



Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: Synergistic effects between antibiotics use and PM₁₀ and second hand smoke

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ABSTRACT

We studied indoor sources of indoor particulate matter (PM), outdoor air pollution and antibiotic use in relation to asthma, rhinitis and eczema among pre-school children and investigated synergistic effects between PM and antibiotics use. Children (3–6y) from randomly selected day care centres in seven cities across China were included ($n = 39,782$). Data on ambient temperature and air pollution were collected from local monitoring stations. Data on indoor PM sources (ETS, burning of incense or mosquito coils and biomass for cooking), antibiotics use and health (doctor diagnosed asthma and rhinitis, lifetime eczema, current wheeze and current rhinitis) were assessed by a parental questionnaire. Associations were calculated by multilevel logistic regression. Asthma diagnosis was associated with outdoor temperature, NO₂ and burning mosquito coils. Rhinitis diagnosis was associated with NO₂, ETS, gas cooking and burning biomass for cooking. Lifetime eczema was associated with temperature, PM₁₀, NO₂, ETS, biomass cooking and burning mosquito coils. Burning incense was associated with current wheeze and current rhinitis. Children using antibiotics had more asthma, wheeze, rhinitis, and eczema. Excluding children with respiratory infections did not change associations with antibiotics use. Antibiotics use enhanced the effects of ETS and PM₁₀ (a synergistic effect). In conclusion, a warmer climate, outdoor NO₂ and PM₁₀, ETS, gas cooking and burning biomass, incense and mosquito coils can increase the risk of asthma, wheeze, rhinitis and eczema among pre-school children in China. Antibiotics use is a risk factor for childhood asthma, wheeze, rhinitis and eczema and ETS and outdoor PM₁₀ can enhance the effect.

1. Introduction

The ISAAC study has demonstrated a global increase of asthma and allergic diseases, especially in middle-income countries (Asher et al., 2006). China is a large middle-income country with a considerable

increase of childhood asthma in the past decades (Zhang et al., 2013; Sha et al., 2015). Thus, there is a need to identify major risk factors linked to this increase to improve the situation. Prenatal and postnatal early life exposure to outdoor air pollution can be a risk factor for the development of asthma (Goldizen et al., 2016; Khreis et al., 2017),

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rhinitis (Deng et al., 2016) and allergic disease (Brandt et al., 2015). Pre-natal exposure may influence the pre-natal programming of the immune system (Gollwitzer and Marsland, 2015). Postnatal exposure to air pollution can cause neutrophilic (Alexis and Carlsen, 2014) and eosinophilic inflammation (Eckel et al., 2016). China has high levels of indoor and outdoor air pollution concluded to contribute substantially to the burden of chronic respiratory diseases (Guan et al., 2016).

In China, indoor sources of particulate mass (PM) include environmental tobacco smoke (ETS), cooking by biomass (coal or wood), burning incense and burning mosquito coils. ETS is a well-known risk factor for childhood asthma and allergy (Heinrich, 2011; Feleszko et al., 2014). In less developed countries, cooking by biomass is a well-recognized cause of increased incidence and exacerbation of respiratory disease (Laumbach and Kipen, 2012). In Asia, it is common to burn incense in temples and in homes which produces emissions of aldehydes, VOC, PAHs and high levels of fine PM (Lin et al., 2008). Exposure to smoke from incense can increase the prevalence of childhood asthma (Wang et al., 2011) and respiratory symptoms (Wang et al., 2011; Yang et al., 1997). Moreover, it is common in Asia to burn mosquito repellent incense (also called mosquito coils). Burning mosquito coils produces various aldehydes and high levels of fine PM which may cause respiratory illness (Wang et al., 2018a, 2018b; Liu et al., 2003) but few epidemiological studies exist on this topic (Yang et al., 1997). The main source of indoor NO₂ emission is gas cooking. A recent review article concluded that gas cooking is a risk factor for childhood asthma and wheeze (Lin et al., 2013).

Recently, there has been a focus on human microbiota and microbial biodiversity in relation to health and disease (Karkman et al., 2017). The early-life microbiome has been recognized as a major influence on long-term human health and development (Stiemsma and Michels, 2018). The microbiome of the gastrointestinal tract (GIT) can balance the activities of the Th1 and Th2 cells and the microbiome of the lung can influence the development of asthma linked to Th2 response (Pascal et al., 2018; McCoy et al., 2018) and there is a link between the gut and the lung microbiome (the gut-lung axis) (Mathieu et al., 2018). Early life exposure to antibiotics can disturb the GIT microflora and cause GIT dysbiosis (Neuman et al., 2018) which can increase the risk of developing asthma and allergic diseases (Kuo et al., 2013; Munyaka et al., 2014). Several studies have found that early life use of antibiotics can increase the risk of childhood asthma (Ahmadizar et al., 2017; Kozyrskyj et al., 2007; Raciborski et al., 2012; Risnes et al., 2011), eczema (Tsakok et al., 2013) and allergic diseases (Raciborski et al., 2012; Risnes et al., 2011; Wang et al., 2013). Broad spectrum antibiotics have been pointed out as especially problematic (Kozyrskyj et al., 2007). Most of these studies are from western countries. However, one review article concluded that protopathic bias can be a confounder in these studies (Murk et al., 2011). Protopathic bias occurs when early symptoms of undiagnosed asthma are attributed by mistake to respiratory infection and are treated with antibiotics. Thus it is important to control for respiratory infections in epidemiological studies on health effects of early life exposure to antibiotics.

There is more and more evidence suggesting that air pollution, especially particulate matter (PM), can influence the microbiota. A recent review concluded that air pollution could change the gut microbial diversity and cause microbiome dysfunction (Vallès and Francino, 2018). Exposure to particle matter (PM) can cause a release of inflammatory cytokines and increase the gut permeability in mice (Mutlu et al., 2011). Another study found that inhalation exposure to PM_{2.5} changed mice gastro-intestinal microbial diversity and composition (Mutlu et al., 2018). Another inhalation study in mice found that chronic exposure to PM_{2.5} causes gut dysbiosis (Wang et al., 2018a, 2018b). Moreover, one mice study found that oral ingestion of PM₁₀ from an urban environment altered the gut microbiota composition and caused an inflammatory response in the intestine (Kish et al., 2013). Finally, one panel study among health subjects found that exposure to PM_{2.5} and PM₁₀ altered the nasal microbiota (Mariani et al., 2018).

China has a high exposure to PM air pollution and antibiotics. Even broad spectrum antibiotics are commonly used and are available even without a doctor's prescription. We found no previous epidemiological study on synergistic effects (interaction) between early life exposure to air pollution and antibiotics use in relation to childhood asthma and allergic disease. During 2010–2012, the multicentre study China-Children-Homes-Health (CCHH) was performed to study associations between the home environment and asthma, allergy and respiratory health among pre-school children (Zhang et al., 2013). The first aim of this article was to study indoor PM sources (environmental tobacco smoke, cooking by biomass burning, incense burning, burning of mosquito coils) and outdoor air pollution (PM₁₀ and NO₂) in relation to asthma, rhinitis and eczema. The second aim was to study associations between early life exposure to antibiotics and asthma, rhinitis and eczema. The third aim was to investigate synergistic effects (interaction) between antibiotics use and indoor and outdoor air pollutants (as mentioned above) in relation to childhood asthma, rhinitis and eczema. By investigating health association for early life exposure to antibiotics, indoor PM sources, outdoor air pollution, as well as interaction between PM exposure and antibiotics use, we want to contribute to the identification of important risk factors possibly linked to the ongoing increase of childhood asthma and allergic disease in China.

2. Materials and methods

2.1. CCHH study population

The study population consisted of pre-school children recruited from randomly selected day care centres in seven major cities in three northern cities (Urumqi, Beijing, Taiyuan) and four southern cities (Nanjing, Shanghai, Chongqing and Changsha) in China (Fig. 1). All children in the selected day care centres were invited to participate. A questionnaire was distributed to the parents or other guardians. A total of 55,301 questionnaires were distributed and 77% participated. The current study was restricted to children 3–6 years old with information on age and sex of the child. Finally, 39,782 children were included and 66.7% were from southern China. Details on the CCHH study have 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.

2.2. Assessment of demographic data

Data on gender, age, birth season, low birth weight (< 2.5 kg), breast feeding, parental asthma or rhinitis, size of the home (m²), number of persons living in the current home, lifetime environmental tobacco smoke (ETS) location of the current home (urban, suburban, rural), and living near (< 200 m) from major roads with heavy traffic were collected from the questionnaire. These covariates were adjusted for in all models. We did not have the home address of the children.

2.3. Assessment of health

There was one yes/no questions asking if the child had ever been diagnosed by a doctor for asthma, and another yes/no question on lifetime ever doctors' diagnosed rhinitis. There were two yes/no questions about eczema. One question asked "Has your child ever had eczema lasting for at least 6 months, diagnosed by a doctor?" The second question asked "Has your child had eczema at any time in the last 12 months, diagnosed by a doctor?" These two questions were combined to one eczema variable (ever eczema). One yes/no question asked about wheeze in the last 12 months. Another question asked about rhinitis in the last 12 months. Moreover, there were two questions about infections use in sensitivity analysis. One question asked about lifetime-ever pneumonia (Norbäck et al., 2018) and another about the

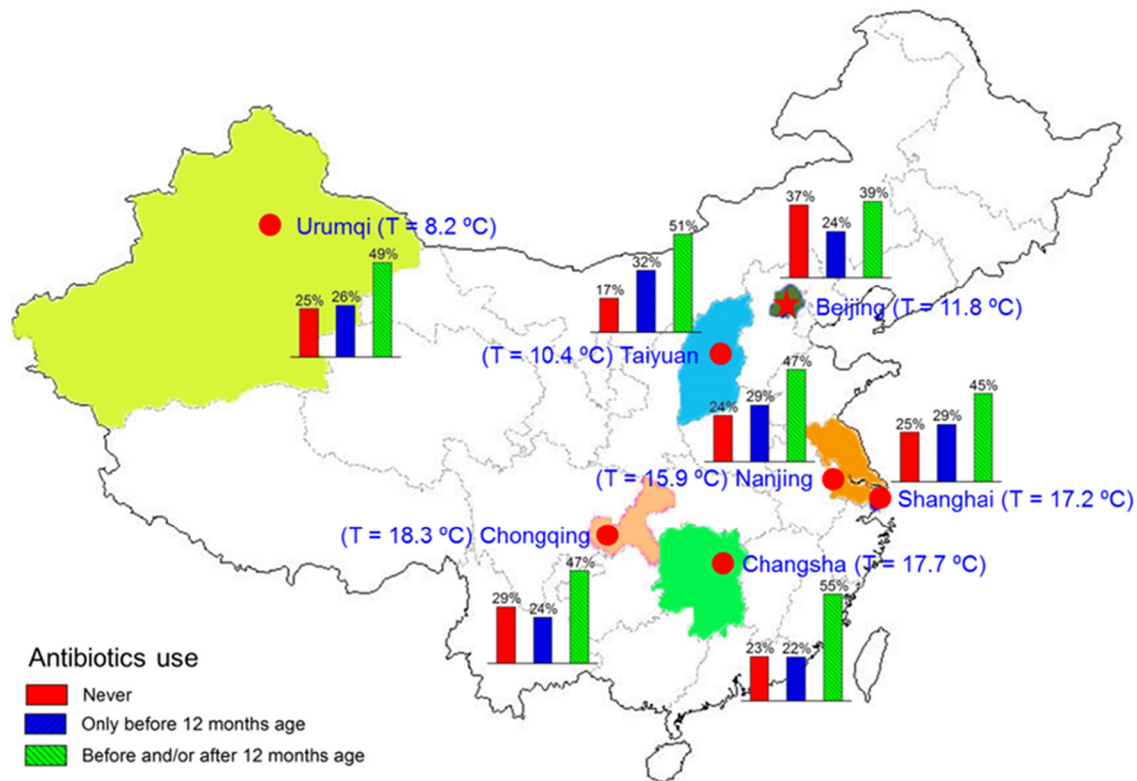


Fig. 1. Distribution of the seven cities that participated in the nationwide “China-Child-Home-Health (CCHH)” survey.

duration of common cold (Norbäck et al., 2017a, 2017b).

2.4. Assessment of meteorological data and outdoor air pollution (PM_{10} and NO_2)

Annual mean data on ambient temperature during 2005–2012 was obtained for each city from the website of Weather Underground (<https://www.wunderground.com>). Annual mean data on PM_{10} and NO_2 during 2005–2012 were downloaded for each city 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. Each city had 7 to 17 air pollution monitoring stations and 8 to 33 monitoring stations for climate (including temperature). 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. Data on SO_2 were available but not included because of a strong positive correlation between SO_2 and PM_{10} and a strong negative correlation between SO_2 and temperature.

2.5. Assessment of antibiotic use

One question asked if the child had ever used antibiotics, with three alternatives: never, first year of life, and after first year of life. More than one alternative could be answered. Another question asked about the frequency of antibiotics use in the first year of life (never, one time, more than one time).

2.6. Statistical analysis

Multilevel logistic regression was used to study associations between early life exposure to antibiotics, outdoor temperature and air pollution and the five health variables. Two levels were used (city and child). We included the co-variables in all models (gender, age, birth season, low birth weight, breast feeding, parental asthma or rhinitis,

size of the home, number of persons in the home, location of the dwelling, ETS in the dwelling, ambient temperature and ambient PM_{10}). PM_{10} was selected as the main air pollutant to be included in all models since ambient particle air pollution is a major health issue in China. To evaluate health associations for NO_2 , we replaced PM_{10} by NO_2 in additional models. Birth season was coded as a categorical variable with spring as the 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. The timing of antibiotic use was coded as a categorical variable at three levels, never, first year of life only, and first year and/or after first year of life, with never as reference category. The frequency of antibiotic use in the first year of life was coded as a categorical variable, with never as reference category. We analysed associations between antibiotics use (one model for timing and another for frequency) and the five health variables, adjusting for the covariates (one model for each health variables). Then we repeated the analysis excluding those with infections (lifetime-ever pneumonia and long duration (> 2 weeks) of common cold). Moreover, we tested statistical interactions of selected particle exposure (ETS, PM_{10} , burning mosquito coils and incense burning) on associations between antibiotic use and the six health variables. In the interaction analysis, PM_{10} was classified into a low and a high exposure group, based on the median. Odds ratios (ORs) with 95% confidence interval (95% CI) were calculated. A two-tailed p-value < 0.05 was considered as significant. $p < 0.1$ was considered as significant for statistical interaction. We used STATA11.0 (STATA Corp., Texas, USA) for the statistical calculations.

3. Results

3.1. Descriptive data

Data on the health variables per city is given in Table 1. In the total

Table 1

Number and prevalence of doctor-diagnosed allergic diseases and current symptoms among children (3–6 years) (n = 39,782).

	Number (n)	Doctor diagnosed asthma ^a		Doctor diagnosed rhinitis ^a		Lifetime eczema ^a		Current wheeze ^b		Current rhinitis ^b	
		Case (n)	(%)	Case (n)	(%)	Case (n)	(%)	Case (n)	(%)	Case (n)	(%)
Urumqi	4302	149	(3.5)	342	(7.9)	1874	(34.2)	926	(16.9)	2731	(49.9)
Beijing	5478	333	(6.1)	405	(7.4)	1471	(29.7)	978	(19.8)	1929	(39.0)
Taiyuan	3453	69	(2.0)	110	(3.2)	1057	(28.7)	726	(19.7)	1678	(45.5)
Nanjing	3349	296	(8.8)	295	(8.8)	942	(28.1)	591	(17.6)	2054	(61.3)
Shanghai	14,570	1448	(9.9)	1739	(11.9)	3080	(21.1)	3095	(21.2)	6506	(44.7)
Chongqing	4945	393	(7.9)	290	(5.9)	478	(13.8)	524	(15.2)	1098	(31.8)
Changsha	3685	248	(6.7)	282	(7.7)	671	(15.6)	991	(23.0)	1913	(44.5)
Total	39,872	2936	(7.4)	3463	(8.7)	9573	(24.1)	7831	(19.7)	17,909	(45.0)

^a Cumulative incidence (life-time ever had).^b In the last 12 months.**Table 2**

Covariates and demographic information among children (3–6 years) (n = 39,782).

	Number (n)	Proportion (%)
Total	39,782	(100)
Sex		
Boys	20,633	(52)
Girls	19,149	(48)
Age (year)		
3	7285	(18)
4	14,060	(35)
5	12,187	(31)
6	6250	(16)
Birth season		
Spring (March–May)	9331	(23)
Summer (June–August)	9934	(25)
Autumn (September–November)	10,072	(25)
Winter (December–February)	9374	(24)
Birth weight (kg)		
< 2.5	977	(2)
≥ 2.5	37,668	(95)
Breast-feeding		
Yes	34,494	(87)
Parental atopy (asthma or rhinitis)		
Yes	4854	(12)
House size (m ²)		
≤ 100	26,799	(67)
> 100	11,837	(30)
Number of persons living in the home (n)		
2	5794	(15)
3–4	21,174	(53)
> 4	9879	(25)
Lifetime environmental tobacco smoke (ETS)		
Yes	22,176	(56)
Residential area		
Urban	29,262	(74)
Suburban	7786	(20)
Rural	1520	(4)
Living near major roads with heavy traffic (< 200 m)		
Yes	13,666	(34)

Sum of the number is not 39,782 due to missing data.

material (N = 39,782), 7.4% had doctor diagnosed asthma (lifetime ever), 8.7% doctor diagnosed rhinitis (lifetime ever), 24.1% eczema (lifetime ever), 19.7% current wheeze (in the last 12 months) and 45.0% current rhinitis (in the last 12 months). Data on the co-variables are given in Table 2. Use of antibiotics per city is given in Fig. 1. Data on ambient temperature, air pollution and type of cooking fuel, incense burning and burning of mosquito coils per city is given in Table 3. In the total material, median life-time temperature was 17.1 °C (range of 7.6–18.9), lifetime median PM₁₀ 91.9 µg/m³ (range of 77–140) and lifetime median NO₂ 51.4 µg/m³ (range of 36–68). The official air pollution website only gives annual mean values per city (not for each monitoring station). Annual means for PM₁₀ and NO₂ for each city from

2005 to 2012 is given in Table S1. To describe the spatial variation within a city, we have been able to get data from each local monitoring station for the city of Changsha for a period relevant for this study (2005–2010) (Table S2).

3.2. Associations between outdoor environment and health

Outdoor temperature was associated with doctor diagnosed asthma (OR 1.18 per 1 °C) and lifetime eczema (OR 1.13 per 1 °C). Outdoor PM₁₀ was associated with lifetime eczema (OR 1.17 per 10 µg/m³), only. Outdoor NO₂ was associated with doctor diagnosed asthma (OR 1.19 per 10 µg/m³), doctor diagnosed rhinitis (OR 1.28 per 10 µg/m³), lifetime eczema (OR 1.16 per 10 µg/m³), current wheeze (OR 1.13 per 10 µg/m³) and current rhinitis (OR 1.21 per 10 µg/m³) (Table 4).

3.3. Associations between indoor PM sources and health

Lifetime ETS was associated with doctor diagnosed rhinitis (OR 1.13), lifetime eczema (OR 1.06), current wheeze (OR 1.18) and current rhinitis (OR 1.12). Gas cooking was associated with doctor diagnosed rhinitis (OR 1.23), only. Biomass cooking was associated with doctor diagnosed rhinitis (OR 1.35), lifetime eczema (OR 1.21) and current rhinitis (OR 1.16). Burning mosquito coils was associated with doctor diagnosed asthma (OR 1.13), lifetime eczema (OR 1.15), current wheeze (OR 1.12) and current rhinitis (OR 1.19). Incense burning was associated with current wheeze (OR 1.20) and current rhinitis (OR 1.25) (Table 4).

3.4. Associations between antibiotics use and health

Use of antibiotics was associated with all five health variables with stronger associations if antibiotics had been used for longer time (not just in the first year of life). Results were similar if we restricted the analysis to children who never had pneumonia and did not have a long duration (> 2 weeks) of common cold. There was a dose-dependent association between use of antibiotics in the first year of life and the health variables. Associations were similar in the restricted analysis but with somewhat lower ORs (Table 5).

3.5. Statistical interaction between antibiotics use and environmental exposure

Finally, we investigated statistical interaction (p < 0.1) of outdoor PM₁₀ and indoor PM sources (ETS, incense and mosquito coil burning) on associations between antibiotics use and doctor diagnosed asthma and doctor diagnosed rhinitis. ETS enhanced the effect of any antibiotics use on doctor diagnosed asthma (p-value for interaction 0.019). Moreover, ETS enhanced the effect of antibiotics in the first year of life on doctor diagnosed rhinitis (p-value for interaction 0.097). High lifetime outdoor PM₁₀ exposure enhanced the effect of any antibiotics use

Table 3Indoor particulate matters (PMs) pollution and lifetime outdoor temperature, PM₁₀, and NO₂ among children (n = 39,782).

City	Cooking fuel (n, %)			Mosquito coils		Incense burning		T		PM ₁₀		NO ₂	
	Only electricity	Natural gas but no biomass	Any biomass (coal/wood)	N	(%)	N	(%)	Median	(Min-max)	Median	(Min-max)	Median	(Min-max)
Urumqi	55 (1.3)	3622 (84.2)	187 (4.3)	170 (4.0)		548 (12.7)		8.0	(7.6–8.1)	137 (135–140)		67 (66–68)	
Beijing	184 (3.4)	4882 (89.1)	119 (2.2)	1112 (20.3)		674 (12.3)		13.2	(13.1–13.4)	120 (118–131)		55 (54–58)	
Taiyuan	600 (17.4)	2361 (68.4)	118 (3.4)	569 (16.5)		230 (6.7)		11.0	(11.0–11.2)	92 (91–107)		22 (22–23)	
Nanjing	494 (14.8)	2515 (75.1)	114 (3.4)	741 (22.1)		321 (9.6)		16.4	(16.2–16.6)	103 (102–106)		50 (48–51)	
Shanghai	2147 (14.7)	9734 (66.8)	1794 (12.3)	3514 (24.1)		1717 (11.8)		17.2	(17.0–17.5)	81 (77–83)		53 (49–53)	
Chongqing	665 (13.4)	3773 (76.3)	224 (4.5)	1136 (23.0)		807 (16.3)		18.8	(18.7–18.9)	105 (100–109)		41 (36–43)	
Changsha	382 (10.4)	2976 (80.8)	94 (2.6)	537 (14.6)		993 (26.9)		18.2	(18.2–18.4)	89 (86–95)		44 (43–45)	
Total	4527 (11.4)	29,863 (75.1)	2650 (6.7)	7779 (19.6)		5290 (13.3)		17.1	(7.6–18.9)	92 (77–140)		51 (22–68)	

Sum of the number is not 39,782 due to missing data.

T (°C) = temperature, PM₁₀ (µg/m³) = particulate matter ≤ 10 µm in aerodynamic, NO₂ (µg/m³) = nitrogen dioxide.

(p-value for interaction 0.008) and antibiotics in the first year of life (p-value for interaction 0.046) on doctor diagnosed asthma. We found no significant statistical interaction effects for incense or mosquito coil burning (Tables 6 and 7).

4. Discussion

We found that early life antibiotics use was associated with asthma, wheeze, rhinitis and eczema, in a dose dependent way. Associations remained significant even when excluding children with a life time history of pneumonia or long duration of common cold. Lifetime exposure to PM₁₀, NO₂ and high ambient temperature were risk factors for asthma, wheeze, rhinitis or eczema. Moreover, gas cooking and indoor sources of PM (ETS, biomass burning, burning incense and mosquito coils) were associated with asthma, wheeze, rhinitis or eczema. Moreover, we found that outdoor PM₁₀ and ETS could enhance the associations between early life antibiotic use and doctor diagnosed asthma and rhinitis, to our knowledge, this is a new finding.

The children were recruited from randomly selected day care centres in seven cities and all were invited to participate. About 80% of all Chinese children aged 3–6 years attend a day care centre (Norbäck et al., 2017a) and in urban areas the attendance is even higher. The one child policy was still valid when the study was performed and thus most of the children had no siblings. We collected information on use of antibiotics and doctor diagnosed asthma, rhinitis, eczema and current symptoms by a parentally administered questionnaire, based on the ISAAC questionnaire (Asher et al., 2006).

We included children aged 3–6 years, which was the majority of the

children in the CCHH study. After 6 years of age the children normally start school. Before 3 years of age, most children stay home taken care by grandparents or another person. Only few children go to a day care center before 3 year age, and then they stay in special units for small children only. By selecting age range 3–6 year we got more representative children for the study.

The study has several strengths. It is a large study including pre-school children from different parts of China. The response rate was good (77%) and the day care centers were randomly selected. Thus it is less likely that the study was influenced by selection bias. The study adds new knowledge on the health risks of outdoor air pollution in China, especially for early life NO₂ exposure. It also adds knowledge on health risks of antibiotic use in China and new knowledge on paediatric health risks of burning incense and mosquito coils. Moreover, it adds new knowledge on possible synergistic effects between PM exposure and antibiotic use.

The study has some limitations. One limitation is that it covers mainly urban areas. Another issue is recall bias. Recall bias can occur when there are subjective reports on exposure as well as symptoms, sometimes called “auto-suggestion” effect. In China, the main focus has been on outdoor air pollution. Health risks linked to indoor PM exposure or early life antibiotics use has not been a public health issue. Thus the observed associations between indoor PM sources or antibiotics use and asthma, wheeze, rhinitis and eczema are not likely due to the “auto-suggestion” effect. Data on outdoor temperature and air pollution were from monitoring stations and should not be affected by information bias. Studies on association between early-life antibiotic exposure can be affected by protopathic bias. However, associations

Table 4Associations (OR, 95% CI) between lifetime outdoor temperature, PM₁₀, and NO₂ and childhood allergic diseases and symptoms by two-level logistic regression models (n = 39,782).

	Doctor diagnosed asthma ^a	Doctor diagnosed rhinitis ^a	Lifetime eczema ^a	Current wheeze ^b	Current rhinitis ^b
T ^c	1.18 (1.11, 1.25)***	1.05 (0.97, 1.14)	1.13 (1.08, 1.19)***	1.02 (0.98, 1.06)	1.04 (0.97, 1.12)
PM ₁₀ ^c	1.07 (0.96, 1.20)	1.02 (0.88, 1.18)	1.17 (1.06, 1.28)***	1.06 (0.98, 1.14)	1.03 (0.92, 1.15)
NO ₂ ^c	1.19 (1.06, 1.34)**	1.28 (1.15, 1.42)***	1.16 (1.01, 1.35)*	1.13 (1.06, 1.22)***	1.21 (1.06, 1.39)**
Lifetime ETS	1.07 (0.98, 1.18)	1.13 (1.04, 1.23)**	1.06 (1.00, 1.12)*	1.18 (1.11, 1.25)***	1.12 (1.07, 1.18)***
Cooking fuel-only electricity	1.00	1.00	1.00	1.00	1.00
Cooking fuel-natural gas but no biomass	0.93 (0.80, 1.08)	1.23 (1.06, 1.44)**	0.98 (0.89, 1.08)	1.02 (0.93, 1.13)	1.04 (0.96, 1.13)
Cooking fuel-any biomass (coal/wood)	1.09 (0.88, 1.35)	1.35 (1.10, 1.66)**	1.21 (1.06, 1.39)**	1.07 (0.93, 1.24)	1.16 (1.03, 1.30)*
Mosquito coil burning	1.13 (1.02, 1.26)*	1.09 (0.98, 1.21)	1.15 (1.07, 1.23)***	1.12 (1.04, 1.20)**	1.19 (1.12, 1.27)***
Incense burning	0.95 (0.83, 1.08)	0.90 (0.80, 1.03)	1.08 (1.00, 1.17)	1.20 (1.10, 1.30)***	1.25 (1.16, 1.34)***

Models were adjusted for all the covariates in Table 2, antibiotics use, lifetime outdoor PM₁₀/NO₂ and lifetime outdoor temperature.^a Cumulative incidence (life-time ever had).^b In the last 12 months.^c OR (95% CI) was estimated for 1 °C for lifetime T and 10 µg/m³ increase in lifetime PM₁₀ and NO₂.

* p ≤ 0.05.

** p ≤ 0.01.

*** p ≤ 0.001.

Table 5

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

	Doctor diagnosed asthma ^a	Doctor diagnosed rhinitis ^a	Lifetime eczema ^a	Current wheeze ^b	Current rhinitis ^b
Antibiotics use					
Model I (n = 39,782)					
Never	1.00	1.00	1.00	1.00	1.00
Only before 12 months age	2.03 (1.72, 2.40)***	1.77 (1.54, 2.03)***	1.20 (1.11, 1.30)***	1.66 (1.52, 1.82)***	1.34 (1.25, 1.44)***
Before and/or after 12 months	3.06 (2.63, 3.55)***	2.18 (1.92, 2.48)***	1.37 (1.27, 1.47)***	1.80 (1.65, 1.95)***	1.48 (1.39, 1.58)***
Model II (n = 25,935)					
Never	1.00	1.00	1.00	1.00	1.00
Only before 12 months age	1.62 (1.26, 2.07)***	1.60 (1.33, 1.93)***	1.16 (1.05, 1.29)**	1.57 (1.40, 1.76)***	1.31 (1.21, 1.43)***
Before and/or after 12 months	2.31 (1.85, 2.89)***	1.93 (1.63, 2.30)***	1.28 (1.17, 1.40)***	1.60 (1.43, 1.78)***	1.37 (1.27, 1.48)***
Times of antibiotics use during 0–12 months age					
Model I (n = 39,782)					
0	1.00	1.00	1.00	1.00	1.00
1	1.26 (1.11, 1.44)***	1.19 (1.06, 1.34)**	1.15 (1.07, 1.24)***	1.24 (1.14, 1.34)***	1.16 (1.09, 1.24)***
> 1	2.08 (1.87, 2.33)***	1.51 (1.36, 1.68)***	1.45 (1.36, 1.56)***	1.57 (1.46, 1.69)***	1.50 (1.41, 1.59)***
Model II (n = 25,935)					
0	1.00	1.00	1.00	1.00	1.00
1	1.10 (0.87, 1.38)	1.12 (0.94, 1.33)	1.07 (0.97, 1.19)	1.15 (1.03, 1.29)*	1.10 (1.01, 1.20)*
> 1	1.81 (1.48, 2.21)***	1.44 (1.22, 1.71)***	1.36 (1.24, 1.50)***	1.44 (1.29, 1.61)***	1.36 (1.25, 1.49)***

Models were adjusted for all the covariates in Table 2, city, lifetime outdoor PM₁₀ and temperature in each city.

Model I was for total children (n = 39,782).

Model II was for the children without lifetime ever pneumonia or long duration of common cold (≥ 2 weeks per cold) (n = 25,935).^a Cumulative incidence (life-time ever had).^b In the last 12 months.* p $\leq$ 0.05.** p $\leq$ 0.01.*** p $\leq$ 0.001.**Table 6**Interaction effects of outdoor PM₁₀, ETS, and mosquito coil and incense burning on associations (OR, 95% CI) between antibiotics use and doctor diagnosed asthma and rhinitis by two-level logistic regression models (n = 39,782).

	Never	Antibiotics only before 12 months	Antibiotics before and/or after 12 months	Interaction p-value
Doctor-diagnosed asthma				
Lifetime PM ₁₀				
Low	1.00	1.96 (1.59, 2.43)***	2.72 (2.23, 3.31)***	0.008 (+)
High	1.00	2.11 (1.62, 2.74)***	3.58 (2.83, 4.53)***	
Lifetime ETS				
No	1.00	2.36 (1.82, 3.07)***	2.87 (2.24, 3.66)***	0.019 (+)
Yes	1.00	1.82 (1.46, 2.25)***	3.22 (2.66, 3.90)***	
Mosquito coils				
No	1.00	2.04 (1.69, 2.47)***	3.08 (2.59, 3.67)***	0.601
Yes	1.00	2.01 (1.42, 2.84)***	2.99 (2.18, 4.11)***	
Incense				
No	1.00	2.27 (1.89, 2.74)***	3.28 (2.76, 3.89)***	0.961
Yes	1.00	1.20 (0.78, 1.84)	2.44 (1.70, 3.52)***	
Doctor-diagnosed rhinitis				
Lifetime PM ₁₀				
Low	1.00	1.92 (1.58, 2.32)***	2.32 (1.94, 2.76)***	0.456
High	1.00	1.61 (1.31, 1.99)***	2.03 (1.68, 2.45)***	
Lifetime ETS				
No	1.00	1.79 (1.43, 2.23)***	2.01 (1.64, 2.47)***	0.180
Yes	1.00	1.74 (1.45, 2.09)***	2.29 (1.94, 2.70)***	
Mosquito coils				
No	1.00	1.74 (1.49, 2.04)***	2.16 (1.87, 2.50)***	0.822
Yes	1.00	1.83 (1.34, 2.50)***	2.15 (1.61, 2.88)***	
Incense				
No	1.00	1.82 (1.55, 2.12)***	2.26 (1.96, 2.61)***	0.910
Yes	1.00	1.78 (1.21, 2.63)**	2.09 (1.46, 2.99)***	

Models were adjusted for all the covariates in Table 2, city, lifetime outdoor PM₁₀ and lifetime outdoor temperature.** p $\leq$ 0.005.*** p $\leq$ 0.001.

remained significant when excluding children with lifetime-ever pneumonia or long duration of common cold. Thus we found no evidence that our results concerning antibiotics use are due to protopathic bias. Our study is a retrospective cohort study on life-time development of asthma, rhinitis and eczema (cumulative incidence) combined with data on current symptoms. Moreover, we used life time data on the

outdoor environmental exposure. However, one limitation of the study is the cross-sectional data collection. Another limitation is that the assessment of outdoor exposure is based on city level data. This can lead to methodological problems linked to ecological fallacy.

Variation of lifetime outdoor exposure in a multi-center study such as the CCHH study is due to variation between cities, variation over

Table 7

Interaction effects of PM₁₀ and mosquito coil and incense use on associations (OR, 95% CI) between times for antibiotics use in the first year of life and doctor diagnosed asthma and rhinitis by two-level logistic regression models (n = 39,782).

	Never	1 time	> 1 times	Interaction p-value
Doctor-diagnosed asthma				
Lifetime PM ₁₀				
Low	1.00	1.17 (0.99, 1.39)	1.91 (1.64, 2.22)***	0.046 (+)
High	1.00	1.41 (1.16, 1.71)***	2.31 (1.96, 2.73)***	
Lifetime ETS				0.224
No	1.00	1.15 (0.94, 1.40)	1.85 (1.56, 2.21)***	
Yes	1.00	1.35 (1.14, 1.60)***	2.25 (1.95, 2.60)***	
Mosquito coils				0.575
No	1.00	1.31 (1.13, 1.52)***	2.08 (1.83, 2.37)***	
Yes	1.00	1.12 (0.86, 1.47)	2.00 (1.60, 2.50)***	
Incense				0.468
No	1.00	1.27 (1.10, 1.46)***	2.10 (1.86, 2.38)***	
Yes	1.00	0.95 (0.73, 1.23)	1.45 (1.16, 1.81)***	
Doctor-diagnosed rhinitis				
Lifetime PM ₁₀				
Low	1.00	1.21 (1.04, 1.42)*	1.55 (1.34, 1.79)***	0.670
High	1.00	1.17 (0.98, 1.39)	1.48 (1.27, 1.73)***	
Lifetime ETS				0.097 (+)
No	1.00	1.15 (0.96, 1.37)	1.33 (1.12, 1.58)***	
Yes	1.00	1.23 (1.06, 1.43)**	1.64 (1.43, 1.87)***	
Mosquito coils				0.581
No	1.00	1.25 (1.10, 1.42)***	1.53 (1.36, 1.73)***	
Yes	1.00	1.12 (0.95, 1.32)	1.35 (1.16, 1.56)***	
Incense				0.943
No	1.00	1.20 (1.06, 1.36)**	1.54 (1.37, 1.73)***	
Yes	1.00	1.14 (0.96, 1.36)	1.41 (1.20, 1.64)***	

Models were adjusted for all the covariates in Table 2, city, lifetime outdoor PM₁₀ and temperature in each city.

* p ≤ 0.05.

** p ≤ 0.01.

*** p ≤ 0.001.

time (from year to year) and spatial variation within each city. Since we used annual mean values per city, we included variation between cities and variation from year to year (different life time mean exposure depending on which year the child is born) but could not include spatial variation within the city. This is a limitation of the study. However, we had a considerable variation of exposure to PM₁₀ and NO₂ between the cities and from year to year in our study. Unfortunately, the official air pollution website only gives annual mean values per city (not for each monitoring station). We could get data from each local monitoring station in one of the cities. This data showed that in this city, year to year variation of air pollution seems to be more important than spatial variation within the city of annual means. Our judgement is that the lack of data on spatial variation within the cities would most likely lead to non-differential misclassification of the exposure.

We found that asthma and eczema were more common in a warmer climate. A warmer climate can facilitate indoor dampness and mould (Norbäck et al., 2017b) and increase exposure to mould (Norbäck and Cai, 2011) and other bio-aerosols. Our results suggest that the global warming can accelerate the ongoing global increase of asthma and allergic diseases. Outdoor NO₂ was a consistent risk factor for asthma, wheeze, rhinitis and eczema. Since the main source of outdoor NO₂ is traffic, we conclude that traffic-related air pollution (TRAP) could be an important risk factor for childhood asthma, rhinitis, and eczema in China. The association between NO₂ and asthma is in agreement with previous studies (Khreis et al., 2017). The association with rhinitis is in agreement with two studies among pre-school children in China (Deng et al., 2016; Liu et al., 2013). The association with eczema agrees with a previous study from China reporting an association between exposure to NO₂ and eczema among pre-school children (Lu et al., 2017). For particulate matter (PM₁₀) we found associations for eczema, only. This association is in agreement with a previous review and meta-analysis, concluding that outdoor PM₁₀ is associated with increased risks of human skin diseases, especially childhood allergic dermatitis (Ngoc

et al., 2017).

Our result that early life antibiotics use is a risk factor for childhood asthma, rhinitis and wheeze is in agreement with previous studies, mainly from western countries (e.g. Ahmadizar et al., 2017; Kozyrskyj et al., 2007; Raciborski et al., 2012; Risnes et al., 2011). Moreover, we found an association between early life exposure to antibiotics and eczema, which is in agreement with a previous review (Tsakok et al., 2013). One explanation to our findings could be disruption of the gastrointestinal microflora causing gastro-intestinal dysbiosis (Neuman et al., 2018; Kuo et al., 2013).

In our study, 56% of the children were exposed to ETS at home. We found that ETS exposure was associated with doctor diagnosed rhinitis, lifetime eczema, current wheeze and current rhinitis. Our results agree with conclusions from previous review articles that ETS is a risk factor for respiratory illness (Vanker et al., 2017). Another review article concluded that it is more unclear if early life ETS exposure is a risk factor for atopic dermatitis (Yang, 2016).

Gas cooking was associated with doctor diagnosed rhinitis, only. A recent review article concluded that many studies have demonstrated that gas cooking is a risk factor for childhood asthma and wheeze (Lin et al., 2013) but we found only one previous studies (from India) demonstrating that gas cooking increased the risk of childhood rhinitis (Kumar et al., 2008). Biomass cooking was associated with doctor diagnosed rhinitis, lifetime eczema and current rhinitis. In less developed countries, cooking by biomass is a well-recognized cause of respiratory disease (Laumbach and Kipen, 2012). However, we found only one study from India demonstrating that biomass burning at home is a risk factor for childhood rhinitis specifically (Kumar et al., 2008) and no study reporting an association between biomass burning for cooking and childhood eczema. Thus, our study adds evidence on associations between biomass burning in homes and childhood rhinitis and dermatitis.

Burning incense was associated with current wheeze and current

rhinitis. Incense burning produces emissions of aldehydes, VOC, PAHs and high levels of fine PM (Lin et al., 2008). Some smaller studies have demonstrated that incense smoke can increase respiratory symptoms (Wang et al., 2011; Yang et al., 1997). However, our study is the largest study so far on associations between incense burning at home and childhood wheeze and rhinitis.

Burning mosquito coils was associated with doctor diagnosed asthma, lifetime eczema, current wheeze and current rhinitis. Smoke from mosquito coils seemed to have a stronger health impact than incense smoke. Burning mosquito coils produces various aldehydes and high levels of fine PM expected to cause respiratory illness (Wang et al., 2018a, 2018b; Liu et al., 2003). One experimental study demonstrated that burning one mosquito coil release the same amount of PM_{2.5} as burning 75–137 cigarettes. The emission of formaldehyde from burning one mosquito coil can be as high as that released from burning 51 cigarettes (Liu et al., 2003). Burning mosquito coils is common in many homes in Asia and in other parts of the world. However, we found only one previous older epidemiological study from Malaysia on respiratory symptoms linked to smoke from mosquito coils (Yang et al., 1997).

We found that exposure to outdoor PM₁₀ and ETS enhanced the associations between antibiotics use and doctor diagnosed asthma and rhinitis. One recent review article concluded that air pollution can change the gut microbial diversity and cause microbiome dysfunction (Vallès and Francino, 2018). Experimental studies in mice have demonstrated that exposure to PM can cause gastro-intestinal inflammation, increase the gut permeability, change gastro-intestinal microbial diversity and composition and cause gut dysbiosis (Mutlu et al., 2011, 2018; Wang et al., 2018b; Kish et al., 2013). Moreover one panel study in humans found that exposure to PM_{2.5} and PM₁₀ altered the nasal microbiota (Mariani et al., 2018). Thus, one explanation to our results could be due to a combined effect (synergism) between early-life exposure to PM and antibiotics use. One explanation to the fact that we found synergistic effects for outdoor PM₁₀ and ETS, but not for smoke from incense or mosquito coils, could be that outdoor PM₁₀ and ETS are dominating sources of indoor PM in homes in Chinese cities. Further epidemiological and experimental studies are needed to confirm our finding.

In conclusion, living in a warmer climate zone, outdoor NO₂ and PM₁₀, ETS, gas cooking, burning biomass for cooking and burning incense and mosquito coils can increase the risk of asthma, wheeze, rhinitis and eczema among pre-school children in China. Early life antibiotics use can increase the risk of getting childhood asthma, wheeze, rhinitis and eczema and enhance the effects of ETS and outdoor PM₁₀. Further studies are needed on synergism between exposure to indoor and outdoor air pollution and disturbed gastrointestinal microflora in relation to human health and disease.

Conflicts of interest

None of the authors declare any conflict of interest.

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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.2019.01.036>.

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Supplemental materials

Table S1

Summary of annual concentrations of PM₁₀ and NO₂ in seven cities during 2005-2012.

Year	Concentration of PM ₁₀ (μg/m ³)							Concentration of NO ₂ (μg/m ³)						
	Urumqi	Beijing	Taiyuan	Nanjing	Shanghai	Chongqing	Changsha	Urumqi	Beijing	Taiyuan	Nanjing	Shanghai	Chongqing	Changsha
2005	114	141	139	110	88	120	122	56	66	20	54	61	48	36
2006	152	162	142	109	86	111	111	64	66	25	52	55	47	39
2007	136	148	124	107	88	108	104	67	66	27	51	54	44	41
2008	145	123	94	98	84	106	97	65	49	21	53	56	43	43
2009	140	121	106	100	81	105	92	68	53	22	48	53	37	42
2010	133	121	89	114	79	102	83	67	57	20	46	50	39	46
2011	132	113	84	97	80	93	83	68	56	23	49	51	31	47
2012	145	109	80	102	71	90	88	68	52	26	51	46	35	44

Table S2

Summary of annual concentrations of PM₁₀ and NO₂ in different monitoring stations of Changsha during 2005-2010.

Year	Concentration of PM ₁₀ (μg/m ³)							Concentration of NO ₂ (μg/m ³)						
	S1	S2	S3	S4	S5	S6	S7	S1	S2	S3	S4	S5	S6	S7
2005	116	136	—	122	119	116	128	28	55	—	30	39	30	34
2006	110	100	133	116	111	115	117	35	56	35	39	41	35	38
2007	109	101	114	103	104	108	107	36	61	31	44	42	43	45
2008	96	104	95	100	94	90	93	37	59	33	50	42	43	44
2009	97	97	92	96	94	89	88	39	60	31	47	42	43	41
2010	80	98	95	101	98	83	78	52	60	42	56	51	44	53

S1: Gaokai district, S2: Railway station, S3: Jingkai district, S4: Mapoling, S5: Shida, S6: Wujialing, S7: Yuhua district.