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Environmental Exposure and Genetic Predisposition as Risk Factors for Asthma in China

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Asthma is the most common chronic pulmonary disease worldwide and places a considerable economic burden on society. China is the world's largest developing country and has the largest population. China has undergone dramatic changes in the past few decades. The traditional lifestyle and living environment have changed in ways that directly affect the prevalence of asthma. The prevalence of asthma is lower in Chinese children and adults than in developed countries, but the prevalence has been on the rise during the past 30 years. The prevalence significantly varies among different parts of China. Polymorphisms of multiple genes, outdoor air pollution caused by PM2.5, PM10, SO_2, NO_2, environmental tobacco smoke, and coal, indoor pollution, and inhaled allergens, such as house dust mites, pollen, and cockroach particles, are risk factors for asthma.

Key Words: Asthma; air pollution; allergen; genetic polymorphism

INTRODUCTION

Asthma is one of the most common chronic lung diseases all over the world. It affects people of all genders, races, and ages. The cost of treatment has consumed an enormous amount of health resources in all affected nations. These issues pose severe social and economic problems. Approximately 3 billion patients have been diagnosed with asthma. The total cost of asthma to society is about 1% of global disability-adjusted life years (DALYs), being comparable to that of diabetes mellitus.[1]

In the past few decades, China has undergone huge social changes. Traditional lifestyle and environment have been challenged by industrialization, urbanism, and the accompanying environmental pollution and changes in the weather and ecological environment. According to the China guideline for management of asthma,[2] the criteria for diagnosis of asthma includes: (1) symptoms, such as episodic breathlessness, wheezing, cough, and chest tightness after an incidental allergen exposure, seasonal variability, exposure to physical and chemical stimulants, upper airway viral infection, and exercise; (2) bilateral and scattered or diffuse expiratory wheezing on auscultation, with expiratory phase extension; (3) the above symptoms and signs that can be relieved automatically or after treatments; (4) symptoms of episodic breathlessness, wheezing, cough, and chest tightness not being caused by other diseases; and (5) reversibility of pulmonary function, such as improvement in forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) measurements after inhalation of a short-acting bronchodilator or more sustained improvement over days or weeks after the introduction of effective controller treatment, such as inhalant glucocorticosteroids. The prevalence of asthma has also changed. Most of the Western countries have followed a similar pattern: the prevalence of asthma first increased and then stabilized or decreased.[3] In contrast, several epidemiological studies have shown the prevalence of asthma to be lower in China than in developed Western countries, but available data suggested a more rapid rising trend.[3] However, the population of China is 1.3 billion and continues to grow. Even small increases in prevalence bring huge increases in the number of patients and place a great burden on families and society. Recent national epidemiological surveys in China have estimated the prevalence and evaluated possible risk factors of asthma, thereby facilitating evidence-based asthma prevention. This review sought to use the data from these surveys to establish the trends and to determine of the prevalence of asth-

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Table 1. Lifetime prevalence of asthma* as indicated by international questionnaires and surveys

Author (yr)	Region	Study year	Questionnaire category	Simple size	Age group (yr)	Prevalence (%)
Lee SL, 2004[4]	Hong Kong	2001	ISAAC	4,448	6-7	7.9
Wong GW, 2004[5]	Hong Kong	2002	ISAAC	3,321	13-14	10.2
Droma Y, 2007[6]	Lhasa	2001	ISAAC	3,196	13-14	1.1
Ma Y, 2009[7]	Beijing	2003-2004	ISAAC	3,531	13-14	6.3
Zhao J, 2011[8]	Beijing	2008-2009	ISAAC	10,372	≤14	3.15
	Chongqing			9,874		7.45
	Guangzhou			4,072		2.09
Wang HY, 2006[9]	Guangzhou	2001	ISAAC	3,516	13-14	4.6
Li J, 2013[10]	Guangzhou	2009-2010	ISAAC	6,928	13-14	6.9
Song N, 2014[11]	Shijiazhuang	2011	ISAAC	10,338	3-18	1.2
Dong GH, 2011[12]	Liaoning	2009	ATS	30,139	3-12	6.6
Wilson, 2008[13]	Liaoning	2002	ATS	31,704	≥14	1.0
Shi Z, 2012[14]	Jiangsu	2007	CNNH	1,486	≥20	1.4

*Asthma: defined as participants self-reported or parents reported "ever had asthma" by questionnaire.
ISAAC, The international study of asthma and allergies in childhood; ATS, The American Thoracic Society questionnaire; CNNH, The Chinese National Nutrition and Health Survey.

ma in China and to identify the environmental and genetic factors associated with asthma.

Regional difference in the prevalence of asthma

The epidemiologic questionnaire surveys conducted after 2000 are shown in Table 1.[4-14] Results showed asthma in China to have the highest prevalence in children in Hong Kong at 10.2%[5] and the lowest in Lhasa at 1.1%.[6] Among inner city environment, the highest prevalence was detected in Chongqing at 7.45%,[8] and the lowest in Shijiazhuang at 1.2%.[11] Another study conducted in 8 inner city settings showed the prevalence of "current asthma" (asthma in the past 12 months) in children at ages 6-7 ranged from 0.9% in Hohhot and 1.1% in Xi'an to 7% in Shanghai.[15]

Table 2 lists the epidemiologic studies of asthma based on physician diagnosis.[16-29] The investigations were performed through screening by questionnaires, followed by medical history taking, physical examination, pulmonary function testing, and airway reversibility tests for suspected patients, and ultimately the diagnosis of asthma was made according to the Chinese asthma diagnosis guideline. In the 3 nationwide epidemiological surveys of childhood asthma, the lowest overall prevalence was found in Lhasa (0.09% in 1990, 0.48% in 2010) and in xining (0.12% in 2000). The highest rates were detected in Chongqing (2.9% in 1990), in Shanghai and Chongqing together (3.34% in 2000), and in Shanghai (7.57% in 2010). In other similar surveys conducted in 10 inner cities, the prevalence ranged from 1.34% in Dalian to 4.56% in Shaoxing.[30-39] The prevalence was higher in children than in adults in all the locations tested except Hainan.[22] The prevalence among individuals older than 14 ranged from 0.31% in Qinghai to 3.6% in Hainan.[22,23]

A preliminary map was created to show geographical differences in the prevalence of asthma (Fig. 1). Overall asthma prevalence was higher in plains areas than in plateau areas, in southern cities than in northern cities, and in eastern China than in further western China. The highest prevalence of childhood asthma in China, as assessed by questionnaires and physician diagnosis, were 10.2% and 7.57%, respectively, far below Australia's 32%, the United States's 24.4%, England's 14.9%, and Singapore's 27.4%.[40-43] For adults, the prevalence of asthma varies by age and urban or rural area. The highest prevalence in China, as assessed by questionnaires and physician evaluations, were 5.1% and 3.58%, respectively, being both lower than in Western countries, such as the United States's 8.4% or Canada's 13.5%.[44,45]

Trends in the epidemiology of asthma

In Hong Kong, the incidence of asthma in children of two age groups showed no change between phases I and III of the International Study of Asthma and Allergies in Childhood (ISAAC) surveys (7.8% and 7.9% at ages 6-7, 11.2% and 10.2% at ages 13-14).[4,5] Furthermore, the prevalences of current wheeze and other asthmatic symptoms in children at ages 13-14 all showed decreased trends in the 2 surveys.[5] As shown in national epidemiological studies of children with asthma in inner cities conducted in 1990, 2000, and 2010, the incidence in most cities increased significantly (Fig. 2).[16-18] The incidences in some large cities that had shown a higher incidence in the past continued to rise. For instance, in these 3 epidemiological studies,[16,18] the incidence in Beijing was 0.77%, 2.05%, and 2.55%, respectively, and the incidence in Shanghai was 1.50%, 3.34%, and 5.73%, respectively. In Suzhou, the incidence was lower in 2010 than in

Table 2. Lifetime prevalence of asthma* by Chinese physician diagnosed surveys

Author (yr)	Region	Study year	Age group (yr)	Sample size	Prevalence (%)
Chen YZ, 2004[16]	27 cities	1990	≤14	399,193	0.09-2.60
Chen YZ, 2003[17]	43 cities	2000	≤14	432,500	0.12-3.34
Chen YZ, 2013[18]	43 cities	2009-2010	≤14	463,982	0.48-7.57
FenXK, 2014[19]	Beijing	2010	>14	57,647	1.19
	Shanghai			17,805	1.14
	Guangdong			14,465	1.13
	Liaoning			18,648	1.69
	Jiangsu			14,069	0.86
	Sichuan			9,030	2.30
	Henan			17,017	0.87
	Shaanxi			15,534	1.21
Wang GB, 2002[20]	Henan	2000	≤14	16,997	1.71
			>14	48,036	0.82
Zhang SZ, 2005[21]	Zaozhuang	2003	≤14	2,923	2.02
			>14	7,687	0.90
Ding YP, 2012[22]	Hainan	2003-2007	≤14	1,352	1.48
			>14	11,698	3.6
Gao F, 2011[23]	Qinghai	2006-2007	≤14	3,510	0.85
			>14	24,341	0.31
Wang, 2013[24]	Jinan	2009	≤14	1,355	0.81
			>14	12,013	0.62
Yang Y, 2012[25]	Qiannan	2010-2011	1-14	2,802	9.28
			>14	18,765	2.73
Qian JJ, 2011[26]	Shanghai	2010-2011	4-14	257	3.89
			>14	4,699	1.81
Cai WS, 2013[27]	Jinzhou	2010-2011	≥4	4,000	1.2
Hwang, 2010[28]	Taiwan	2000-2007	All age	997,729	2.9
Lei M, 2005[29]	Xianing	2002	All age	14,216	0.96

*Asthma is defined as physician diagnosed base on the Chinese diagnostic criteria. Participants screened by questionnaires, and suspected cases were diagnosed by case history, clinical signs, and lung function tests.

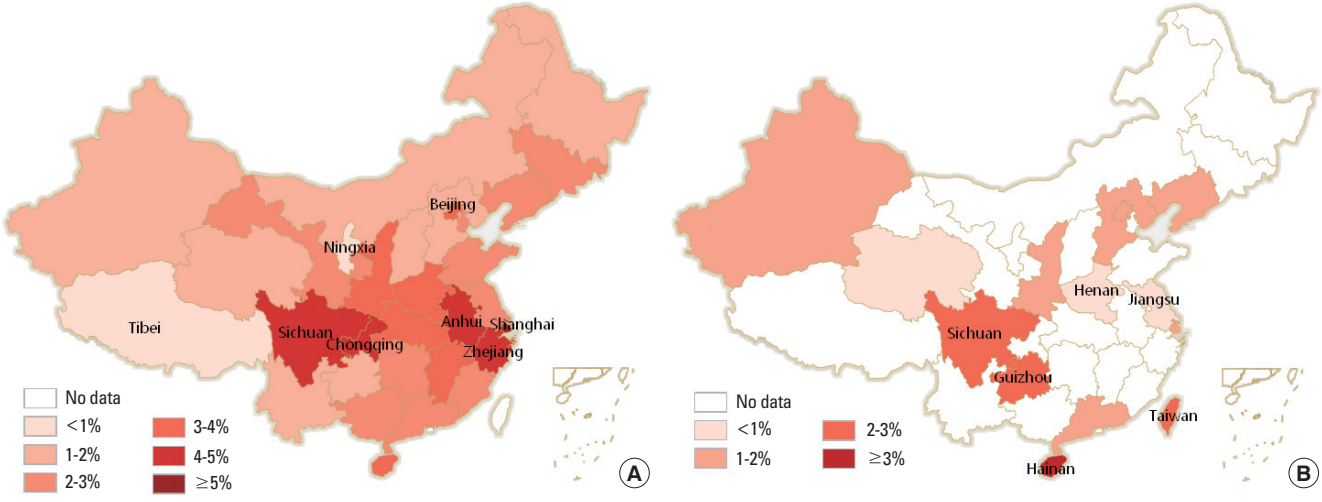

Fig. 1. Geographic differences in the prevalence of asthma in (A) children and (B) adults. Childhood asthma prevalence was retrieved from the 2010 nationwide data. Adult asthma prevalence was determined using data from local area studies.

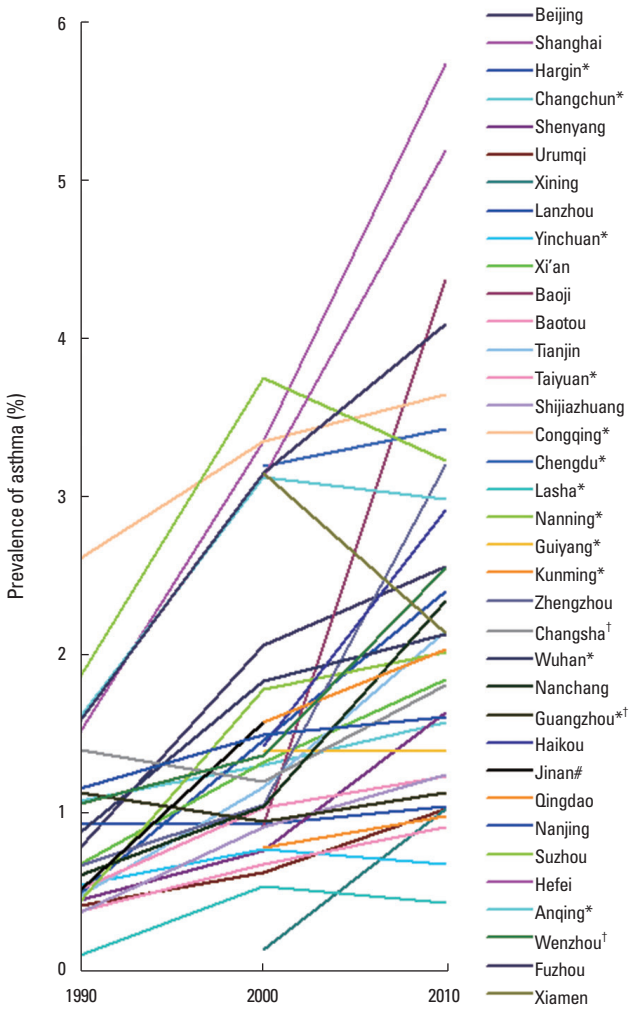

Fig. 2. The Prevalence and trend of asthma among children in the last 3 decades.
*no significant difference between 2000 and 2010 surveys; †no significant difference between 1990 and 2000 surveys.

2000 (3.22% vs 3.74%) but higher than in 1990 (1.85%). Guangzhou is the only one city that showed no change across these 3 epidemiological studies. However, from the results of the ISAAC study, the prevalence of children aged 13-14 years in Guangzhou increased significantly, from 3.9% in 1996 and 4.6% in 2002 to 6.9% in 2010.[10] In these 3 epidemiological studies of children with asthma,[16,18] the prevalence in children at ages 0-14 increased from 0.91% in 1990 and 1.97% in 2000 to 3.02% in 2010, increases of 64.84% and 52.8%, respectively. The 2-year cumulative incidence increased from 1.54% in 2000 to 2.32% in 2010, by 50.6%.

The incidence of asthma in other age groups showed a similar upward trend. In 2010, the incidences in individuals over 14 years in Guangdong, Liaoning, and Henan Provinces were 1.13%, 1.69%, and 0.87%, respectively.[19] These rates represented 14.14%, 21.58%, and 6.1% increases, when compared with their respective prevalences. They were only 0.99% in 1999 for Guangdong,[46] 1.39% in 1999 for Liaoning,[47] and 0.82% in 2000 for Henan.[20] Jinzhou showed a significant increase from 0.71% in 1999 to 1.2% in 2010 in a survey of individuals above 4 years old.[27]

Genetics and asthma

The study of Wang *et al.*[48] indicated that ethnicity is a risk factor among urban Chinese children at ages between 6 and 14 (OR=1.61, 95% CI: 1.26-2.06). A series of studies have given considerable attention to the idea that genetic polymorphism might contribute to the development of asthma and may possibly be one of the reasons for these difference.[49-51] Liu found that the genotype and allele frequencies of the 2 SNPs Rs2289276 and Rs2289278 in the *TSLP* were significantly different between Chinese Han asthma patients and the healthy controls. The C allele of rs2289278 showed a close association with the decrease in FEV1:FVC.[52] Chen *et al.*[53] found that IL-17 G-152A polymorphism (rs2275913) is a risk factor for allergic asthma of children in southwestern China and the AA genotype presents an association with an increase in IgE serum levels of asthmatic children and abnormal pulmonary function. The distribution frequency of the *ADAM33* and *CD14* gene polymorphisms differed between the Uighur people of the Turpan region, Chinese Han individuals, and Caucasian individuals. The Hap3 (CAC) and Hap4 (CAG) haplotypes are risk factors for asthma, whereas the Hap2 (TGC) haplotype may be a protective factor against the disease among Uighur individuals.[54] The interaction of coal combustion type of air pollution (PM4, SO_2, CO) with the Gly/Gly genotype of β2-AR 16 loci and the DD genotype of the *ACE* gene might increase the risk of childhood asthma.[55] The polymorphism of 17q21 may be related to adult-onset asthma in China.[56] Leung *et al.*[57] compares more than 20 SNPs from asthma candidate genes between southern Han Chinese subjects in Hong Kong and other populations, including other Han Chinese subjects in the rest of China, Japanese subjects, European white subjects, Yoruba African subjects, and American Puerto Rican subjects. Substantial interethnic differences in the genetic epidemiology of many SNPs were found.

Prevalence of asthma in urban and rural areas

Some epidemiological surveys compared the prevalence of asthma in urban and rural areas (Fig. 3). Almost all the surveys showed remarkable differences between urban and rural areas. The prevalence of asthma in children in rural parts of Lhasa was 2.5%. It was only 1.1% in urban areas.[6,58] The prevalence of asthma in individuals older than 14 years was higher in rural parts of Hainan and Henan than in cities in those provinces.[20,22] In areas other than the ones listed above, the prevalence of asthma was higher in urban areas than in rural areas. Children at ages 13-14 showed a much higher prevalence in urban areas in Beijing (6.3%) than in rural areas (1.1%).[7] The prevalence of children aged 13-14 with asthma and recent wheezing in urban

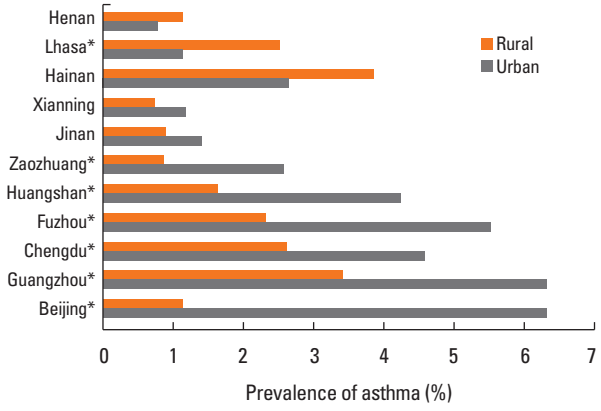

Fig. 3. The difference in asthma prevalence (%) between urban and rural areas. *data from surveys in children

parts of Guangzhou were 6.9% and 6.1%, respectively. These values were higher than the 3.4% and 1.6% in rural areas.[10,59] Among the children at ages 0-14, those in urban parts of Chengdu and other cities showed significantly higher prevalences of asthma than in rural parts.[32,36,60,61] Similar results were observed in surveys of adults and children in Jinan and Xianning.[24,29] Gao *et al.*[23] showed that urban parts of Qinghai Province had a higher prevalence of asthma than rural areas (0.27% vs 0.64%), but the pastoral and half-farming/half-herding areas had an even lower prevalence (0.04% and 0.15%). A comparative study between urban and rural areas in Guangzhou revealed that the concentration and load of endotoxin were higher in rural areas than in urban areas. Endotoxin levels have been shown to be correlated with PD20–FEV1, but negatively with allergic skin tests against house dirt mites and dust mites. This might be a possible reason for the lower prevalence of asthma in rural areas.[62]

Air pollution and asthma

Air pollution is one of the major contributors to airway disease. Air pollution can induce and aggravate asthma symptoms.[63] The frequencies of emergency department visits and hospitalizations in asthmatic patients increase with the levels of specific air pollutants, such as O_3, PM10, PM2.5, NO_2, and SO_2.[64-66] The investigation of over 30,000 adults in Liaoning Province, a northern China's great industrial province, indicated that the prevalences of persistent cough, persistent sputum production, and wheezing were increased progressively with proximity of housing to major traffic roads, factories, and large smokestacks (persistent cough $\chi^2=24.58$, $P<0.001$; persistent sputum production $\chi^2=16.47$, $P<0.00l$; wheezing $\chi^2=8.49$, $P<0.05$).[13] Another investigation of children in the same province showed that the prevalence of asthma increased 1.34-fold, 1.23-fold, and 1.31-fold for each additional 31 m μg/m^3 of PM10, 21 m μg/m^3 of SO_2, 10 m μg/m^3 of NO_2, and 23 m μg/m^3 of O_3.[67] The improved air quality during Beijing Olympics was associated with

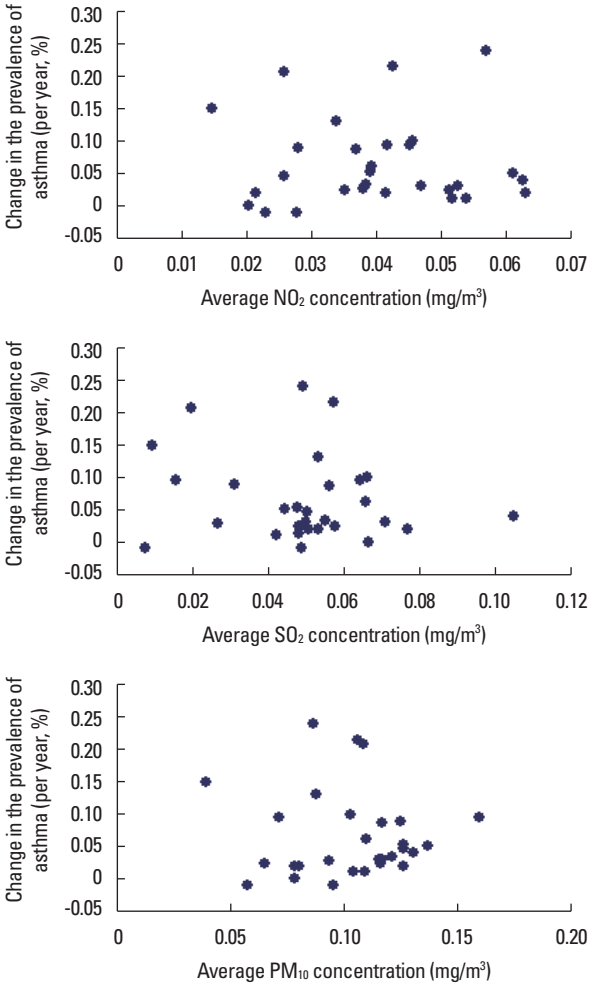

Fig. 4. Bland-Altman plots showing the average air-pollution index vs the mean change in prevalence of asthma from 2004 to 2010.

a significant reduction in the frequency of outpatient visits by asthmatics. This provides further evidence that outdoor air pollution is related to asthma attacks.[68]

Indoor air quality has similar effects on asthma. Rural areas showed a higher prevalence of asthma than urban areas in Hainan Provinc. The pattern may be related to the habit of using biomass, heavy smoke air pollution, and airway injury caused by long-term inhalation of those gases. This is consistent with previous findings reported by Smith.[69] Based on a study of ISAAC, the use of open fire as a cooking method was associated with the increased risk of asthma symptoms.[70] Another study among 4 cities in China, children exposed to heating coal smoke more easily presented with wheezing and sputum production. Children exposed to environmental tobacco smoke (ETS) present with chronic coughing with sputum. However, increased indoor air ventilation was associated with a lower frequency of these symptoms.[71]

In the absence of a birth cohort study, it is difficult to confirm whether air pollution is related directly to the development of

asthma. Average air quality index data in 2004-2010 were collected from National Bureau of Statistics of China for correlation analysis that measures the change rate of children asthma prevalence in 2000-2010.[72] No correlation was found between asthma prevalence and PM10, SO_2, or NO_2 (Fig. 4). Zhang *et al.*[73] conducted a study of 10 cities, including Beijing, and found no correlation between the PM10 level and the prevalence of childhood asthma at ages between 3 and 6 years. Another paradox is that the air pollution index is 3-to 4-fold higher in China than in Western countries, but the prevalence of asthma is much lower in China. Air pollution is more likely to cause exacerbations in those with pre-existing asthma and may not play an important role in the inception of asthma.

Environmental allergen and asthma

Allergens are important influential factors for asthma. The most common inhaled allergen in China is the house dust mites (HDMs). A recent study showed that 59.0%, 57.6%, and 40.7% of patients with allergic diseases were allergic to *Dermatophagoides (D.) farinae*, *D. pteronyssinus* and *Blomia tropicalis* respectively.[74] HDMs multiply easily in warm, humid indoor environment found in southern China. Dust samples were collected from 107 participating households in Guangzhou. Dust mite allergens were detected in 99% of the dust samples. The level of HDM allergens in 88% of the bedding samples was above 10 μg/g.[75] Another study in Guangzhou showed the prevalence of wheezing symptoms in children with sensitization to *D. farinae* increased from 14.4% in 2001 to 30.9% in 2009. The prevalence of wheezing symptoms in children with sensitization to *D. pteronyssinus* also increased from 15.3% in 2001 to 33.1% in 2009.

The prevalence of wheezing was higher in children with sensitization to HDMs than in those without sensitization to HDMs (33.1% vs 6.8% for positive and negative reaction to *D. pteronyssinus*, and 30.9% vs 9.5% for positive and negative reaction to *D. farinae*). It has been demonstrated that sensitization against HDMs is an important risk factor for the increasing prevalence of childhood asthma.[10]

In the dry climate of northern China, the concentration of HDMs is very low. A previous study on families with asthmatic children in Beijing reported that the average concentrations of *D. pteronyssinus* and *D. farinae* were 0.02 μg/g and 0.13 μg/g, respectively.[76] Another important inhalant allergen in northern area is pollen. *Artemisia* and *Humulus* (including *Cannabis Sativa L*) are the main airborne pollen in autumn in Beijing, accounting for 31% and 51%, respectively. The daily average concentrations of *Artemisia* and *Humulus* pollen allergens are 71 g/m^3 and 672 g/m^3 with an average of 124 g/m^3 during *Artemisia* pollen season from August to October, respectively. In summer and autumn, 88.5% of out-patients with hay fever, asthma, or both were positive for *Artemisia* pollen, and 28.2% were positive for *Humulus* pollen.[77] An other study of asthmatic patients allergic to *Artemisia* and *Humulus* showed significant correlations between asthmatic symptoms, PEF values and pollen concentrations. The higher the pollen concentration, the lower the patient's PEF value, the higher the asthma symptom score and PEF daily variation. Pollen is found to play a critical role in allergic asthma during summer and autumn in northern China.[78]

Other common inhaled allergens include cockroach, cat fur, and dog fur. Cockroach exposure is a major risk factor for the development of asthma[79] and common in southern China, especially in rural areas.[62,80] A multicenter study on sensitizations in patients with rhinitis and/or asthma in China showed that the rate of sensitization to *Periplaneta americana* and *Blattella germanica* were 26.34% and 19.37%, respectively. Although skin reaction against cockroach was mild in our patients, there was a significant relationship between cockroach sensitization and prevalence of asthma.[81] In the past few decades, more and more Chinese families started keeping pets. The presence of cats in households is strongly associated with the detection of cat allergen Fel d1.[82] Most investigations have suggested a strong association between the positive IgE antibody or positive skin test reaction against Fel d1 or cat and asthma. Nevertheless, some studies have shown a lower asthma prevalence to be associated with a high level of Fel d 1 IgG but not IgE indicated that children were highly exposed to cat.[83] Birth cohort studies showed that the first year after birth is a critical period for inducing tolerance to cat allergen. Among children who came into contact with cats in the first year of life, sensitivity to cats at age of 18 years decreased by more than half.[84]

CONCLUSIONS

The prevalence of asthma is lower in Chinese children and adults than in those of developed countries but has rapidly risen during the past 30 years. The prevalence significantly varies among different parts of China. The polymorphism of multiple genes, outdoor air pollution caused by PM2.5, PM10, SO_2, NO_2, ETS, and coal, indoor pollution, and inhaled allergens, such as HDMs, pollen, and cockroach particles, are risk factors for asthma. In-depth studies of both genetic factors and their interaction with different environmental factors are crucial for our understanding of true causes of asthma.

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REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summa-

ry of the GINA Dissemination Committee report. Allergy 2004; 59:469-78.
2. Asthma Group of Chinese Society of Respiratory Diseases. Guidelines for prevention and treatment of asthma. Chin J Tuberc Respir Dis 2008;31:177-85.
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.
4. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). Pediatr Allergy Immunol 2004;15:72-8.
5. Wong GW, Leung TF, Ko FW, Lee KK, Lam P, Hui DS, et al. Declining asthma prevalence in Hong Kong Chinese schoolchildren. Clin Exp Allergy 2004;34:1550-5.
6. Droma Y, Kunii O, Yangzom Y, Shan M, Pingzo L, Song P. Prevalence and severity of asthma and allergies in schoolchildren in Lhasa, Tibet. Clin Exp Allergy 2007;37:1326-33.
7. Ma Y, Zhao J, Han ZR, Chen Y, Leung TF, Wong GW. Very low prevalence of asthma and allergies in schoolchildren from rural Beijing, China. Pediatr Pulmonol 2009;44:793-9.
8. Zhao J, Bai J, Shen KL, Xiang L, Huang Y, Huang S, et al. Questionnaire-based survey of allergic diseases among children aged 0-14 years in the downtown of Beijing, Chongqing and Guangzhou. Zhonghua Er Ke Za Zhi 2011;49:740-4.
9. Wang HY, Zheng JP, Zhong NS. Time trends in the prevalence of asthma and allergic diseases over 7 years among adolescents in Guangzhou city. Zhonghua Yi Xue Za Zhi 2006;86:1014-20.
10. Li J, Wang H, Chen Y, Zheng J, Wong GW, Zhong N. House dust mite sensitization is the main risk factor for the increase in prevalence of wheeze in 13- to 14-year-old schoolchildren in Guangzhou city, China. Clin Exp Allergy 2013;43:1171-9.
11. Song N, Shamssain M, Zhang J, Wu J, Fu C, Hao S, et al. Prevalence, severity and risk factors of asthma, rhinitis and eczema in a large group of Chinese schoolchildren. J Asthma 2014;51:232-42.
12. Dong GH, Chen T, Liu MM, Wang D, Ma YN, Ren WH, et al. Gender differences and effect of air pollution on asthma in children with and without allergic predisposition: northeast Chinese children health study. PLoS One 2011;6:e22470.
13. Wilson D, Takahashi K, Pan G, Chan CC, Zhang S, Feng Y, et al. Respiratory symptoms among residents of a heavy-industry province in China: prevalence and risk factors. Respir Med 2008;102:1536-44.
14. Shi Z, Yuan B, Wittert GA, Pan X, Dai Y, Adams R, et al. Monosodium glutamate intake, dietary patterns and asthma in Chinese adults. PLoS One 2012;7:e51567.
15. Li F, Zhou Y, Li S, Jiang F, Jin X, Yan C, et al. Prevalence and risk factors of childhood allergic diseases in eight metropolitan cities in China: a multicenter study. BMC Public Health 2011;11:437.
16. Chen YZ; National Cooperation Group On Childhood Asthma China. Comparative analysis of the state of asthma prevalence in children from two nation-wide surveys in 1990 and 2000 year. Zhonghua Jie He He Hu Xi Za Zhi 2004;27:112-6.
17. Chen YZ; National Cooperation Group On Childhood Asthma. A nationwide survey in China on prevalence of asthma in urban children. Zhonghua Er Ke Za Zhi 2003;41:123-7.
18. National Cooperative Group on Childhood Asthma; Institute of Environmental Health and Related Product Safety, Chinese Center for Disease Control and Prevention; Chinese Center for Disease Control and Prevention. Third nationwide survey of childhood asthma in urban areas of China. Zhonghua Er Ke Za Zhi 2013;51: 729-35.
19. Feng XK. An epidemiology survey on the prevalence and associated risk factors of asthma among adults in China [dissertation]. Beijing: Peking Union Medical College; 2015.
20. Wang G, Peng Y, Du C, Tang B, Liu J, Zhen X, et al. Epidemiological survey on bronchial asthma in Henan province. Zhonghua Jie He He Hu Xi Za Zhi 2002;25:25-8.
21. Zhang SZ, Xi Q, Kong WS, Li ZH, Kong XT, Kong LY, et al. Study on prevalence and correlation factors of bronchial asthma in Zaozhuang area, Shandong province. Zhonghua Liu Xing Bing Xue Za Zhi 2005;26:273-6.
22. Ding YP, Yao HX, Tang XL, He HW, Shi HF, Lin L, et al. An epidemiology study of bronchial asthma in the Li ethnic group in China. Asian Pac J Trop Med 2012;5:157-61.
23. Gao F, Yang QJ, Zhang HG. An epidemiological study of bronchial asthma in Qinghai province. Zhonghua Jie He He Hu Xi Za Zhi 2011;34:165-8.
24. Wang D, Xiao W, Ma D, Zhang Y, Wang Q, Wang C, et al. Cross-sectional epidemiological survey of asthma in Jinan, China. Respirology 2013;18:313-22.
25. Yang Y, Li P, Song FY, Xiong QJ, Li ZF, Wei YP, et al. Analysis of the prevalence and risk factors of miao nationality population in the rural areas of qiannan autonmous preffcture of Guizhou province. Xian Dai Yu fang Yi Xue 2012;39:2142-4, 2147.
26. Qian JJ, Ma JY, Zhou M, Zhou X. A survey on epidemiology and risk factors of bronchial asthma in Baoshan district of Shanghai. J Intern Med Concepts Pract 2011;6:121-4.
27. Chai WS, Zhang DD, Pan DZ, Che LY. Epidemiological survey of asthma condition and risk factors in Jinzhou city. Chin Gen Pract 2013;16:413-4,424.
28. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC, et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. Acta Derm Venereol 2010;90:589-94.
29. Lei M, Zeng HY, Yu Y. Epidemiological investigation of bronchial asthma in Xianning city. China Trop Med 2005;5:258-60.
30. Cui ZZ, Wang WL, Huang Y, Mu HM, Jing SJ, Zhao XH. Epidemiological investigation on children under 14 years old with asthma in DaLian city. Bull Med Res (Chin) 2002;31:57-9.
31. Yuan BH, Cheng LY, Tao Y, Li L. Epidemiological investigation on asthma in 0-14 years old children in Xiangtan city. Zhongguo Fu You Bao Jian 2012;27:98-99.
32. Wang SY, Ding H, Wang SQ. Survey on prevalence rate of children with asthma in Zaozhuang city. Mod Prev Med 2007;34:83-4.
33. Shi CH, Zhang W, Jing YH, Wang LX, Zhang G, Cheng YL, et al. Epidemiological study on bronchial asthma among 0-14 years old children in Jilin. Chin J Child Health Care 2013;21:645-8.
34. Song J, Li Q, Sun YH, Gong MY. Analysis of the risk factors for asthma in children in WeiHai city. Matern Chilld Health Care Chin 2013;28:4667-8.
35. Kong Y, Ren CY, Cheng YJ, Yang A, Wang LZ, Xia JH. Epidemiological study on the sickness rate of asthma in children of 0-14 years old in urban area of Huainan city. Chin J Child Health Care 2006: 295-6.
36. Zhou BJ, Pan JH, Yu XK, Cheng AP, Zhou XL, Bi SF. Epidemiological investigation on 0-14 childhood asthma in Huangshan district. Chin J Dis Control Prev 2012;16:268-70.

37. Sun LB, Wang YT, Wan WJ, Ren HL, Gu AL. Epidemiological investigation on children under 14 years old with asthma in Chaohu city. Chin J Dis Control Prev 2008;12:498-500.
38. Kong T. Analysis of epidemiological investigation and prevention of childhood asthma. Clin J Chin Med 2014;6:27-8.
39. Liu SM, Wang XX, Liang QQ, Wang W, Dong CF. Epidemiological study on asthma among children aged 0 to 14 years in Shaoxing. J Pract Med (Chin) 2006;22:2546-7.
40. Schernhammer ES, Vutuc C, Waldhör T, Haidinger G. Time trends of the prevalence of asthma and allergic disease in Austrian children. Pediatr Allergy Immunol 2008;19:125-31.
41. Mvula M, Larzelere M, Kraus M, Moisiewicz K, Morgan C, Pierce S, et al. Prevalence of asthma and asthma-like symptoms in inner-city schoolchildren. J Asthma 2005;42:9-16.
42. Kurukulaaratchy RJ, Fenn M, Twiselton R, Matthews S, Arshad SH. The prevalence of asthma and wheezing illnesses amongst 10-year-old schoolchildren. Respir Med 2002;96:163-9.
43. Wang XS, Tan TN, Shek LP, Chng SY, Hia CP, Ong NB, et al. The prevalence of asthma and allergies in Singapore; data from two ISAAC surveys seven years apart. Arch Dis Child 2004;89:423-6.
44. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012:1-8.
45. Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: a population study. Am J Epidemiol 2010;172:728-36.
46. Tang T, Ding Y, Zhen J. Epidemiological survey and analysis on bronchial asthma in Guangdong province. Zhonghua Jie He He Hu Xi Za Zhi 2000;23:730-3.
47. Chen P, Yu R, Hou X, Tan P, Xie H, Kong L, et al. Epidemiological survey on bronchial asthma in Liaoning province. Zhonghua Jie He He Hu Xi Za Zhi 2002;25:603-6.
48. Wang Q, Xu C, Xu D, Liu C, Chen Y. Risks on asthma among city children in China:a nationwide case-control study. Zhonghua Liu Xing Bing Xue Za Zhi 2014;35:237-41.
49. Leung TF, Wong GW. The Asian side of asthma and allergy. Curr Opin Allergy Clin Immunol 2008;8:384-90.
50. Lee JH, Park CS. Gene-Gene interactions among MCP genes polymorphisms in asthma. Allergy Asthma Immunol Res 2014;6:333-40.
51. Zhao CN, Fan Y, Huang JJ, Zhang HX, Gao T, Wang C, et al. The association of GSDMB and ORMDL3 gene polymorphisms with asthma: a meta-analysis. Allergy Asthma Immunol Res 2015;7:175-85.
52. Liu W, Xu LS, Liu QJ, Dong FZ, Qiu RF, Wen MC, et al. Two single nucleotide polymorphisms in *TSLP* gene are associated with asthma susceptibility in Chinese Han population. Exp Lung Res 2012;38:375-82.
53. Chen J, Deng Y, Zhao J, Luo Z, Peng W, Yang J, et al. The polymorphism of IL-17 G-152A was associated with childhood asthma and bacterial colonization of the hypopharynx in bronchiolitis. J Clin Immunol 2010;30:539-45.
54. Wang J, Simayi M, Wushouer Q, Xia Y, He Y, Yan F, et al. Association between polymorphisms in ADAM33, CD14, and TLR4 with asthma in the Uygur population in China. Genet Mol Res 2014;13:4680-90.
55. Yuan P, Wei L, Hao S, Qiao L, Liu Y, Liu P, et al. Association between indoor coal-burning pollutants associated with asthmatic susceptible genetic polymorphisms in childhood asthma. Wei Sheng Yan Jiu 2008;37:159-63.
56. Fang Q, Zhao H, Wang A, Gong Y, Liu Q. Association of genetic variants in chromosome 17q21 and adult-onset asthma in a Chinese Han population. BMC Med Genet 2011;12:133.
57. Leung TF, Ko FW, Sy HY, Tsui SK, Wong GW. Differences in asthma genetics between Chinese and other populations. J Allergy Clin Immunol 2014;133:42-8.
58. Yangzong, Nafstad P, Madsen C, Bjertness E. Childhood asthma under the north face of Mount Everest. J Asthma 2006;43:393-8.
59. Chen Y, Li J, Zhong NS. Investigation of the different prevalence of asthma and allergies in Conghua rural area. Hainan Med J (Chin) 2011:135-6.
60. Li M, Zhang Q, Shi WJ, Li L, Li Y, Pang Y, et al. Epidemiological survey and analysis of asthma in children aged 0-14 years old in urban and rural areas of Chengdu region. Zhongguo Dang Dai Er Ke Za Zhi 2013;15:609-13.
61. Tang S, Wang S, Zheng J, Liu Y, Cheng C, Zhang M, et al. Comparison of the risk factors for asthma in children between urban and rural areas in Fuzhou city. Zhonghua Er Ke Za Zhi 2014;52:282-6.
62. Pan LY, Feng ML, Lai XX, Xian M, Huang XF, Chen Y, et al. The influence of house dust endotoxin on airway responsiveness and allergen sensitization in adolescence in urban and rural areas of Guangdong province. Chin J Microbiol Immunol 2012;32:440-8.
63. Jung DY, Leem JH, Kim HC, Kim JH, Hwang SS, Lee JY, et al. Effect of traffic-related air pollution on allergic disease: results of the children's health and environmental research. Allergy Asthma Immunol Res 2015;7:359-66.
64. Hua J, Yin Y, Peng L, Du L, Geng F, Zhu L. Acute effects of black carbon and PM(2.5) on children asthma admissions: a time-series study in a Chinese city. Sci Total Environ 2014;481:433-8.
65. Kuo HW, Lai JS, Lee MC, Tai RC, Lee MC. Respiratory effects of air pollutants among asthmatics in central Taiwan. Arch Environ Health 2002;57:194-200.
66. Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. Clin Exp Allergy 2006;36:1138-46.
67. Liu F, Zhao Y, Liu YQ, Liu Y, Sun J, Huang MM, et al. Asthma and asthma related symptoms in 23,326 Chinese children in relation to indoor and outdoor environmental factors: the Seven Northeastern Cities (SNEC) Study. Sci Total Environ 2014;497-498:10-7.
68. Li Y, Wang W, Kan H, Xu X, Chen B. Air quality and outpatient visits for asthma in adults during the 2008 Summer Olympic Games in Beijing. Sci Total Environ 2010;408:1226-7.
69. Smith KR, Samet JM, Romieu I, Bruce N. Indoor air pollution in developing countries and acute lower respiratory infections in children. Thorax 2000;55:518-32.
70. Wong GW, Brunekreef B, Ellwood P, Anderson HR, Asher MI, Crane J, et al. Cooking fuels and prevalence of asthma: a global analysis of phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Lancet Respir Med 2013;1:386-94.
71. Qian Z, Zhang J, Korn LR, Wei F, Chapman RS. Factor analysis of household factors: are they associated with respiratory conditions in Chinese children? Int J Epidemiol 2004;33:582-8.
72. Annual data of air pollution index by Province [Internet]. Beijing: National Bureau of Statistics of China; 2015 [cited 2015 May 1st]. Available from: http://data.stats.gov.cn/.
73. Zhang YP, Li BZ, Huang C, Yang X, Qian H, Deng QH, et al. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. Chin Sci Bull 2013;58:4182-9.
74. Li J, Sun B, Huang Y, Lin X, Zhao D, Tan G, et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma

and/or rhinitis in China. Allergy 2009;64:1083-92.
75. Zhang C, Gjesing B, Lai X, Li J, Spangfort MD, Zhong N. Indoor allergen levels in Guangzhou city, southern China. Allergy 2011;66:186-91.
76. Xiang L, Fu YN, Wang J, Wang Q. Distribution Characteristics and environmental influencing factors of house dust mite allergens' content in household dust from house dust mite-allergic asthmatic children. Chin J Allergy Clin Immunol 2013;7:314-21.
77. Yao L, Zhang H. Concentration of airborne pollen in Beijing city with burkard sampler. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2009;23:913-6.
78. Wen ZH, Yin J. Correlation of the artemisia and humulus scandens pollen count in the air and the severity of asthma symptoms in patients with autumnal pollinosis. Chin J Allergy Clin Immunol 2012;6:10-9
79. Sohn MH, Kim KE. The cockroach and allergic diseases. Allergy Asthma Immunol Res 2012;4:264-9.
80. Li CL, Xie WW, Liu S, Meng G, Cai QX. Cockroach allergens skin prick test in 500 patients with allergic rhinitis in Hainan province. Hainan Med J (Chin) 2011;22:16-7.
81. Sun BQ, Li J, Zhong NS. Skin sensitization to cockroach allergens: a nationwide, multi-center survey on bronchial asthma and allergic rhinitis among outpatients. Int J Respir (Chin) 2008;28:1281-4.
82. Leung TF, Wong YS, Chan IH, Yung E, Sy HY, Lam CW, et al. Domestic exposure to aeroallergens in Hong Kong families with asthmatic children. Pediatr Pulmonol 2011;46:632-9.
83. Lau S, Illi S, Platts-Mills TA, Riposo D, Nickel R, Grüber C, et al. Longitudinal study on the relationship between cat allergen and endotoxin exposure, sensitization, cat-specific IgG and development of asthma in childhood--report of the German Multicentre Allergy Study (MAS 90). Allergy 2005;60:766-73.
84. Wegienka G, Johnson CC, Havstad S, Ownby DR, Nicholas C, Zoratti EM. Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. Clin Exp Allergy 2011;41:979-86.