012 and was returned within one week. A total of 55,301 questionnaires were distributed and 42,666 were completed (77% response rate). We restricted the current study to children 3–6 years old with information on age and sex of the child. A total of 39,782 children were included (66.7% from southern China). The full CCHH questionnaire has been published elsewhere (Zhang et al., 2013). The study and the consent procedure were approved by the Medical Research Ethics Committee of School of Public Health, Fudan University, Shanghai. The participants and parents gave informed consent.

2.3. Assessment of demographic data

Data on covariates (sex, age, birth season, birth weight, breast feeding, parental asthma or rhinitis) and individual exposure were collected by the parentally administered questionnaire.

2.4. Assessment of meteorological data, ambient air pollution and income per capita

Outdoor exposure included ambient temperature, NO₂, SO₂, and PM₁₀ (life-time means on city level) and self-reported closeness of the home to heavy traffic roads (< 200 m). Annual data on ambient temperature from 2005 to 2012 was obtained from the website of Weather Underground (<https://www.wunderground.com>). Annual data on NO₂, SO₂, and PM₁₀ from 2005 to 2012 were downloaded from the website of National Bureau of Statistics of the People's Republic of China (<http://www.stats.gov.cn/>). PM_{2.5} data was not available in China before 2013. The official air pollution and climate data on the websites only included annual average data for each city. Each city had 7 to 17 air pollution monitoring stations and 8 to 33 monitoring stations for climate (including temperature). The largest numbers were for Shanghai and Beijing, the largest cities. For each child, a life-time mean value was calculated, based on means of annual data for each city from year of birth until the year the questionnaire was answered.

2.5. Assessment of exposure at home

Indoor risk factors included dampness and mould and passive smoking at home. There was one yes/no question on passive smoking at home and one about location of the home near major roads with heavy traffic (< 200 m). We included dampness and mould exposure during two time windows: at birth (perinatal exposure) and in the current home (current exposure). The questions on the current home did not specify the recall period. There were two yes/no questions on exposure at birth, asking about indoor mould or damp stains in the child's bedroom. In addition, there were two yes/no questions on the current home exposure asking about indoor mould or damp stains in the child's

bedroom and one asking about water damage in the home. All five questions were combined to one variable, coded as yes if at least one of the five variables had a yes answer.

2.6. Assessment of socioeconomic status (SES)

Indicators of SES included mothers occupation during pregnancy, size of the home (m²), number of persons living in the home, living area (urban, suburban, and rural) and GDP per capita (life-time means on city level). All these information, except data on city GDP per capita, were obtained from the questionnaire. Size of the home has been demonstrated to be a good socioeconomic indicator related to family income (Juhn et al., 2011). Annual data on income per capita from 2005 to 2012 on city level was obtained from China Statistical Yearbook. The economic development in China is rapid and city GDP per capita usually increase year by year. For each child, a life-time mean value was calculated based on annual means from year of birth until the year the questionnaire was answered.

2.7. Assessment of health

There was one yes/no question asking if the child had ever been diagnosed with asthma by a doctor (DD-asthma). Another yes/no question asking if the child had ever been diagnosed with rhinitis by a doctor (DD-rhinitis). In addition, there were three yes/no questions asking about wheeze, rhinitis and night time dry cough in the past 12 months (current symptoms). The questions on current symptoms were from the ISAAC questionnaire (Asher et al., 2006) and were used in China in detailed studies on early life exposure to outdoor air pollution in the city of Changsha (Deng et al., 2016).

2.8. Statistical analysis

Multilevel logistic regression was used to study associations between exposure and the five health variables. Two levels were used (city and child). Since we were interested in the independent effect of each exposure, we created one mutually adjusted model for each health variable, including all co-variables (sex, age, birth season, breast feeding), all exposure variables (ambient temperature, outdoor NO₂, indoor dampness/mould, passive smoking, living near traffic road) and the SES variables (mother's occupation during pregnancy, size of the home, location of the home, number of persons in the home, city GDP per capita). Association for PM₁₀ was tested separately by replacing NO₂ and by PM₁₀ in the models. Association for SO₂ was not analysed since SO₂ was too closely associated with PM₁₀, temperature and city GDP per capita. Birth season was coded as a categorical variable with spring as the reference category. Mothers' occupation during pregnancy was coded as a categorical variable with those not occupationally active (unemployed or house wives) as reference category. Number of persons in the current home was coded as a categorical variable with 3 or 4 persons as the reference category. Location of the dwelling was coded as a categorical variable with urban location as the reference category. Odds ratios (ORs) with 95% confidence interval (95% CI) were calculated. A two-tailed p-value < 0.05 was considered as significant. We used STATA11.0 (STATA Corp., Texas, USA) for the statistical calculations.

3. Results

3.1. Characteristic of population

Data on asthma, rhinitis and respiratory symptoms, stratified by city, is given in Table 1. All health variables differed significantly between the cities. Data on the covariates and the indoor exposure, stratified by city is given in Table 2. Half of the children were exposed to passive smoking at home, one third had mould or dampness and

more than one third lived near major roads with heavy traffic. Descriptive data on the indicators of socio-economic status (SES), stratified by city, are given in Table 3. Crude analysis of associations between the indicators of SES and the health variables are given in Table 4. All crude analyses were statistically significant ($p < 0.001$) except for wheeze and maternal occupation during pregnancy. Descriptive data on mean values of lifetime city GDP per capita and lifetime outdoor temperature and air pollution levels, addressed to each child, are given in Table 5.

Correlations between these parameters, on individual level, are given in Supplement Table S1. There were negative correlations between city GDP per capita and PM₁₀ and SO₂ but positive correlation for NO₂. NO₂ had only weak correlations with the other outdoor variables ($r = 0.02$ – 0.41) and was chosen as the main air pollutant to be evaluated in the regression models. Additional regression models were run, replacing NO₂ with PM₁₀ in the models. SO₂ was not used in any regression models due to strong correlation with city GDP per capita, ambient temperature and PM₁₀.

3.2. Associations for co-variables and indoor and outdoor exposure

In the mutually adjusted logistic regression models (Table 6), breast feeding was negatively associated with DD-asthma (protective) while male gender, higher age, parental atopy, indoor mould/dampness, living near major roads, a higher ambient temperature and NO₂ levels were risk factors. Breast feeding and low birth weight (< 2.5 kg) were negatively associated with DD-rhinitis while male gender, higher age, parental atopy, indoor mould/dampness, passive smoking, living near major roads, higher ambient temperature and higher NO₂ levels were risk factors. For current wheeze, male gender, lower age, birth season (lowest in spring), parental atopy, passive smoking, indoor mould/dampness, living near major roads and higher NO₂ levels were risk factors. For current rhinitis symptoms, male gender, parental atopy, passive smoking, indoor mould/dampness, living near major roads and higher NO₂ levels were risk factors. For current night-time dry cough, lower age, parental atopy, indoor mould/dampness, living near major roads, higher ambient temperature and NO₂ levels were risk factors (Table 6).

We made a separate analysis of associations with PM₁₀ by replacing NO₂ with PM₁₀ in the models. Outdoor PM₁₀ was significantly associated with nocturnal cough, only (OR = 1.17; 95% CI 1.12–1.22 per 10 µg/m³).

3.3. Associations for indicators of socio-economic status (SES)

Associations for SES indicators and city GDP were obtained from the same mutually adjusted models and are given in Table 7. Table 6 and 7 are based on the same regression models. DD-asthma was more common if the mother did not work during pregnancy and less common in suburban and rural areas. DD-rhinitis was less common if the mother had worked as farmer during pregnancy and more common if the mother did not have a job. Moreover, DD-rhinitis was less common in suburban and rural areas, less common in larger families (≥ 5 persons), more common in larger homes (an indicator of higher family income) and positively associated with GDP per capita on city level. Current wheeze was more common in suburban or rural areas and negatively associated with GDP per capita on city level. Current rhinitis symptoms were more common if the mother did not work during pregnancy, more common in larger homes and less common in suburban or rural areas. Finally, night-time dry cough was more common in larger homes and less common in rural areas (Table 7).

3.4. Sensitivity analysis

Some of the questions on the home environment asked about the situation in the current home. Since 39% of the children did not live in

Table 1

Statistics of doctor-diagnosed allergic asthma and rhinitis (cumulative incidence) and prevalence of current symptoms among children (n = 39,782).

	Number (n)	(%)	Doctor-diagnosed asthma		Doctor-diagnosed rhinitis		Wheeze		Rhinitis symptoms		Nocturnal cough	
			Cases (n)	(%)	Cases (n)	(%)	Cases (n)	(%)	Cases (n)	(%)	Cases (n)	(%)
Total	39,782	(100.0)	2936	(7.4)	3463	(8.7)	7831	(19.7)	17,909	(45.0)	6732	(16.9)
Urumqi	4,302	(10.8)	149	(3.5)	342	(7.9)	991	(23.0)	1913	(44.5)	470	(10.9)
Beijing	5,478	(13.8)	333	(6.1)	405	(7.4)	926	(16.9)	2731	(49.9)	1038	(18.9)
Taiyuan	3,453	(8.7)	69	(2.0)	110	(3.2)	524	(15.2)	1098	(31.8)	284	(8.2)
Nanjing	3,349	(8.4)	296	(8.8)	295	(8.8)	591	(17.6)	2054	(61.3)	602	(18.0)
Shanghai	14,570	(36.6)	1448	(9.9)	1739	(11.9)	3095	(21.2)	6506	(44.7)	2796	(19.2)
Chongqing	4,945	(12.4)	393	(7.9)	290	(5.9)	978	(19.8)	1929	(39.0)	905	(18.3)
Changsha	3,685	(9.3)	248	(6.7)	282	(7.7)	726	(19.7)	1678	(45.5)	637	(17.3)
p-Value			< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	

Sum of the numbers are not 39,782 due to missing data. p-Values calculated by Chi-2 analysis.

the same home since birth, this could lead to a misclassification of life-time exposure. We performed a sensitivity analysis, including only children who had lived in the same home since birth (Supplement S1 and S2). The results were almost identical as the results from Tables 6 and 7 where all subjects were included.

4. Discussion

Our study is one of few larger multi-centre studies across China on risk factors for asthma, rhinitis and respiratory symptoms among pre-school children including indoor and outdoor exposure variables and

indicators of socio-economic status (SES) in the same study in mutually adjusted models. We found that higher ambient temperature, NO₂, PM₁₀, and closeness to major roads, passive smoking and indoor dampness/mould were risk factors for DD-asthma, DD-rhinitis or respiratory symptoms. A higher city GDP per capita was positively associated with rhinitis but negatively associated with current wheeze. Breast feeding, living in suburban or rural areas, large family size (≥ 5 persons), smaller house size and farm exposure during pregnancy could be protective factors. Our study confirms that risk factors identified in previous studies from western countries are also risk factors in China.

The pre-school children were recruited from randomly selected day

Table 2

Covariates and demographic information for the pre-school children (n = 39,782).

	Total		Urumqi		Beijing		Taiyuan		Nanjing		Shanghai		Chongqing		Changsha	
	Number (n)	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Sex																
Boys	20,633	(51.9)	2300	(53.5)	2887	(52.7)	1807	(52.3)	1706	(50.9)	7412	(50.9)	2533	(51.2)	1988	(53.9)
Girls	19,149	(48.1)	2002	(46.5)	2591	(47.3)	1646	(47.7)	1643	(49.1)	7158	(49.1)	2412	(48.8)	1697	(46.1)
Age (year)																
3	7285	(18.3)	475	(11.0)	1386	(25.3)	981	(28.4)	450	(13.4)	2067	(14.2)	1032	(20.9)	894	(24.3)
4	14,060	(35.3)	1496	(34.8)	1650	(30.1)	1290	(37.4)	929	(27.7)	5678	(39.0)	1667	(33.7)	1350	(36.6)
5	12,187	(30.6)	1,441	(33.5)	1,506	(27.5)	1,016	(29.4)	992	(29.6)	4516	(31.0)	1,532	(30.8)	1,193	(32.4)
6	6250	(15.7)	890	(20.7)	936	(17.1)	166	(4.8)	978	(29.2)	2309	(15.8)	723	(14.6)	248	(6.7)
Birth season																
Spring (March–May)	9331	(23.5)	1001	(23.3)	1371	(25.0)	800	(23.2)	880	(26.3)	3296	(22.6)	1144	(23.1)	839	(22.8)
Summer (June–August)	9934	(25.0)	1065	(24.8)	1348	(24.6)	946	(27.4)	876	(26.2)	3600	(24.7)	1098	(22.2)	1001	(27.2)
Autumn (September–November)	10,072	(25.3)	1165	(27.1)	1369	(25.0)	895	(25.9)	747	(22.3)	3601	(24.7)	1359	(27.5)	936	(25.4)
Winter (December–February)	9374	(23.6)	996	(23.2)	1302	(23.8)	784	(22.7)	792	(23.6)	3443	(23.6)	1230	(24.9)	827	(22.4)
Birth weight (kg)																
< 2.5	977	(2.5)	92	(2.1)	113	(2.1)	63	(1.8)	70	(2.1)	397	(2.7)	142	(2.9)	100	(2.7)
≥ 2.5	37,668	(94.7)	4207	(97.8)	5225	(95.4)	3290	(95.3)	3199	(95.5)	13,655	(93.7)	4609	(93.2)	3483	(94.5)
Breast-feeding																
No	4341	(10.9)	489	(11.4)	461	(8.4)	339	(9.8)	293	(8.7)	1887	(13.0)	552	(11.2)	320	(8.7)
Yes	34,494	(86.7)	3584	(83.3)	4932	(90.0)	3054	(88.4)	3020	(90.2)	12,366	(84.9)	4248	(85.9)	3290	(89.3)
Parental atopy (asthma or rhinitis)																
No	33,626	(84.5)	3578	(83.2)	4471	(81.6)	3154	(91.3)	2946	(88.0)	11,865	(81.4)	4380	(88.6)	3232	(87.7)
Yes	4854	(12.2)	493	(11.5)	834	(15.2)	213	(6.2)	355	(10.6)	2278	(15.6)	303	(6.1)	378	(10.3)
Lifetime passive smoking																
No	15,510	(39.0)	1658	(38.5)	2679	(48.9)	942	(27.3)	1256	(37.5)	6161	(42.3)	1598	(32.3)	1216	(33.0)
Yes	22,176	(55.7)	2425	(56.4)	2668	(48.7)	1572	(45.5)	2010	(60.0)	7990	(54.8)	3090	(62.5)	2421	(65.7)
Lifetime mould/dampness ^a																
No	23,573	(59.3)	2516	(58.5)	4448	(81.2)	2536	(73.4)	2572	(76.8)	9840	(67.5)	3510	(71.0)	2599	(70.5)
Yes	11,271	(28.3)	1670	(38.8)	1030	(18.8)	882	(25.5)	761	(22.7)	4653	(31.9)	1208	(24.4)	1067	(29.0)
Living near major roads with heavy traffic (< 200 m)																
No	19,572	(49.2)	2854	(66.3)	2823	(51.5)	2245	(65.0)	1768	(52.8)	7727	(53.0)	2540	(51.4)	2469	(67.0)
Yes	13,666	(34.4)	1448	(33.7)	1748	(31.9)	1006	(29.1)	1118	(33.4)	5277	(36.2)	1979	(40.0)	1090	(29.6)

Sum of the numbers are not 39,782 due to missing data.

^a Mould/dampness was defined as visible mould or damp stains on the floor, wall, and ceiling in the children's bedroom, and/or water damage in the house, from birth to the questionnaire survey.

Table 3

Statistics of indicators of socioeconomic status (SES) among the children (n = 39,782).

	Total		Urumqi		Beijing		Taiyuan		Nanjing		Shanghai		Chongqing		Changsha	
	Number (n)	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Maternal occupation during pregnancy																
Not occupationally active*	15,255	(38.3)	1269	(29.5)	2476	(45.2)	1173	(34.0)	1181	(35.3)	6446	(44.2)	1279	(25.9)	1431	(38.8)
Farmer	635	(1.6)	41	(1.0)	39	(0.7)	29	(0.8)	28	(0.8)	168	(1.2)	288	(5.8)	42	(1.1)
Industrial worker	1492	(3.8)	318	(7.4)	103	(1.9)	85	(2.5)	248	(7.4)	458	(3.1)	229	(4.6)	51	(1.4)
White-collar worker†	22,116	(55.6)	2623	(61.0)	2813	(51.4)	2164	(62.7)	1884	(56.3)	7375	(50.6)	3109	(62.9)	2148	(58.3)
Current home size (m ²)																
≤ 60	10,825	(27.2)	784	(18.2)	1203	(22.0)	1028	(29.8)	834	(24.9)	5031	(34.5)	1333	(27.0)	612	(16.6)
60–100	15,974	(40.2)	2377	(55.3)	1940	(35.4)	1407	(40.7)	1612	(48.1)	5013	(34.4)	2067	(41.8)	1558	(42.3)
> 100	11,837	(29.8)	976	(22.7)	2141	(39.1)	963	(27.9)	861	(25.7)	4170	(28.6)	1272	(25.7)	1454	(39.5)
Number of people living in the home (n)																
≤ 2	3,066	(7.7)	78	(1.8)	727	(13.3)	623	(18.0)	305	(9.1)	527	(3.6)	471	(9.5)	335	(9.1)
3–4	23,902	(60.1)	2439	(56.7)	3324	(60.7)	2,728	(79.0)	1993	(59.5)	8209	(56.3)	2935	(59.4)	2274	(61.7)
≥ 5	9,879	(24.8)	669	(15.6)	1232	(22.5)	100	(2.9)	860	(25.7)	4861	(33.4)	1231	(24.9)	926	(25.1)
Current residential area																
Urban	29,262	(73.6)	3517	(81.8)	4379	(79.9)	2823	(81.8)	2166	(64.7)	9784	(67.2)	3313	(67.0)	3280	(89.0)
Suburban	7786	(19.6)	520	(12.1)	771	(14.1)	466	(13.5)	1022	(30.5)	3868	(26.5)	885	(17.9)	254	(6.9)
Rural	1520	(3.8)	84	(2.0)	101	(1.8)	87	(2.5)	102	(3.0)	635	(4.4)	480	(9.7)	31	(0.8)

Sum of the numbers are not 39,782 due to missing data.

*House wife (8%) or unemployed (30%); †White-collar worker was defined as office staff (30%), teacher (7%), medical staff (6%), student (4%), shop assistant (1%) and other occupations (9%).

Table 4

Statistics of doctor-diagnosed allergic diseases (cumulative incidence) and prevalence of current symptoms among the children (n = 39,782).

	Doctor-diagnosed asthma		Doctor-diagnosed rhinitis		Wheeze		Rhinitis symptoms		Nocturnal cough	
	Case (n)	(%)	Case (n)	(%)	Case (n)	(%)	Case (n)	(%)	Case (n)	(%)
Maternal occupation during pregnancy										
Not occupationally active*	1276	(8.4)	1571	(10.3)	3092	(20.3)	7233	(47.4)	2761	(18.1)
Farmer	25	(3.9)	13	(2.0)	124	(19.5)	228	(35.9)	73	(11.5)
Industrial worker	95	(6.4)	99	(6.6)	306	(20.5)	664	(44.5)	230	(15.4)
White-collar worker†	1531	(6.9)	1767	(8.0)	4271	(19.3)	9698	(43.9)	3652	(16.5)
p-Value	< 0.001		< 0.001		0.111		< 0.001		< 0.001	
Home size (m ²)										
≤ 60	766	(7.1)	791	(7.3)	2,209	(20.4)	4,596	(42.5)	1,697	(15.7)
60–100	1,168	(7.3)	1,351	(8.5)	3,170	(19.8)	7,277	(45.6)	2,752	(17.2)
> 100	927	(7.8)	1253	(10.6)	2275	(19.2)	5674	(47.9)	2142	(18.1)
p-Value	0.159		< 0.001		0.031		< 0.001		< 0.001	
Number of people living in the home (n)										
≤ 2	187	(6.1)	232	(7.6)	561	(18.3)	1,375	(44.8)	482	(15.7)
3–4	1,766	(7.4)	2,110	(8.8)	4,668	(19.5)	10,691	(44.7)	3,993	(16.7)
≥ 5	810	(8.2)	926	(9.4)	2037	(20.6)	4487	(45.4)	1876	(19.0)
p-Value	< 0.001		0.008		0.006		0.318		< 0.001	
Residential area										
Urban	2291	(7.8)	2790	(9.5)	5692	(19.5)	13,675	(46.7)	5027	(17.2)
Suburban	523	(6.7)	573	(7.4)	1607	(20.6)	3255	(41.8)	1327	(17.0)
Rural	63	(4.1)	50	(3.3)	344	(22.6)	551	(36.3)	214	(14.1)
p-Value	< 0.001		< 0.001		0.001		< 0.001		0.010	

Sum of the number is not 39,782 due to missing data. p-Values calculated by Chi-2 analysis.

care centres in seven cities. All children in the selected day care centres were invited to participate. We used multilevel logistic regression models since the data had a hierarchic structure. In China, the children start school at 6 yr. age. In China about 80% of all children aged 3–5 years attended a day care centre and in urban areas, the day care attendance is even higher (Norbäck et al., 2017a, 2017b). The one child policy was still valid when CCHH was performed and thus most of the children had no siblings. We collected information on doctors' diagnosed asthma, rhinitis, eczema and current symptoms by a parentally administered questionnaire. The medical questions have been used in previous studies (Deng et al., 2016) and are based on the ISAAC questionnaire (Asher et al., 2006).

Epidemiological studies can be influenced by selection bias and

information bias. Most of the invited day care centers participated in the study. The individual response rate was reasonably good (77%) and the day care centers were randomly selected. Thus it is less likely that the study was influenced by selection bias, but one limitation is that it covers mainly urban areas and only seven cities. Recall bias can occur when there are subjective reports on exposure as well as symptoms, sometimes called “auto-suggestion” effect. In China, air pollution is suggested as a major risk factor for asthma and allergic disease but indoor environmental factors or mothers' occupation as risk factors for asthma and rhinitis have not been a public health issue. Since we used monitoring data to calculate a life-time mean ambient temperature and mean exposure to NO₂ and PM₁₀ (based on annual city level data), these associations should not be influenced by recall bias. For the same

Table 5

Lifetime average GDP per capita, outdoor temperature and concentrations of ambient air pollutants calculated from data on city level in the seven cities.

City	GDP per capita (RenMinBi)		T		PM ₁₀		SO ₂		NO ₂	
	Mean	(Min-Max)	Mean	(Min-Max)	Mean	(Min-Max)	Mean	(Min-Max)	Mean	(Min-Max)
Urumqi	51,088	(47,110–56,084)	7.9	(7.6–8.1)	137	(135–140)	91	(87–94)	67	(66–68)
Beijing	104,880	(95,932–112,000)	13.2	(13.1–13.4)	123	(118–131)	34	(31–38)	55	(54–58)
Taiyuan	48,721	(42180–51,234)	11.0	(11.0–11.2)	94	(91–107)	69	(68–73)	22	(22–23)
Nanjing	72,036	(58,017–81,623)	16.4	(16.2–16.6)	104	(102–106)	43	(35–50)	49	(48–51)
Shanghai	116,670	(106,000–133,000)	17.2	(17.0–17.5)	81	(77–83)	36	(27–42)	52	(49–53)
Chongqing	19,133	(16,555–24,665)	18.8	(18.7–18.9)	105	(100–109)	58	(46–63)	41	(36–43)
Changsha	63,783	(53,843–71,140)	18.3	(18.2–18.4)	90	(86–95)	44	(40–53)	44	(43–45)

T (°C) = ambient temperature; PM₁₀ (µg/m³) = particulate matter ≤ 10 µm in aerodynamic diameter; SO₂ (µg/m³) = sulfur dioxide; NO₂ (µg/m³) = nitrogen dioxide. Lifetime-exposure was calculated for each child (n = 39,782) from birth to the questionnaire survey, based on annual data on city level.

reason, associations with income should not be subjected to recall bias. Thus, the overall conclusions in our study are not likely to be due to recall bias or selection bias.

One strength of the study is that it is a large study on environmental and socio-economic risk factors for childhood asthma and rhinitis. It is one of the largest multi-center studies on asthma and rhinitis among pre-school children in China. By including personal factors, indoor factors, outdoor air pollution and indicators of socio-economic status and city GDP per capita in mutually adjusted models, we get a better understanding of the individual contribution of each factor.

One limitation is that some data were assessed on city level, only. This can lead to methodological problems linked to ecological fallacy. However, we have data on closeness of the home to major roads (< 200 m) and the location of the home (urban, suburban, and rural location) which means we have individual proxy variables for air pollution as well. The study can be characterised as a retrospective cohort study, with a combination of lifetime data and current data on exposure and respiratory health. However, the cross-sectional data collection can limit the possibility to draw conclusion on causality.

We found an average of 7.4% doctors diagnosed asthma (cumulative incidence) in our study with the lowest level (2.0%) in Taiyuan and the

highest (9.9%) in Shanghai. In our previous studies among school children in these two cities, similar cumulative incidences of doctors' diagnosed asthma were found, 1.2% in Taiyuan (Zhao et al., 2006) and 8.9% in Shanghai (Mi et al., 2006). One limitation in our study is that we have no information on current asthma medication, which could influence the prevalence of current respiratory symptoms. In our previous studies among school children in China we found a low prevalence of current asthma medication, 0.5% in Taiyuan (Zhao et al., 2006) and 2.3% in Shanghai (Mi et al., 2006). Thus, it is likely that most of the children in our study with asthma diagnosis did not have asthma medication.

We found that indoor dampness and mould were associated with asthma, rhinitis and current respiratory symptoms. This is in agreement with conclusions from previous reviews (Heinrich, 2011; Tischer et al., 2011; WHO, 2009). Passive smoking was associated with rhinitis and wheeze, which is in agreement with previous studies (Heinrich, 2011; Johansson et al., 2008). We found that outdoor concentrations of NO₂ on city level, and living near major roads, were associated with asthma, rhinitis and current respiratory symptoms. Moreover, living in suburban or rural areas was associated with less asthma, rhinitis and night dry cough. Since the main source of NO₂ is from traffic emission and the

Table 6

Associations (OR, 95% CI) between covariates and doctor-diagnosed asthma and rhinitis and prevalence of current symptoms by two-level logistic regression models (n = 39,782).

		Doctor-diagnosed asthma	Doctor-diagnosed rhinitis	Wheeze	Rhinitis symptoms	Nocturnal cough
Personal factors						
Sex	Male vs. female	1.55 (1.40, 1.71)***	1.45 (1.32, 1.59)***	1.23 (1.15, 1.31)***	1.19 (1.13, 1.26)***	1.04 (0.97, 1.11)
Age (years)	Continuous (3–6)	1.14 (1.08, 1.20)***	1.20 (1.14, 1.27)***	0.87 (0.84, 0.90)***	0.98 (0.94, 1.01)	0.84 (0.81, 0.87)***
Birth season	Spring (Reference)	1.00	1.00	1.00	1.00	1.00
	Summer vs. spring	1.09 (0.95, 1.25)	1.03 (0.90, 1.17)	1.17 (1.07, 1.28)**	1.03 (0.96, 1.11)	1.03 (0.94, 1.13)
	Autumn vs. spring	0.99 (0.86, 1.13)	0.98 (0.86, 1.12)	1.15 (1.05, 1.26)**	1.06 (0.98, 1.14)	1.05 (0.95, 1.15)
	Winter vs. spring	1.05 (0.92, 1.21)	1.02 (0.89, 1.16)	1.13 (1.02, 1.24)*	1.02 (0.94, 1.10)	0.98 (0.89, 1.08)
Birth weight (kg)	< 2.5 vs. ≥ 2.5	1.21 (0.92, 1.60)	0.64 (0.46, 0.90)**	1.10 (0.90, 1.34)	1.09 (0.93, 1.29)	0.88 (0.71, 1.09)
Breast-feeding	Yes vs. no	0.83 (0.72, 0.96)*	0.86 (0.75, 0.99)*	1.01 (0.91, 1.12)	0.97 (0.89, 1.06)	1.02 (0.91, 1.14)
Parental atopy	Yes vs. no	3.29 (2.95, 3.67)***	5.09 (4.61, 5.62)***	2.27 (2.08, 2.47)***	2.34 (2.15, 2.54)***	1.85 (1.69, 2.02)***
Indoor factors						
Lifetime passive smoking	Yes vs. no	1.03 (0.93, 1.14)	1.11 (1.01, 1.21)*	1.13 (1.06, 1.21)***	1.11 (1.05, 1.17)***	1.05 (0.98, 1.12)
Lifetime mould/dampness†	Yes vs. no	1.25 (1.13, 1.39)***	1.23 (1.11, 1.35)***	1.48 (1.38, 1.58)***	1.34 (1.26, 1.42)***	1.50 (1.39, 1.61)***
Outdoor factors						
Living near traffic	Yes vs. no	1.13 (1.02, 1.25)*	1.14 (1.03, 1.25)**	1.12 (1.05, 1.20)***	1.09 (1.03, 1.15)**	1.10 (1.02, 1.18)**
Lifetime outdoor T	Continuous	1.15 (1.11, 1.20)***	1.07 (1.05, 1.10)***	1.01 (0.99, 1.03)	1.05 (0.99, 1.11)	1.09 (1.06, 1.12)***
Lifetime outdoor NO ₂	Continuous	1.16 (1.02, 1.33)*	1.20 (1.09, 1.32)***	1.13 (1.06, 1.21)***	1.18 (1.02, 1.38)*	1.12 (1.02, 1.24)*
Lifetime outdoor PM ₁₀	Continuous	1.07 (0.95, 1.20)	1.06 (0.96, 1.18)	1.02 (0.94, 1.12)	0.94 (0.74, 1.19)	1.17 (1.12, 1.22)***

Mutual models, one model for each dependent variable, including all personal factors (sex, age, birth season, birth weight, breast-feeding, parental atopy), all indoor factors (lifetime passive smoking, lifetime mould/dampness) and outdoor factors (living near traffic, lifetime outdoor T, lifetime outdoor NO₂), and socioeconomic status (SES) factors (maternal occupation during pregnancy, home size, number of persons living in the current home, current residential area, and GDP per capita).

OR with 95% CI was expressed per degree Celsius and per 10 µg/m³ respectively for lifetime outdoor temperature and NO₂. OR for PM₁₀ was from the model with adjustment for all the variables in Tables 1 and 2, lifetime outdoor temperature and PM₁₀.

#Associations for PM₁₀ were calculated from an alternative model replacing NO₂ with PM₁₀.

* p ≤ 0.05.

** p ≤ 0.01.

*** p ≤ 0.001.

Table 7

Associations (OR, 95% CI) between socioeconomic status (SES), allergic diseases and current symptoms by two-level logistic regression models (n = 39,782).

	Doctor-diagnosed asthma	Doctor-diagnosed rhinitis	Wheeze	Rhinitis symptoms	Nocturnal cough
Maternal occupation during pregnancy					
Not occupationally active*	1.14 (1.03, 1.26)**	1.16 (1.06, 1.28)**	1.06 (0.99, 1.13)	1.12 (1.06, 1.19)***	1.03 (0.96, 1.10)
Farmer	0.61 (0.35, 1.08)	0.30 (0.13, 0.69)**	1.08 (0.82, 1.42)	1.02 (0.81, 1.29)	0.86 (0.62, 1.18)
Industrial worker	1.08 (0.82, 1.42)	1.05 (0.80, 1.38)	1.13 (0.95, 1.34)	1.08 (0.94, 1.25)	1.07 (0.88, 1.29)
White-collar worker†	1.00	1.00	1.00	1.00	1.00
Current home size (m ²)					
≤ 60	1.00	1.00	1.00	1.00	1.00
60–100	1.03 (0.92, 1.16)	1.14 (1.01, 1.28)*	0.99 (0.92, 1.08)	1.14 (1.07, 1.22)***	1.17 (1.07, 1.27)***
> 100	1.05 (0.92, 1.19)	1.44 (1.28, 1.63)***	0.93 (0.86, 1.02)	1.25 (1.17, 1.35)***	1.16 (1.06, 1.27)***
Number of persons living in the current home (n)					
≤ 2	0.89 (0.72, 1.09)	1.02 (0.84, 1.23)	0.97 (0.85, 1.11)	1.05 (0.94, 1.17)	0.91 (0.79, 1.05)
3–4	1.00	1.00	1.00	1.00	1.00
≥ 5	0.92 (0.82, 1.02)	0.89 (0.80, 0.99)*	1.01 (0.94, 1.09)	0.95 (0.90, 1.02)	0.99 (0.92, 1.07)
Current residential area					
Urban	1.00	1.00	1.00	1.00	1.00
Suburban	0.84 (0.75, 0.96)**	0.82 (0.73, 0.93)***	1.17 (1.08, 1.27)***	0.80 (0.75, 0.86)***	0.97 (0.89, 1.06)
Rural	0.41 (0.29, 0.59)***	0.29 (0.19, 0.44)***	1.33 (1.13, 1.55)***	0.68 (0.59, 0.78)***	0.78 (0.65, 0.95)*
Gross domestic product (GDP) per capita					
Lifetime GDP per capita on city level	1.00 (0.96, 1.04)	1.03 (1.01, 1.06)**	0.97 (0.95, 0.99)*	0.99 (0.94, 1.05)	1.02 (0.98, 1.05)

Mutual models, one model for each dependent variable, including all personal factors (sex, age, birth season, birth weight, breast-feeding, parental atopy), all indoor factors (lifetime passive smoking, lifetime mould/dampness) and outdoor factors (living near traffic, lifetime outdoor T, lifetime outdoor NO₂), and socioeconomic status (SES) factors (maternal occupation during pregnancy, home size, number of persons living in the current home, current residential area, and GDP per capita). OR with 95% CI was expressed per 10,000 RenMinBi/capita for GDP on city level.

*House wife (8%) or unemployed (30%); †White-collar worker was defined as office staff (30%), teacher (7%), medical staff (6%), student (4%), shop assistant (1%) and other occupations (9%).

*p ≤ 0.05. **p ≤ 0.01. ***p ≤ 0.001.

exposure to TRAP is less in suburban or rural areas, and thus the overall conclusion from our study is that TRAP could be an important risk factor for asthma, rhinitis and respiratory symptoms among pre-school children in China. This is in agreement with previous studies mainly from western countries (Antó, 2012; Khreis et al., 2017). Moreover, one study among Chinese pre-school children found an association between ambient NO₂ and rhinitis (Liu et al., 2013). For particulate matter (PM₁₀) we found associations for dry cough only. One previous Chinese study in pre-school children found a similar association (Liu et al., 2013). We have no data on PM_{2.5} in our study, but our results indicate that there should be more focus on TRAP in China, not just on PM. We can expect that the significance of TRAP in China will increase in the future.

We found that asthma, rhinitis and night-time dry cough were positively associated with ambient temperature, in models adjusting for outdoor air pollution, city GDP and indoor factors. Worldwide associations between climate and childhood asthma and rhinitis per capita have been analysed in 146 centres participating in the international ISAAC study. Rhino-conjunctivitis was more common at higher ambient temperature among older children (13–14 y) (Weiland et al., 2004). On the northern hemisphere, lower latitude is associated with a higher ambient temperature. One study from Australia reported that associations between latitude and asthma were complex. They found more current asthma among atopic individual living more close to the equator but the opposite association with latitude among non-atopic subjects (Oktaria et al., 2013). The microbial indoor environment is influenced by the ambient temperature. In a warmer climate zone, the prevalence of indoor dampness and mould is higher (Norbäck et al., 2017b; Haverinen-Shaughnessy, 2012) and the fungal diversity can be lower (Amend et al., 2010). Moreover, the indoor level of fungal DNA can be higher and the fungal flora at lower latitudes is more dominated by *Aspergillus* and *Penicillium* species (Norbäck and Cai, 2011). An alternative explanation to our findings could be that in a warmer climate zone, there is more window opening (especially in winter) and this could lead to a higher indoor exposure to outdoor air pollution (a higher indoor/outdoor ratio). The role of UV-B radiation and vitamin D

levels have also been discussed as factors related to climate zone that can influence the prevalence of asthma and allergies (Oktaria et al., 2013).

Different symptoms had different associations with our indicators of SES and urbanization. Rhinitis assessed as doctors' diagnosed rhinitis or as current rhinitis symptoms had similar associations. Rhinitis was positively associated with city level GDP, larger size of the home and negatively associated with crowdedness (family size). This indicates that rhinitis is associated with higher economic development and urbanization. Moreover, for rhinitis there can be a specific protective effect of prenatal exposure to the farm environment, as previously reported (Campbell et al., 2015; Wlasiuk and Vercelli, 2012). However, we should be aware that being exposed to the farm environment means less exposure to air pollution, including TRAP. Thus it can be difficult to differentiate between the protective 'farm factor' and the beneficial effect of being exposed to less outdoor air pollution in China.

Asthma was assessed as doctors' diagnosed asthma or as current asthmatic symptoms (wheeze or dry cough). Doctors' diagnosed asthma was positively associated with degree of urbanization (measured as location of the home), but not linked to our indicators of SES. In contrast, wheeze was more common in cities with lower GDP per capita and more common in suburban and rural areas, indicating that wheeze is associated with lower economic development and less degree of urbanization. Night-time cough was more common in larger homes, indicating an association with higher SES. Thus, associations between different indicators of asthma and SES or urbanization are more complex than associations for rhinitis. All day care centres were located in urban or suburban areas (not rural areas) and all centres had their own health care facilities for the children. Thus, it is less likely that the differences in associations for doctors' diagnosed asthma versus wheeze are due to differences in access to medical services linked to asthma diagnosis. It is more likely that current wheeze reported in a questionnaire by parents of pre-school children in China sometimes reflects symptoms that are not a part of asthma. Different environmental associations for doctors' diagnosed asthma versus current wheeze have been reported among pre-school children in Denmark. Doctors'

diagnosed asthma was positively associated with passive smoking and negatively associated with cat allergen in dust while wheeze was positively associated with di-ethyl-hexyl phthalate (DEHP) and dog allergen in dust (Callesen et al., 2014).

If the mother was not occupationally active (not working) during pregnancy, the prevalence of asthma and rhinitis in their offspring was higher. One explanation could be the economic status of the family, or that the mother spend more time in the home environment with longer prenatal exposure for the child to domestic indoor factors. Another explanation could be selection effects, where mothers with a higher risk of getting a child with asthma or rhinitis tend to avoid being occupationally active. Occupational selection effects in relation to health status, e.g. asthma or allergies in the workforce, are sometimes called “the healthy worker effect”.

In conclusion, higher income per capita, higher ambient temperature, NO₂, TRAP, PM₁₀, passive smoking and indoor mould/dampness can be risk factors for doctor's diagnosed asthma, doctor's diagnosed rhinitis or respiratory symptoms. Current wheeze can be associated with lower SES. Breast feeding, large family size (≥5 persons), a smaller home size (an indicator of lower SES) and farm exposure during pregnancy could be protective for asthma and rhinitis. Since China is a large country with a rapid economic development, there can be a large social impact of health effects due to indoor and outdoor air pollution or socio-economic factors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2018.02.023>.

References

- Amend, A.S., Seifert, K.A., Samson, R., et al., 2010. Indoor fungal composition is geographically patterned and more diverse in temperate zones than in the tropics. *Proc. Natl. Acad. Sci. U. S. A.* 107, 13748–137553.
- Antó, J.M., 2012. Recent advances in the epidemiologic investigation of risk factors for asthma: a review of the 2011 literature. *Curr Allergy Asthma Rep* 12, 192–200.
- Appleton, A.A., Holdsworth, E.A., Kubzansky, L.D., 2016. A systematic review of the interplay between social determinants and environmental exposures for early-life outcomes. *Curr. Environ. Health Rep.* 3, 287–301.
- Asher, M.I., Montefort, S., Björkstén, B., et al., 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phase One and Three repeat multicountry cross-sectional surveys. *Lancet* 368, 733–743.
- Brandt, E.B., Myers, J.M., Ryan, P.H., et al., 2015. Air pollution and allergic diseases. *Curr. Opin. Pediatr.* 27, 724–735.
- Burr, M.L., Wat, D., Evans, C., et al., 2006. Asthma prevalence in 1993, 1988 and 2003. *Thorax* 61, 296–299.
- Callesen, M., Bekö, G., Weschler, C.J., et al., 2014. Associations between selected allergens, phthalates, nicotine, polycyclic aromatic hydrocarbons, and bedroom ventilation and clinically confirmed asthma, rhinoconjunctivitis, and atopic dermatitis in preschool children. *Indoor Air* 24, 136–147.
- Campbell, B.E., Lodge, C.J., Lowe, A.J., et al., 2015. Exposure to ‘farming’ and objective markers of atopy: a systematic review and meta-analysis. *Clin. Exp. Allergy* 45, 744–757.
- Ciaccio, C.E., Gentile, D., 2013. Effects of tobacco smoke exposure in childhood on atopic diseases. *Curr Allergy Asthma Rep* 13, 687–692.
- Deng, Q., Lu, C., Ou, C., et al., 2016. Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children. *Chemosphere* 152, 459–467.
- Haverinen-Shaughnessy, U., 2012. Prevalence of dampness and mold in European housing stock. *J. Expo. Environ. Epidemiol.* 22, 461–467.
- Heinrich, J., 2011. Influence of indoor factors in dwellings on the development of childhood asthma. *Int J Hyg 7. Environ. Health* 214, 1–25.
- Huang, C., Liu, W., Hu, Y., et al., 2015. Updated prevalences of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in Shanghai, China. *PLoS One* 10, e0121577.
- Jassal, M.S., 2015. Pediatric asthma and ambient pollutant levels in industrializing nations. *Int. Health* 7, 7–15.
- Jie, Y., Isa, Z.M., Jie, X., et al., 2013. Urban vs. rural factors that affect adult asthma. *Rev. Environ. Contam. Toxicol.* 226, 33–63.
- Johansson, A., Ludvigsson, J., Hermansson, G., 2008. Adverse health effects related to tobacco smoke exposure in a cohort of three-year olds. *Acta Paediatr.* 97, 354–357.
- Juhn, Y.J., Beebe, T.J., Finnie, D.M., et al., 2011. Development and initial testing of a new socioeconomic status measure based on housing data. *J. Urban Health* 88, 933–944.
- Khreis, H., Kelly, C., Tate, J., et al., 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. *Environ. Int.* 100, 1–31.
- Liu, M.M., Wang, D., Zhao, Y., et al., 2013. Effects of outdoor and indoor air pollution on respiratory health of Chinese children from 50 kindergartens. *J. Epidemiol.* 23, 280–287.
- Mi, Y.H., Norbäck, D., Tao, J., et al., 2006. Current asthma and respiratory symptoms among pupils in Shanghai, China: influence of building ventilation, nitrogen dioxide, ozone and formaldehyde in classrooms. *Indoor Air* 16, 454–464.
- National Cooperation Group on Childhood asthma of China, 1998. Comparative analysis of the state of asthma prevalence in children from two nation-wide surveys in 1990 and 2000. *Chin. J. Pediatr.* 36, 352–355 (in Chinese).
- Norbäck, D., Cai, G.H., 2011. Fungal DNA in hotel rooms in Europe and Asia—associations with latitude, precipitation, building data, room characteristics and hotel ranking. *J. Environ. Monit.* 13, 2895.
- Norbäck, D., Lu, C., Zhang, Y., et al., 2017a. Common cold among pre-school children in China - associations with ambient PM₁₀ and dampness, mould, cats, dogs, rats and cockroaches in the home environment. *Environ. Int.* 103, 13–22.
- Norbäck, D., Zock, J.P., Plana, E., et al., 2017b. Building dampness and mould in European homes in relation to climate, building characteristics and socio-economic status: the European Community Respiratory Health Survey ECRHSII. *Indoor Air* 27, 921–932.
- Oktaria, V., Dharmage, S.C., Burgess, J.A.S., et al., 2013. Associations between latitude and allergic diseases: a longitudinal study from childhood to middle-age. *Ann Allergy Asthma Immunol* 110, 80–85.
- Schröder, P.C., Li, J., Wong, G.W., et al., 2015. The rural-urban enigma of allergy: what can we learn from studies around the world? *Pediatr. Allergy Immunol.* 26, 95–102.
- Sha, L., Shao, M., Liu, C., et al., 2015. The prevalence of asthma in children: a comparison between the year of 2010 and 2000 in urban China. *Zhonghua Jie He He Hu Xi Za Zhi* 38, 664–668 (Article in Chinese).
- Spencer, N.J., Blackburn, C.M., Read, J.M., 2015. Disabling chronic conditions in childhood and socioeconomic disadvantage: a systematic review and meta-analyses of observational studies. *BMJ Open* 5, e007062.
- Strachan, D.P., Ait-Khaled, N., Foliaki, S., et al., 2015. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clin. Exp. Allergy* 45, 126–136.
- Tischer, C., Chen, C.M., Heinrich, J., 2011. Association between domestic mould and mould components, and asthma and allergy in children: a systematic review. *Eur. Respir. J.* 38, 812–824.
- Tzivian, L., 2011. Outdoor air pollution and asthma in children. *J. Asthma* 48, 470–481.
- Victora, C.G., Bahl, R., Barros, A.J., et al., Lancet Breastfeeding Series Group, 2016. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 387 (10017), 475–490.
- Weiland, S.K., Hüsing, A., Strachan, D.P., et al., 2004. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup. Environ. Med.* 61 (609–605).
- WHO Guidelines Approved by the Guidelines Review Committee, 2009. WHO Guidelines for Indoor Air Quality: Dampness and Mould. World Health Organization, Geneva.
- Wlasiuk, G., Vercelli, D., 2012. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. *Curr. Opin. Allergy Clin. Immunol.* 12, 461–466.
- Zhang, Y.P., Li, B.Z., Huang, C., et al., 2013. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. *Chin. Sci. Bull.* 58, 4182–4189.
- Zhao, Z.H., Elfman, L., Wang, Z.H., et al., 2006. A comparative study on asthma, pollen, cat and dog allergy among pupils and allergen levels in schools in Taiyuan city, China and Uppsala, Sweden. *Indoor Air* 16, 404–413.

Supplemental materials
Table S1

Pearson correlation between lifetime annual GDP per capita, outdoor temperature and concentration of ambient air pollutants on city level in the seven cities.

	GDP per capita	T	PM ₁₀	SO ₂	NO ₂
GDP per capita	1.00	0.17 **	-0.46 **	-0.73 **	0.37 **
T		1.00	-0.71 **	-0.68 **	-0.24 **
PM ₁₀			1.00	0.60 **	0.41 **
SO ₂				1.00	0.02 **
NO ₂					1.00

** Correlation is significant at the 0.01 level

Lifetime-exposure was calculated for each child (n=39,782), based on annual data from birth to the questionnaire survey

Table S2

Associations (OR, 95% CI) between covariates and allergic diseases and current symptoms among children living in the same home since birth by two-level logistic regression models (n=24,350)

		Doctor-diagnosed asthma	Doctor-diagnosed rhinitis	Wheeze	Rhinitis symptoms	Nocturnal cough
Personal factors						
Sex	Male vs. female	1.64 (1.45, 1.85)***	1.42 (1.26, 1.60)***	1.20 (1.11, 1.31)***	1.20 (1.12, 1.29)***	1.05 (0.97, 1.15)
Age (years)	Continuous (3-6)	1.21 (1.12, 1.29)***	1.24 (1.17, 1.33)***	0.89 (0.84, 0.93)***	0.99 (0.95, 1.04)	0.84 (0.80, 0.89)***
Birth season	Spring	1.00	1.00	1.00	1.00	1.00
	Summer vs. spring	1.06 (0.89, 1.26)	1.06 (0.90, 1.25)	1.18 (1.05, 1.33)**	1.04 (0.95, 1.15)	1.06 (0.94, 1.19)
	Autumn vs. spring	0.95 (0.80, 1.13)	0.97 (0.83, 1.15)	1.15 (1.02, 1.29)*	1.06 (0.97, 1.17)	1.03 (0.91, 1.16)
	Winter vs. spring	1.08 (0.91, 1.28)	1.00 (0.85, 1.18)	1.13 (1.00, 1.27)	1.03 (0.93, 1.13)	0.99 (0.87, 1.12)
Birth weight (kg)	<2.5 vs. ≥2.5	1.10 (0.75, 1.59)	0.63 (0.41, 0.97)*	0.97 (0.74, 1.26)	1.04 (0.84, 1.29)	0.94 (0.71, 1.25)
Breast-feeding	Yes vs. no	0.75 (0.63, 0.89)***	0.93 (0.78, 1.12)	0.94 (0.83, 1.07)	1.00 (0.90, 1.12)	1.08 (0.94, 1.25)
Parental atopy	Yes vs. no	3.11 (2.70, 3.58)***	5.10 (4.49, 5.78)***	2.24 (2.01, 2.50)***	2.29 (2.06, 2.54)***	1.85 (1.65, 2.07)***
Indoor factors						
Lifetime passive smoking	Yes vs. no	1.03 (0.91, 1.17)	1.15 (1.02, 1.30)*	1.15 (1.06, 1.26)***	1.13 (1.05, 1.21)***	1.07 (0.97, 1.17)
Lifetime mould/dampness †	Yes vs. no	1.32 (1.16, 1.50)***	1.19 (1.06, 1.35)**	1.47 (1.34, 1.60)***	1.34 (1.24, 1.45)***	1.58 (1.44, 1.73)***
Outdoor factors						
Living near traffic	Yes vs. no	1.22 (1.08, 1.38)**	1.16 (1.03, 1.30)*	1.11 (1.02, 1.21)*	1.11 (1.03, 1.19)**	1.09 (1.00, 1.19)
Lifetime outdoor T	Continuous	1.16 (1.11, 1.22)***	1.09 (1.06, 1.12)***	1.00 (0.98, 1.03)	1.06 (0.99, 1.13)	1.09 (1.06, 1.11)***
Lifetime outdoor NO ₂	Continuous	1.09 (0.93, 1.29)	1.27 (1.13, 1.43)***	1.17 (1.08, 1.27)***	1.24 (1.05, 1.48)*	1.16 (1.06, 1.28)**
Lifetime outdoor PM ₁₀ #	Continuous	1.04 (0.91, 1.18)	1.09 (0.96, 1.23)	1.03 (0.94, 1.14)	0.96 (0.69, 1.33)	1.16 (1.10, 1.23)***

Mutual models, one model for each dependent variable, including all personal factors (sex, age, birth season, birth weight, breast-feeding, parental atopy), all indoor factors (lifetime passive smoking, lifetime mould/dampness) and outdoor factors (living near traffic, lifetime outdoor T, lifetime outdoor NO₂), and socioeconomic status (SES) factors (maternal occupation during pregnancy, home size, number of persons living in the current home, current residential area, and GDP per capita).

OR with 95% CI was expressed per degree Celsius and per 10 µg/m³ respectively for lifetime outdoor temperature and NO₂. OR for PM₁₀ was from the model with adjustment for all the variables in Table 1 and Table 2, lifetime outdoor temperature and PM₁₀.

† mould/dampness was defined as visible mould or damp stains on the floor, wall, and ceiling in the children's bedroom, and/or water damage in the house, from birth to the time of the questionnaire survey.

#Associations for PM₁₀ were calculated from an alternative model replacing NO₂ with PM₁₀

* p≤0.05 ** p≤0.01 *** p≤0.001

Table S3

Associations (OR, 95% CI) between indicators of socioeconomic status (SES), allergic diseases and current symptoms among children living in the same home since birth by two-level logistic regression models (n=24,350)

	Doctor-diagnosed asthma	Doctor-diagnosed rhinitis	Wheeze	Rhinitis symptoms	Nocturnal cough
Maternal occupation during pregnancy					
Not occupationally active *	1.18 (1.04, 1.33)*	1.14 (1.01, 1.28)*	1.13 (1.04, 1.23)**	1.07 (1.00, 1.15)	0.98 (0.89, 1.07)
Farmer	0.72 (0.35, 1.50)	0.28 (0.09, 0.88)*	1.07 (0.72, 1.59)	1.07 (0.77, 1.48)	0.83 (0.53, 1.31)
Industrial worker	1.01 (0.72, 1.43)	1.22 (0.89, 1.68)	1.11 (0.89, 1.38)	1.20 (0.99, 1.44)	1.12 (0.89, 1.42)
White-collar worker †	1.00	1.00	1.00	1.00	1.00
Home size (m²)					
≤60	1.00	1.00	1.00	1.00	1.00
60-100	0.99 (0.85, 1.15)	1.02 (0.87, 1.18)	0.92 (0.83, 1.03)	1.11 (1.02, 1.21)*	1.10 (0.98, 1.22)
>100	1.02 (0.87, 1.21)	1.34 (1.15, 1.57)***	0.90 (0.80, 1.00)	1.24 (1.13, 1.36)***	1.08 (0.96, 1.21)
Number of persons living in the home (n)					
<3	0.86 (0.66, 1.12)	1.08 (0.85, 1.37)	1.04 (0.87, 1.24)	1.11 (0.96, 1.28)	0.89 (0.74, 1.07)
3-4	1.00	1.00	1.00	1.00	1.00
>4	0.90 (0.79, 1.03)	0.91 (0.80, 1.03)	1.08 (0.98, 1.19)	0.99 (0.91, 1.07)	1.01 (0.92, 1.11)
Residential area					
Urban	1.00	1.00	1.00	1.00	1.00
Suburban	0.88 (0.75, 1.03)	0.79 (0.67, 0.92)**	1.18 (1.06, 1.31)**	0.77 (0.70, 0.84)***	1.02 (0.91, 1.15)
Rural	0.45 (0.28, 0.72)***	0.26 (0.14, 0.47)***	1.23 (0.99, 1.54)	0.67 (0.56, 0.82)***	0.88 (0.68, 1.12)
Gross domestic product (GDP) per capita					
Lifetime GDP per capita on city level	1.01 (0.97, 1.05)	1.04 (1.02, 1.06)***	0.96 (0.94, 0.99)**	1.00 (0.93, 1.06)	1.00 (0.98, 1.03)

Mutual models, one model for each dependent variable, including all personal factors (sex, age, birth season, birth weight, breast-feeding, parental atopy), all indoor factors (lifetime passive smoking, lifetime mould/dampness) and outdoor factors (living near traffic, lifetime outdoor T, lifetime outdoor NO₂), and socioeconomic status (SES) factors (maternal occupation during pregnancy, home size, number of persons living in the current home, current residential area, and GDP per capita). OR with 95% CI was expressed per 10,000 RenMinBi/capita for GDP on city level.

* p≤0.05 ** p≤0.01 *** p≤0.001.

* House wife (8%) or unemployed (30%); † White-collar worker was defined as office staff (30%), teacher (7%), medical staff (6%), student (4%), shop assistant (1%) and other occupations (9%).