BMJ Open

Associations between sensitisation to allergens and allergic diseases: a hospital-based case–control study in China

Wei Zhang ,[1] Biao Xie,[2] Meina Liu,[1] Yupeng Wang[1]

To cite: Zhang W, Xie B, Liu M, *et al*. Associations between sensitisation to allergens and allergic diseases: a hospital-based case–control study in China. *BMJ Open* 2022;**12**:e050047. doi:10.1136/bmjopen-2021-050047

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-050047).

Received 10 February 2021
Accepted 11 January 2022

[1]Department of Biostatistics, Harbin Medical University, Harbin, Heilongjiang, China
[2]Department of Biostatistics, Chongqing Medical University, Chongqing, Sichuan, China

Correspondence to
Dr Yupeng Wang;
wangyupeng@hrbmu.edu.cn

ABSTRACT

Objectives To assess the associations of sensitisation to common allergens with atopic dermatitis, allergic rhinitis and allergic asthma in adults.

Design Case–control study.

Setting Data were collected from the First Affiliated Hospital of Harbin Medical University in Harbin, China.

Participants Cases were 5111 patients with physician-diagnosed atopic dermatitis (n=2631), allergic asthma (n=1320) and allergic rhinitis (n=1160) recruited from the department of allergy from March 2009 to December 2017. Controls were 2576 healthy adults who underwent physical examination at the same hospital during the same period.

Main outcome measures Specific IgE levels to 16 common food, indoor and outdoor allergens were assessed in all participants. Adjusted ORs and 95% CIs for the association between allergen sensitisation and allergic diseases were estimated using multivariate logistic regression.

Results The prevalence of allergen sensitisation was higher in patients with atopic dermatitis (indoor=17.14%, outdoor=12.85%, food=21.44%), allergic rhinitis (indoor=23.18%, outdoor=26.81%, food=8.94%) and allergic asthma (indoor=24.65%, outdoor=16.46%, food=14.31%) compared with controls (indoor=11.03%, outdoor=6.84%, food=5.83%). After adjustment for potential confounding variables, there was a dose–response relevance between the levels of allergen-specific IgE and allergic diseases (p trend <0.0001). The number of allergens to which a patient was sensitised increased the risk of allergic diseases (atopic dermatitis: highest adjusted OR=4.28, 95% CI 2.57 to 7.11; allergic rhinitis: highest adjusted OR=13.00, 95% CI 3.76 to 45.00; allergic asthma: OR=2.37, 95% CI 1.67 to 3.37).

Conclusion There was a dose–response relevance between levels of allergen-specific IgE and allergic diseases' prevalence, and multiple sensitisations increased the risk of allergic diseases. This study provides evidence for the prophylaxis of allergic diseases.

Strengths and limitations of this study

- ► We assessed the dose–response relationship between allergen-specific IgE levels to 16 different allergens and prevalence of allergic diseases using logistic regressions.
- ► Various types of allergens were considered and categorised into indoor, outdoor and food allergens.
- ► Adjusted ORs and 95% CIs for the association between allergen sensitisation and allergic diseases were estimated using multivariate logistic regression.
- ► The combined effects of multiple allergens on allergic diseases were inspected through multivariate logistic regression analyses, which were conducted with different number of sensitising allergens (1, 2, ≥3 allergens).
- ► Although this was not a multicentre study, it was a population-based study with a large sample size.

INTRODUCTION

Allergic diseases are global and can profoundly affect the quality of life of patients.[1] The incidence of allergic diseases, including atopic dermatitis, allergic rhinitis and allergic asthma, has been increasing rapidly around the world, especially in China and other low-income and middle-income countries.[2–4] As triggering factors, allergens stimulate the body to produce abnormal immune responses, which eventually lead to allergic diseases.[5] The type and dose of allergens determine the type of allergic disease and its severity.[6] Therefore, it is crucial to clarify the distributions of positive allergens among patients with different allergic diseases.

Currently, many studies have been devoted to explore the association between sensitisation to allergens and allergic diseases. Gray *et al* randomly enrolled 100 children aged 6 months to 10 years with atopic dermatitis and found that a high prevalence of egg sensitisation of 54%, and Skin Prick Test (SPT) to fresh egg white showed a high predictive value for egg allergy.[7] A Japanese study explored the causal relationships among pollen counts, tweet numbers and patient numbers for seasonal allergic rhinitis and

reported a positive correlation between pollen counts and the patient numbers.[8] Sensitisation and exposure to indoor allergens (such as dust mites, cockroaches, wild rodents, pets and fungi) have been reported to be associated with allergic diseases, especially the development of asthma.[9] Patients with allergies usually have different levels of specific IgE to a certain allergen and allergens are often coexistent, so it is critical to understand the associations between multiple allergens sensitisation and allergic diseases.[10] According to previous studies, the incidence of allergic diseases varies among different geographical locations and subpopulations. For Koreans, high sensitisations to various types of pollen were in the Gangwon region, whereas sensitisation to Japanese cedar pollen was unique in the Jeju region.[11] Among the individuals from the Americas, grass pollen and animal dander allergies were relatively common, while weed and grass pollen allergies were common in people from Central Asia.[11] Therefore, it is suggested that genetic and environmental features may play important roles in allergic diseases, and it is interesting to understand the underlying causes of those variations. At present, most relevant studies have a limited sample size, and few such studies have been conducted in northeastern China with its distinctive environmental and climate conditions.[12-14]

In the present study, we assessed the associations between sensitisation to 16 allergens and three common allergic diseases in northeastern China and explored if there is a dose–response connection between the specific IgE levels to an allergen and of allergic diseases' prevalence. We also examined the combined effects of multiple allergens on a specific allergic disease. Our study aimed to supply basis for the prevention and management of allergic diseases.

MATERIALS AND METHODS

Participants and public involvement

Harbin is located in northeast of China with longitude spanning 125°42'–130°10' E and latitude 44°04'–46°40' N, which is the provincial capital of Heilongjiang Province. Under the direct influence of the Siberian Anticyclone, the average daily temperature is −19.7°C (−3.5) in winter. Annual low temperatures below −35.0°C (−31.0) are not uncommon. Nicknamed 'Ice City' due to its freezingly cold winter. We recruited the participants into our research from Harbin. Only those who signed the informed consent form were recruited into our study. This project was authorised by the Institutional Review Board of Harbin Medical University. Adult patients aged 18 years or older with one of the three common allergic diseases (atopic dermatitis, allergic asthma or allergic rhinitis), who visited the Department of Allergy of the First Affiliated Hospital of Harbin Medical University during March 2009 and December 2017, were collected as the candidate cases. Healthy adults without any clinical symptoms and diseases who underwent physical examination at the same hospital during the same period were recruited as the candidate controls. All participants carried on allergen-specific IgE tests to 16 kinds of allergens and a questionnaire investigation.

Allergen-specific IgE testing

Serum allergen-specific IgE concentrations of 16 common allergens were measured in all eligible participants using the AllergyScreen system (Mediwise Analytic GmbH, Germany). As shown in online supplemental information, the 16 allergens were defined as three types: indoor allergens, outdoor allergens and food allergens.[15] Based on previous research, allergen-specific IgE >0.35 kU/L was considered as allergen sensitisation in this study, and specific IgE concentration of 0.35–0.70 kU/L was defined as class 1, 0.70–3.50 kU/L as class 2 and >3.50 kU/L as class 3.[16]

Allergic diseases definition

We focused on three common allergic diseases (atopic dermatitis, allergic asthma and allergic rhinitis) in Harbin. The three allergic diseases are diagnosed by experienced physicians using existing benchmarks for atopic dermatitis,[17] allergic rhinitis[18] and allergic asthma.[19] The detailed diagnostic criteria are shown in online supplemental information. Besides, the following criteria should be obeyed:

1. There were at least have one positive outcome of the 16 allergen-specific IgE results.
2. The patients had been diagnosed with one of the allergic diseases using current guidelines mentioned above.

Demographic, lifestyle characteristics and family history

All of the participants in this study answered the questionnaire face to face to collect data on demographic, lifestyle characteristics and family history. Gender, age, level of education, residential region and marital status were analysed as demographic characteristics. Smoking, drinking and physical exercise were included in lifestyle factors. The definition of those factors is shown in the online supplemental information.

Statistical analysis

To assess the dose–response relationship between levels of allergen-specific IgE to 16 different allergens and prevalence of allergic diseases, we applied logistic regressions to evaluate the ORs and their CIs. Multivariate logistic regression models were adjusted for potential confounding variables significantly associated with allergic diseases identified from univariate analysis or as suggested in previous literature. They included gender, age, BMI (body mass index: weight (in kg)/ height^2 (in m^2)), level of education, smoking, drinking, living region, marital status, family history of allergic diseases, physical exercise and other 15 allergen-specific IgE responses. To inspect the combined effects of multiple allergens on allergic diseases, multivariate logistic regression analyses were conducted with different number of sensitising allergens (1, 2, ≥3 allergens). The statistical analysis software

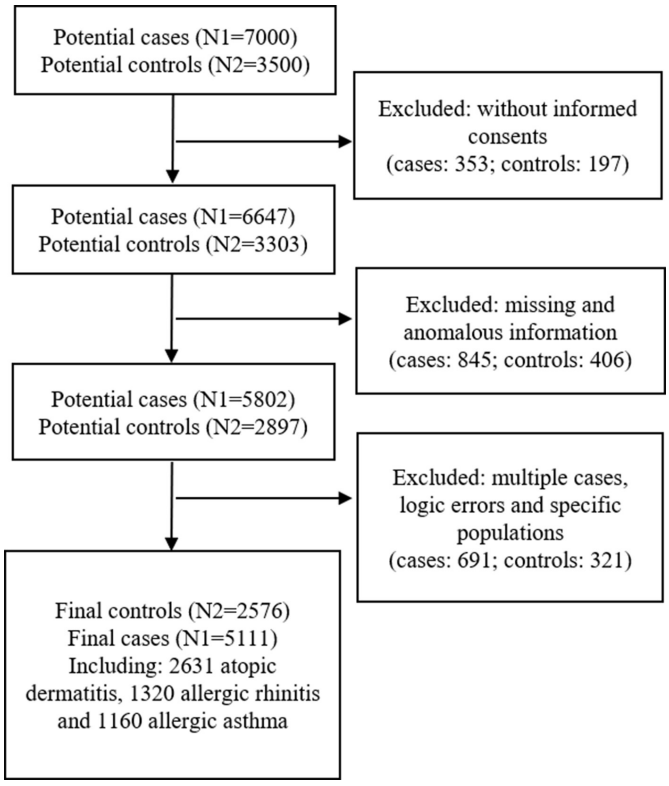

Figure 1 The flow diagram of study participants.

of this study was SAS V.9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Participants

In the present study, 7000 candidate cases and 3500 candidate controls were initially recruited. Excluding those without written informed consents, 6647 candidate cases and 3303 candidate controls remained. After excluding those with missing values and logic errors, and some special populations (sportsmen, pregnant or lactating women), we had 5111 cases (2631 atopic dermatitis, 1320 allergic rhinitis and 1160 allergic asthma) and 2576 controls for our final analysis. The flow diagram of the screening process of study participants is summarised in figure 1.

Characteristics in cases and controls

There are statistical differences between patients with atopic dermatitis and controls in terms of gender, age, height, weight, BMI, residential region, smoking, education and family history (p<0.05). Patients with allergic rhinitis were significantly different from controls in gender, height, weight, BMI, education and family history (p<0.05). Gender, age, weight, BMI, residential region, smoking, levels of education, marital status and physical exercise were different between those with allergic asthma and controls (p<0.05). Detail demographic characteristics are summarised in table 1.

Prevalence of allergen sensitisation in patients with atopic dermatitis, allergic rhinitis and allergic asthma

Patients with different allergic diseases had different prevalence of allergens sensitisation. Among patients with atopic dermatitis, the prevalence of food allergens sensitisation was higher than other allergens. The prevalence of outdoor allergens sensitisation was higher in those with allergic rhinitis while that of indoor allergens was higher in patients with allergic asthma (figure 2).

Adjusted for gender, age, BMI, level of education, smoking, drinking, living region, family history, physical exercise and other 15 allergen-specific IgE responses, specific IgE to common ragweed and mugwort, Dermatophagoides pteronyssinus, dog fur and cat fur were significantly related to the risk of allergic asthma (tables 2 and 3). Allergic rhinitis was significantly associated with common ragweed and mugwort, mould mixture, tree pollen mixture and Hop (table 3), while atopic dermatitis was significantly associated with egg white/egg yolk, crab, blue mussel, milk, fish and shrimp (tables 4 and 5). There was a dose–response relationship between specific IgE levels, from class 1 to class 3, and the prevalence of allergic diseases, the prevalence of allergic diseases increased along with the increasing levels of allergen-specific IgE to allergens (p trend <0.0001).

Combined effects of sensitization to multiple allergens on allergic diseases

ORs and their 95% CIs of allergic diseases with the different number of allergens are shown in table 6. Although the three allergic diseases had different ORs and 95% CI, the patterns of the relationships between allergic diseases and the number of allergens were similar. ORs increased as the number of sensitive allergens increased (p trend <0.0001). The associations between two or more allergens and atopic dermatitis were strong, adjusted OR=4.28 (95% CI 2.57 o 7.11). The combination of specific IgE to three or more sensitive allergens possessed the highest OR for allergic rhinitis (adjusted OR=13.00, 95% CI 3.76 to 45.00), while the combination of specific IgE to two or more allergens showed the highest OR for allergic asthma (adjusted OR=2.37, 95% CI 1.67 to 3.37).

DISCUSSION

In our present hospital-based case–control research, we found that different allergens are significantly related to different allergic diseases. There is a dose–response relationship between allergen-specific IgE levels and allergic diseases, and multiple sensitisations increase the risk of allergic diseases. The incidence of allergic diseases has increased rapidly worldwide.[2–4] The World Allergy Organization reported that, among 1.39 billion people in 33 countries, 22% of the population suffered from allergic diseases.[20] The WHO has clearly stipulated that allergic disease is an extremely considerable disease that the whole world should attach importance to.[21] Identifying specific allergens that trigger allergic diseases is

Table 1 Characteristics of patients with atopic dermatitis, allergic rhinitis, allergic asthma and controls.

	Control	Atopic dermatitis	P*	Allergic rhinitis	P*	Allergic asthma	P*
Number	2576	2631		1320		1160	
Men, n (%)	732 (28.42)	684 (26.00)	0.0499	532 (40.30)	<0.0001	398 (34.31)	0.0003
Age, years †	34.96 (16.13)	36.70 (15.33)	<0.0001	34.59 (13.76)	0.4868	41.60 (17.25)	<0.0001
Height, cm †	160.40 (14.71)	163.00 (11.14)	<0.0001	164.90 (11.07)	<0.0001	160.90 (14.59)	0.3205
Weight, kg †	58.43 (15.95)	60.34 (13.70)	<0.0001	62.49 (15.22)	<0.0001	60.02 (15.20)	0.0041
BMI, kg/m^2†	22.26 (4.17)	22.51 (3.95)	0.0268	22.71 (3.98)	0.0009	22.79 (4.04)	0.0003
Rural, n (%)	750 (29.12)	1020 (38.75)	<0.0001	374 (28.32)	0.6533	416 (35.88)	0.0003
Married, n (%)	1661 (64.49)	1708 (64.92)	0.8370	875 (66.31)	0.4722	891 (76.85)	<0.0001
smoking, n (%)	338 (13.12)	437 (16.61)	0.0004	194 (14.70)	0.1752	296 (25.52)	<0.0001
Alcohol drinking, n (%)	317 (12.31)	349 (13.26)	0.3002	192 (14.55)	0.0496	156 (13.45)	0.3313
Physical exercise, n (%)	893 (34.68)	897 (34.08)	0.7735	490 (37.15)	0.3281	319 (27.52)	0.0015
Education, n (%)							
Junior high school or lower	1253 (48.64)	1084 (41.20)	<0.0001	459 (34.77)	<0.0001	610 (52.59)	0.0220
Senior high school	618 (23.99)	734 (27.90)		315 (23.86)		280 (24.14)	
University or higher	705 (27.37)	813 (30.90)		546 (41.36)		270 (23.28)	
Family history, n (%)	452 (17.55)	1937 (26.38)	<0.0001	379 (28.71)	<0.0001	202 (17.41)	0.9213

*P values comparing cases with controls.
†The quantitative variables were expressed as means and their SD.
BMI, body mass index.

particularly significant for the prophylaxis and treatment of allergic diseases.

Our findings indicated that atopic dermatitis was significantly related to food allergen sensitisation, while allergic rhinitis and allergic asthma were significantly associated with both indoor and outdoor allergen sensitisation. The recognition to food allergens through antigen-presenting cells in eczematous skin plays an important role in the link between food allergy and allergic dermatitis. In addition, the dysfunction of filaggrin or Th2-related cytokines or rare genetic syndromes may also involve in the mechanism.[22] Different types of allergens induce different allergic diseases, which may due to the properties or size of allergens. Allergic rhinitis is associated with outdoor allergens, mainly pollen, probably because pollen particles are slightly larger than indoor dust and are more likely to stay in the nose.[23] Inhalation of indoor dust, mites and fungi can increase the airway reactivity and causes allergic asthma.[24] Our findings were consistent with previous studies that sensitisation to indoor allergens is important risk factors in patients with allergic rhinitis and allergic asthma.[9 25 26] Some studies also stated that there was a relevance between sensitisation to outdoor allergens and allergic rhinitis and allergic asthma.[27–29] Food allergens were found to be crucial in the development of atopic dermatitis in some observations.[29 30] Allergens, commonly proteins, induce allergic diseases through complex interactions with the immune system. Due to the presence of

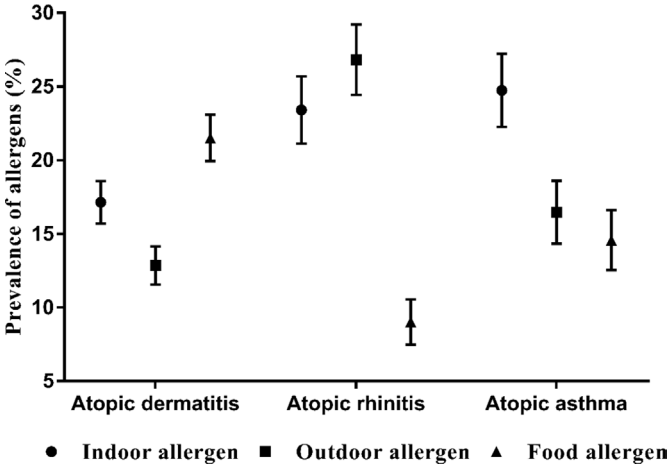

Figure 2 Prevalence of allergens sensitisation among patients with atopic dermatitis, allergic rhinitis and allergic asthma.

Table 2 ORs for allergic diseases with specific IgE class to indoor allergens

Allergen category	Control (n=2576)	Atopic dermatitis (n=2631)			Allergic rhinitis (n=1320)			Allergic asthma (n=1160)		
		n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)
Dermatophagoides pteronyssinus										
No	2098	2107	1.00 (ref)	1.00 (ref)	1038	1.00 (ref)	1.00 (ref)	852	1.00 (ref)	1.00 (ref)
Class 1	177	203	1.14 (0.93 to 1.41)	1.17 (0.93 to 1.47)	90	1.03 (0.79 to 1.34)	0.89 (0.63 to 1.24)	70	0.97 (0.73 to 1.30)	1.19 (0.85 to 1.66)
Class 2	228	243	1.06 (0.88 to 1.28)	1.11 (0.91 to 1.36)	155	1.37 (1.11 to 1.71)	1.16 (0.90 to 1.51)	153	1.65 (1.33 to 2.06)	1.40 (1.07 to 1.83)
Class 3	73	78	1.06 (0.77 to 1.47)	1.19 (0.84 to 1.69)	37	1.02 (0.69 to 1.53)	0.80 (0.51 to 1.26)	85	2.87 (2.08 to 3.96)	3.68 (2.50 to 5.40)
P trend			0.3415			0.0306			<0.0001	
Cat and dog fur										
No	2513	2539	1.00 (ref)	1.00 (ref)	1287	1.00 (ref)	1.00 (ref)	1089	1.00 (ref)	1.00 (ref)
Class 1	35	54	0.95 (0.59 to 1.53)	0.90 (0.54 to 1.49)	18	1.00 (0.57 to 1.78)	1.08 (0.58 to 2.01)	20	1.32 (0.76 to 2.30)	1.08 (0.58 to 1.99)
Class 2	14	20	1.40 (0.71 to 2.78)	1.67 (0.78 to 3.59)	8	1.12 (0.47 to 2.67)	1.26 (0.46 to 3.44)	16	2.64 (1.28 to 5.42)	4.10 (1.67 to 9.91)
Class 3	14	18	1.26 (0.63 to 2.54)	1.29 (0.62 to 2.69)	7	0.98 (0.39 to 2.43)	1.17 (0.46 to 3.22)	35	5.77 (3.09 to 10.77)	7.13 (3.44 to 14.79)
P trend			0.3498			0.9260			<0.0001	
Mould mixture										
No	2205	2252	1.00 (ref)	1.00 (ref)	1059	1.00 (ref)	1.00 (ref)	990	1.00 (ref)	1.00 (ref)
Class 1	234	245	1.03 (0.85 to 1.24)	1.05 (0.86 to 1.29)	123	1.09 (0.87 to 1.38)	0.81 (0.61 to 1.08)	106	1.01 (0.79 to 1.28)	0.98 (0.74 to 1.29)
Class 2	100	97	0.95 (0.71 to 1.26)	1.07 (0.79 to 1.44)	80	1.67 (1.23 to 2.26)	1.58 (1.12 to 2.22)	46	1.03 (0.72 to 1.46)	0.67 (0.44 to 1.01)
Class 3	37	37	0.98 (0.62 to 1.55)	1.04 (0.65 to 1.67)	58	3.26 (2.15 to 4.96)	3.32 (2.14 to 5.14)	18	1.09 (0.62 to 1.91)	1.01 (0.55 to 1.86)
P trend			0.8736			<0.0001			0.7814	

*OR values of three allergic disease compared with controls.
aOR, adjusted OR; cOR, crude OR.

Table 3 ORs for allergic diseases with specific IgE class to outdoor allergens.

Allergen category	Control (n=2576)	Atopic dermatitis (n=2631) n	cOR* (95% CI)	aOR* (95% CI)	Allergic rhinitis (n=1320) n	cOR* (95% CI)	aOR* (95% CI)	Allergic asthma (n=1160) n	cOR* (95% CI)	aOR* (95% CI)
Common ragweed and mugwort										
No	2325	2378	1.00 (ref)	1.00 (ref)	1130	1.00 (ref)	1.00 (ref)	1020	1.00 (ref)	1.00 (ref)
Class 1	113	114	0.99 (0.76 to 1.29)	0.97 (0.72 to 1.30)	58	1.06 (0.76 to 1.46)	0.95 (0.64 to 1.40)	38	0.77 (0.53 to 1.12)	0.75 (0.49 to 1.15)
Class 2	72	73	0.99 (0.71 to 1.38)	1.09 (0.74 to 1.60)	52	1.49 (1.03 to 2.14)	1.92 (1.23 to 2.99)	41	1.30 (0.88 to 1.92)	1.95 (1.17 to 3.27)
Class 3	66	66	0.98 (0.69 to 1.38)	0.75 (0.50 to 1.13)	80	2.49 (1.79 to 3.48)	1.87 (1.24 to 2.81)	61	2.11 (1.48 to 3.01)	2.26 (1.43 to 3.56)
P trend			0.8767			<0.0001			0.0002	
German cockroach										
No	2391	2438	1.00 (ref)	1.00 (ref)	1225	1.00 (ref)	1.00 (ref)	1073	1.00 (ref)	1.00 (ref)
Class 1	113	114	0.99 (0.76 to 1.29)	0.79 (0.58 to 1.09)	58	1.00 (0.73 to 1.39)	0.75 (0.47 to 1.19)	52	1.03 (0.73 to 1.44)	1.35 (0.89 to 2.06)
Class 2	61	59	0.95 (0.66 to 1.36)	0.69 (0.44 to 1.09)	31	0.99 (0.64 to 1.54)	0.59 (0.32 to 1.10)	27	0.99 (0.62 to 1.56)	0.70 (0.37 to 1.31)
Class 3	11	20	1.78 (0.85 to 3.73)	1.32 (0.58 to 3.04)	6	1.07 (0.39 to 2.89)	0.57 (0.17 to 1.84)	8	1.62 (0.65 to 4.04)	1.84 (0.67 to 5.08)
P trend			0.5522			0.9707			0.5848	
Tree pollen mixture										
No	2249	2297	1.00 (ref)	1.00 (ref)	1078	1.00 (ref)	1.00 (ref)	1003	1.00 (ref)	1.00 (ref)
Class 1	169	174	1.01 (0.81 to 1.26)	0.99 (0.77 to 1.27)	76	0.94 (0.71 to 1.24)	0.86 (0.61 to 1.22)	74	0.98 (0.74 to 1.30)	0.96 (0.67 to 1.38)
Class 2	129	132	1.00 (0.78 to 1.29)	1.09 (0.81 to 1.46)	102	1.65 (1.26 to 2.16)	1.50 (1.06 to 2.14)	73	1.27 (0.94 to 1.71)	0.78 (0.51 to 1.18)
Class 3	29	28	0.95 (0.56 to 1.59)	0.82 (0.45 to 1.51)	64	4.60 (2.95 to 7.18)	3.79 (2.28 to 6.29)	10	0.77 (0.38 to 1.59)	0.51 (0.21 to 1.23)
P trend			0.9430			<0.0001			0.4338	
Hop										
No	2412	2461	1.00 (ref)	1.00 (ref)	1150	1.00 (ref)	1.00 (ref)	1076	1.00 (ref)	1.00 (ref)
Class 1	90	89	0.97 (0.72 to 1.31)	0.89 (0.63 to 1.27)	46	1.07 (0.75 to 1.54)	1.28 (0.81 to 2.03)	50	1.25 (0.88 to 1.77)	1.15 (0.74 to 1.79)
Class 2	45	52	1.13 (0.76 to 1.69)	1.21 (0.77 to 1.91)	50	2.33 (1.55 to 3.51)	3.71 (2.24 to 6.13)	20	1.00 (0.59 to 1.70)	0.70 (0.36 to 1.35)
Class 3	29	29	0.98 (0.58 to 1.65)	0.85 (0.45 to 1.61)	74	5.35 (3.46 to 8.27)	6.89 (4.05 to 11.73)	14	1.08 (0.57 to 2.06)	0.68 (0.31 to 1.53)
P trend			0.8221			<0.0001			0.5204	

*OR values of three allergic disease compared with controls.
aOR, adjusted OR; cOR, crude OR.

Table 4 ORs for allergic diseases with specific IgE class to food allergens (fish and seafood)

		Atopic dermatitis (n=2631)			Allergic rhinitis (n=1320)			Allergic asthma (n=1160)		
Allergen category	Control (n=2576)	n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)
Blue mussel										
No	2521	2503	1.00 (ref)	1.00 (ref)	1289	1.00 (ref)	1.00 (ref)	1126	1.00 (ref)	1.00 (ref)
Class 1	40	38	0.96 (0.61 to 1.50)	0.57 (0.33 to 0.98)	20	0.98 (0.57 to 1.68)	1.29 (0.64 to 2.60)	18	1.01 (0.58 to 1.77)	0.64 (0.30 to 1.36)
Class 2	7	29	4.17 (1.82 to 9.54)	3.27 (1.40 to 7.65)	6	1.68 (0.56 to 5.00)	0.94 (0.22 to 4.03)	8	2.56 (0.93 to 7.07)	0.80 (0.23 to 2.84)
Class 3	8	61	7.66 (3.66 to 16.04)	5.98 (2.79 to 12.80)	5	1.22 (0.40 to 3.74)	1.09 (0.31 to 3.80)	8	2.24 (0.84 to 5.98)	0.98 (0.28 to 3.35)
P trend			<0.0001			0.5126			0.0335	
Fish										
No	2378	2354	1.00 (ref)	1.00 (ref)	1215	1.00 (ref)	1.00 (ref)	1068	1.00 (ref)	1.00 (ref)
Class 1	155	163	1.06 (0.85 to 1.33)	1.09 (0.83 to 1.42)	80	1.01 (0.77 to 1.34)	0.94 (0.64 to 1.39)	74	1.06 (0.80 to 1.42)	1.28 (0.88 to 1.86)
Class 2	27	53	1.98 (1.24 to 3.16)	2.13 (1.28 to 3.55)	16	1.16 (0.62 to 2.16)	0.74 (0.35 to 1.59)	8	0.66 (0.30 to 1.46)	0.53 (0.22 to 1.28)
Class 3	16	61	3.85 (2.21 to 6.70)	2.24 (1.18 to 4.25)	9	1.10 (0.49 to 2.50)	1.01 (0.38 to 2.71)	10	1.39 (0.63 to 3.08)	1.14 (0.43 to 3.03)
P trend			<0.0001			0.6747			0.7889	
Crab										
No	2423	2409	1.00 (ref)	1.00 (ref)	1235	1.00 (ref)	1.00 (ref)	1094	1.00 (ref)	1.00 (ref)
Class 1	120	122	1.02 (0.79 to 1.32)	0.95 (0.70 to 1.28)	62	1.01 (0.74 to 1.39)	0.92 (0.61 to 1.38)	44	0.81 (0.57 to 1.16)	0.79 (0.52 to 1.20)
Class 2	22	46	2.10 (1.26 to 3.51)	1.80 (1.04 to 3.12)	13	1.16 (0.58 to 2.31)	0.55 (0.25 to 1.20)	12	1.21 (0.60 to 2.45)	0.72 (0.31 to 1.66)
Class 3	11	54	4.94 (2.58 to 9.46)	4.75 (2.27 to 9.91)	10	1.78 (0.76 to 4.21)	0.66 (0.23 to 1.87)	10	2.01 (0.85 to 4.76)	1.45 (0.55 to 3.82)
P trend			<0.0001			0.2796			0.5212	
Shrimp										
No	2455	2434	1.00 (ref)	1.00 (ref)	1270	1.00 (ref)	1.00 (ref)	1098	1.00 (ref)	1.00 (ref)
Class 1	102	102	1.01 (0.76 to 1.34)	0.92 (0.66 to 1.28)	39	0.74 (0.51 to 1.08)	0.66 (0.40 to 1.08)	46	1.01 (0.71 to 1.44)	0.87 (0.56 to 1.37)
Class 2	9	24	2.69 (1.25 to 5.80)	4.07 (1.62 to 10.22)	5	1.07 (0.36 to 3.21)	0.58 (0.15 to 2.18)	8	1.99 (0.77 to 5.17)	2.03 (0.65 to 6.34)
Class 3	10	71	7.15 (3.68 to 13.89)	5.18 (2.49 to 10.75)	6	1.16 (0.42 to 3.20)	0.85 (0.25 to 2.82)	8	1.79 (0.70 to 4.55)	1.92 (0.69 to 5.35)
P trend			<0.0001			0.4474			0.1490	

*OR values of three allergic disease compared with controls.
aOR, adjusted OR; cOR, crude OR.

Table 5 ORs for allergic diseases with specific IgE class to food allergens (non-fish and seafood)

Allergen category	Control (n=2576)	Atopic dermatitis (n=2631)			Allergic rhinitis (n=1320)			Allergic asthma (n=1160)		
		n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)
Egg white/egg yolk										
No	2461	2415	1.00 (ref)	1.00 (ref)	1267	1.00 (ref)	1.00 (ref)	1106	1.00 (ref)	1.00 (ref)
Class 1	78	79	1.03 (0.75 to 1.42)	1.12 (0.78 to 1.61)	32	0.80 (0.53 to 1.21)	0.64 (0.38 to 1.08)	35	1.00 (0.67 to 1.50)	0.90 (0.55 to 1.46)
Class 2	17	42	2.52 (1.43 to 4.44)	2.32 (1.28 to 4.19)	10	1.14 (0.52 to 2.50)	1.39 (0.55 to 3.55)	9	1.18 (0.52 to 2.65)	0.72 (0.29 to 1.81)
Class 3	20	95	4.84 (2.98 to 7.86)	2.65 (1.53 to 4.61)	11	1.07 (0.51 to 2.24)	1.55 (0.67 to 3.57)	10	1.11 (0.52 to 2.39)	0.75 (0.30 to 1.85)
P trend			<0.0001			0.8415			0.7029	
Mutton										
No	2408	2450	1.00 (ref)	1.00 (ref)	1234	1.00 (ref)	1.00 (ref)	1078	1.00 (ref)	1.00 (ref)
Class 1	118	123	1.03 (0.79 to 1.33)	1.12 (0.85 to 1.48)	60	0.99 (0.72 to 1.36)	0.93 (0.63 to 1.36)	52	0.98 (0.71 to 1.38)	1.04 (0.72 to 1.51)
Class 2	31	39	1.24 (0.77 to 1.99)	1.28 (0.75 to 2.19)	16	1.01 (0.55 to 1.85)	0.74 (0.33 to 1.68)	15	1.08 (0.58 to 2.01)	0.48 (0.22 to 1.04)
Class 3	19	19	0.98 (0.52 to 1.86)	0.54 (0.25 to 1.14)	10	1.03 (0.48 to 2.22)	1.29 (0.50 to 3.35)	15	1.76 (0.89 to 3.48)	1.63 (0.72 to 3.66)
P trend			0.5808			0.9746			0.2266	
Milk										
No	2424	2398	1.00 (ref)	1.00 (ref)	1243	1.00 (ref)	1.00 (ref)	1090	1.00 (ref)	1.00 (ref)
Class 1	126	119	0.96 (0.74 to 1.23)	1.00 (0.76 to 1.32)	64	0.99 (0.73 to 1.35)	0.93 (0.65 to 1.33)	50	0.88 (0.63 to 1.23)	0.95 (0.66 to 1.37)
Class 2	16	51	3.22 (1.83 to 5.67)	3.61 (1.96 to 6.65)	7	0.85 (0.35 to 2.08)	1.28 (0.42 to 3.93)	10	1.39 (0.63 to 3.07)	1.36 (0.55 to 3.40)
Class 3	10	63	6.36 (3.26 to 12.43)	5.84 (2.73 to 12.50)	6	1.17 (0.42 to 3.23)	1.02 (0.26 to 4.07)	10	2.22 (0.92 to 5.36)	1.40 (0.48 to 4.09)
P trend			<0.0001			0.9814			0.2746	
Beef										
No	2443	2498	1.00 (ref)	1.00 (ref)	1250	1.00 (ref)	1.00 (ref)	1097	1.00 (ref)	1.00 (ref)
Class 1	94	91	0.95 (0.71 to 1.27)	0.91 (0.66 to 1.26)	48	1.00 (0.70 to 1.42)	0.94 (0.62 to 1.41)	34	0.81 (0.54 to 1.20)	0.86 (0.55 to 1.33)
Class 2	19	21	1.08 (0.58 to 2.02)	0.22 (0.09 to 0.51)	11	1.13 (0.54 to 2.39)	1.07 (0.42 to 2.76)	14	1.64 (0.82 to 3.29)	1.04 (0.45 to 2.38)
Class 3	20	21	1.03 (0.56 to 1.90)	0.53 (0.25 to 1.14)	11	1.08 (0.51 to 2.25)	1.56 (0.55 to 4.44)	15	1.67 (0.85 to 3.28)	1.31 (0.57 to 3.03)
P trend			0.9970			0.7771			0.1923	

Continued

Table 5 Continued

Allergen category	Control (n=2576)	Atopic dermatitis (n=2631)			Allergic rhinitis (n=1320)			Allergic asthma (n=1160)		
		n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)	n	cOR* (95% CI)	aOR* (95% CI)
Wheat										
No	2354	2400	1.00 (ref)	1.00 (ref)	1195	1.00 (ref)	1.00 (ref)	1054	1.00 (ref)	1.00 (ref)
Class 1	175	183	1.03 (0.83 to 1.27)	0.95 (0.74 to 1.22)	100	1.13 (0.87 to 1.45)	0.73 (0.53 to 1.02)	79	1.01 (0.77 to 1.33)	0.91 (0.66 to 1.27)
Class 2	26	26	0.98 (0.57 to 1.69)	1.00 (0.52 to 1.94)	13	0.99 (0.50 to 1.92)	0.61 (0.27 to 1.38)	14	1.20 (0.63 to 2.31)	0.89 (0.37 to 2.18)
Class 3	21	22	1.03 (0.56 to 1.87)	0.86 (0.44 to 1.68)	12	1.13 (0.55 to 2.30)	0.66 (0.27 to 1.60)	13	1.38 (0.69 to 2.77)	1.36 (0.59 to 3.11)
P trend			0.8730			0.4715			0.3747	

*OR values of three allergic disease compared with controls.
aOR, adjusted OR; cOR, crude OR.

epitopes with allergenic potential, glycosylation status, resistance to proteolysis and enzymatic activity, some proteins are more allergenic than others and different allergens may cause different allergic diseases through various underlying mechanisms.[31] However, some studies showed inconsistent findings. Several studies showed that indoor allergens have a bearing on the prevalence of atopic dermatitis in some individuals.[32 33] Other studies showed a relationship between sensitisation to food allergens and allergic rhinitis and allergic asthma.[34] The inconsistency of those studies may be related to regional variation and different climate characteristics, which affect the morphology of the allergen-carrying agents and modify their allergenic potential.[35 36] In addition, genetic susceptibility and socioeconomic status of the populations may influence the occurrence of allergic diseases.[3 37 38]

This study revealed that there was a dose–response relationship between specific IgE levels of allergens and prevalence of allergic diseases, in which the odds of allergic diseases increase with increasing allergen-specific IgE levels. Our findings are in line with a study in America revealing a dose–response relationship between exposure to mouse allergen and the morbidity of allergic asthma in urban children and adolescents.[39] Another research evaluated that whether TPI ASM8 (a drug product containing two antisense oligonucleotides: TOP004 directed against the human beta subunit of IL-3, IL-5, and GM-CSF receptors and TOP005 directed against the human chemokine receptor CCR3) induced a dose–dependent reduction in the inflammatory and physiological changes following inhaled allergen challenge.[40] It is worth noting that there was a combined effect of sensitisation to different allergens on allergic diseases. Multiple sensitisations to several allergens had a relatively stronger association with allergic diseases than single sensitisation to one allergen. Some research results were similar to our findings. Kumar *et al* reported that simultaneous sensitisation to food and inhalant allergens (insect and pollen) may increase the risk of asthma and rhinitis or exacerbate symptoms.[41] A cross-sectional population-based case–control study in Finland adults found that the pathomechanisms of sensitisation to one allergen are different from those of sensitisation to several allergen types, and the latter are more likely to induce asthma.[42] In addition, most allergens were significantly associated with allergic diseases only when their IgE level classes ≥2 according to our study. Such findings may be of more clinical value than a dichotomous designation of sensitised or not sensitised to allergens and can potentially be used for improving the diagnosis of allergic diseases.

According to the previous studies, genetic and environmental factors play important roles in sensitisation to allergens.[18 43–46] In our study, the family history of atopic dermatitis and allergic rhinitis were significantly different compared with the controls, while there was no difference in family history between allergic asthma and controls. The proportion living in rural was significantly higher in patients with atopic dermatitis and allergic asthma than

Table 6 ORs for allergic diseases in relation to number of allergens

	Control (n=2576)	n	cOR* (95% CI)	aOR* (95% CI)
		Atopic dermatitis (n=2631)		
Number of allergens†				
No	2422	2142	1.00 (ref)	1.00 (ref)
1	135	375	3.14 (2.56 to 3.86)	3.00 (2.44 to 3.69)
2	19	79	4.70 (2.84 to 7.78)	4.28 (2.57 to 7.11)
≥3	0	35	–	–
P trend			<0.0001	
		Allergic rhinitis (n=1320)		
Number of allergens‡				
No	2181	893	1.00 (ref)	1.00 (ref)
1	286	312	2.66 (2.23 to 3.19)	2.64 (2.20 to 3.18)
2	106	97	2.24 (1.68 to 2.98)	2.13 (1.58 to 2.87)
≥3	3	18	14.65 (4.31 to 49.87)	13.00 (3.76 to 45.00)
P trend			<0.0001	
		Allergic asthma (n=1160)		
Number of allergens§				
No	2183	845	1.00 (ref)	1.00 (ref)
1	319	243	1.97 (1.64 to 2.37)	2.06 (1.70 to 2.49)
2	74	68	2.37 (1.69 to 3.33)	2.37 (1.67 to 3.37)
≥3	0	4	–	–
P trend			<0.0001	

*OR values of three allergic disease compared with controls.
†Allergens excluding those allergens which were not related with atopic dermatitis in tables 2–5.
‡Allergens excluding those allergens which were not related with allergic rhinitis in tables 2–5
§Allergens excluding those allergens which were not related with allergic asthma in tables 2–5.
aOR, adjusted OR; cOR, crude OR.

controls, while there was no difference in location of residence between allergic rhinitis and controls. We can investigate the family history and location of residence and combine clinical symptoms to speculate whether the patients are likely to be sensitive to allergens and recommend further appropriate testing.

It is obvious that allergens avoidance is the most effective means of prevention for allergy sufferers considering that allergic diseases are triggered by those allergens. However, this may not be true in some cases. Completely avoiding contact with some indoor and outdoor allergens is not always feasible. Moreover, early exposure to food allergens has been turned out to be a successful method for the prevention of peanut allergy.[47] Many studies reported that allergen immunotherapy was an effective treatment strategy for allergic diseases.[48 49] However, for some patients with severe symptoms, allergen avoidance and treatment of symptoms may be necessary. Our findings could provide some evidence for clinicians about avoidance or specific immunotherapy treatment for patients with allergic diseases.

There are several strengths in this study. First, the sample size of this study was relatively large, which enabled us to classify specific IgE levels of 16 common allergens into three levels: class 1, class 2 and class 3. This enabled us to analyse the dose–response relationship between specific IgE levels and the prevalence of allergic diseases and the combined effect of sensitisation to multiple allergens with allergic diseases. Second, the 16 allergens were categorised into three categories: indoor allergens, outdoor allergens and food allergens, and the associations between each type of allergens and different allergic diseases were analysed. However, there are some limitations in this study. First, we cannot determine when the patients were first sensitised to allergens or when they first developed an allergic disease. We did not collect the specific date of the patient's visit to the hospital, so we could not analyse the impact of seasonal factors on allergic diseases. Second, this study was performed only in one hospital in Harbin, the generalisability of our results to the whole of China still needs to be further explored.

In conclusion, food allergen sensitisation is associated with atopic dermatitis, while indoor and outdoor allergen sensitisations are related to allergic rhinitis and asthma in northeastern China. There is a dose–response relationship between allergen-specific IgE levels and allergic diseases, and multiple sensitisations increase the risk of allergic diseases. Our findings could provide evidence for the control and management of allergic diseases, and may have important public health implications.

Contributors WZ and BX designed the process of this study and the structure of this article. YW and ML designed the questionnaire. WZ and BX participated in case collection and questionnaire investigation and analysed the data. WZ wrote the manuscript, and all other authors read and confirmed the final version. YW is responsible for the overall content as guarantor.

Funding This article was supported by the Youth Science Foundation Project of the National Natural Science Foundation of China (82003556) and the National Science and Technology Major Project of China (2016Z×08011005).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but participants were not subjected to intervention and gave informed consent to participate in the study before taking part, so the Institutional Review Board (IRB) of Harbin Medical University exempted our study according to the regulations of our school, exempted this study. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD

Wei Zhang http://orcid.org/0000-0002-1199-8924

REFERENCES

1 Ana B, de la Torre F, EpidMite Study Group. Characteristics, quality of life and control of respiratory allergic diseases caused by house dust mites (HDMs) in Spain: a cross-sectional study. *Clin Transl Allergy* 2019;9:39.
2 Tremlett H, Rodney R, Lucas R. Can falling infection rates in one country explain rising incidence of autoimmune and allergic diseases in other countries? caution when (over) interpreting ecological data from disparate areas. *Mult Scler Relat Disord* 2018;21:A3–5.
3 D'Amato G, Holgate ST, Pawankar R, *et al*. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the world allergy organization. *World Allergy Organ J* 2015;8:25.
4 Reinmuth-Selzle K, Kampf CJ, Lucas K, *et al*. Air pollution and climate change effects on allergies in the Anthropocene: abundance, interaction, and modification of allergens and adjuvants. *Environ Sci Technol* 2017;51:4119–41.
5 Smoldovskaya O, Feyzkhanova G, Voloshin S, *et al*. Allergen-specific IgE and IgG4 patterns among patients with different allergic diseases. *World Allergy Organ J* 2018;11:35.
6 Kiotseridis H, Cilio CM, Bjermer L, *et al*. Grass pollen allergy in children and adolescents-symptoms, health related quality of life and the value of pollen prognosis. *Clin Transl Allergy* 2013;3:19.
7 Gray CL, Levin ME, du Toit G. Egg sensitization, allergy and component patterns in African children with atopic dermatitis. *Pediatr Allergy Immunol* 2016;27:709–15.
8 Wakamiya S, Matsune S, Okubo K, *et al*. Causal relationships among pollen counts, Tweet numbers, and patient numbers for seasonal allergic rhinitis surveillance: retrospective analysis. *J Med Internet Res* 2019;21:e10450.
9 Pomés A, Chapman MD, Wünschmann S. Indoor allergens and allergic respiratory disease. *Curr Allergy Asthma Rep* 2016;16:43.
10 Hose AJ, Depner M, Illi S, *et al*. Latent class analysis reveals clinically relevant atopy phenotypes in 2 birth cohorts. *J Allergy Clin Immunol* 2017;139:1935–45. e12.
11 Park SC, Hwang CS, Chung HJ, *et al*. Geographic and demographic variations of inhalant allergen sensitization in Koreans and non-Koreans. *Allergol Int* 2019;68:68–76.
12 Yan YR, YH X, Zheng Q, *et al*. The prevalence and sex difference of allergen sensitization among adult patients with allergic diseases in Shanghai, China. *Asian Pacific journal of allergy and immunology* 2018.
13 Sun X, Zhao J, Wang Q, *et al*. Prevalence of allergen sensitization among 15,534 patients with suspected allergic diseases in Henan Province, China. *Asian Pac J Allergy Immunol* 2019;37:57–64.
14 Sun B-Q, Zheng P-Y, Zhang X-W, *et al*. Prevalence of allergen sensitization among patients with allergic diseases in Guangzhou, southern China: a four-year observational study. *Multidiscip Respir Med* 2014;9:2.
15 Nickel R, Kulig M, Forster J, *et al*. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;99:613–7.
16 Kerkhof M, Postma DS, Schouten JP, *et al*. Allergic sensitization to indoor and outdoor allergens and relevance to bronchial hyperresponsiveness in younger and older subjects. *Allergy* 2003;58:1261–7.
17 Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: mimics, overlaps, and complications. *J Clin Med* 2015;4:884–917.
18 Cheng L, Chen J, Fu Q, *et al*. Chinese Society of allergy guidelines for diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res* 2018;10:300–53.
19 McCracken JL, Veeranki SP, Ameredes BT, *et al*. Diagnosis and management of asthma in adults: a review. *JAMA* 2017;318:279–90.
20 Warner JO, Kaliner MA, Crisci CD, *et al*. Allergy practice worldwide: a report by the world allergy organization specialty and training Council. *Int Arch Allergy Immunol* 2006;139:166–74.
21 Simons FER, Ardusso LRF, Bilò MB, *et al*. World allergy organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587–93. e1-22.
22 Amat F, Soria A, Tallon P, *et al*. New insights into the phenotypes of atopic dermatitis linked with allergies and asthma in children: an overview. *Clin Exp Allergy* 2018;48:919–34.
23 Boulet LP, Turcotte H, Laprise C, *et al*. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. *Clin Exp Allergy* 1997;27:52–9.
24 Eguiluz-Gracia I, Mathioudakis AG, Bartel S, *et al*. The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. *Allergy* 2020;75:2170–84.
25 Okamoto Y, Fujieda S, Okano M, *et al*. House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis. *Allergy* 2017;72:435–43.
26 Custovic A, Sonntag H-J, Buchan IE, *et al*. Evolution pathways of IgE responses to grass and mite allergens throughout childhood. *J Allergy Clin Immunol* 2015;136:1645–52.
27 Yoshida K, Adachi Y, Akashi M, *et al*. Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren. *Allergy* 2013;68:757–63.
28 Siroux V, Boudier A, Nadif R, *et al*. Association between asthma, rhinitis, and conjunctivitis multimorbidities with molecular IgE sensitization in adults. *Allergy* 2019;74:824–7.
29 Marchetti P, Pesce G, Villani S, *et al*. Pollen concentrations and prevalence of asthma and allergic rhinitis in Italy: evidence from the GEIRD study. *Sci Total Environ* 2017;584-585:1093–9.
30 Chang A, Robison R, Cai M, *et al*. Natural history of Food-Triggered atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract* 2016;4:229–36. e1.
31 Huby RD, Dearman RJ, Kimber I. Why are some proteins allergens? *Toxicol Sci* 2000;55:235–46.

32 Cid BJ, Perez-Mateluna G, Iturriaga C, *et al*. Is there an association between indoor allergens and the severity of atopic dermatitis? *Int J Dermatol* 2019;58:433–9.
33 Capristo C, Romei I, Boner AL. Environmental prevention in atopic eczema dermatitis syndrome (AEDS) and asthma: avoidance of indoor allergens. *Allergy* 2004;59 Suppl 78:53–60.
34 Pénard-Morand C, Raherison C, Kopferschmitt C, *et al*. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy* 2005;60:1165–71.
35 Lombardi C, Canonica GW, Passalacqua G, *et al*. The possible influence of the environment on respiratory allergy: a survey on immigrants to Italy. *Ann Allergy Asthma Immunol* 2011;106:407–11.
36 D'Amato G, Cecchi L. Effects of climate change on environmental factors in respiratory allergic diseases. *Clin Exp Allergy* 2008;38:1264–74.
37 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International study of asthma and allergies in childhood (ISAAC) Steering Committee. *Lancet* 1998;351:1225–32.
38 Papadopoulos NG, Agache I, Bavbek S, *et al*. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.
39 Torjusen EN, Diette GB, Breysse PN, *et al*. Dose-Response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. *Indoor Air* 2013;23:268–74.
40 Gauvreau GM, Pageau R, Séguin R, *et al*. Dose-Response effects of TPI ASM8 in asthmatics after allergen. *Allergy* 2011;66:1242–8.
41 Kumar R. Association of sensitization to food and inhalant allergens in patients of asthma and rhinitis. *Clin Transl Allergy* 2011;1:P119.
42 Toppila-Salmi S, Huhtala H, Karjalainen J, *et al*. Sensitization pattern affects the asthma risk in Finnish adult population. *Allergy* 2015;70:1112–20.
43 Chen H, Li J, Cheng L, *et al*. China consensus document on allergy diagnostics. *Allergy Asthma Immunol Res* 2021;13:177–205.
44 Feng M, Yang Z, Pan L, *et al*. Associations of early life exposures and environmental factors with asthma among children in rural and urban areas of Guangdong, China. *Chest* 2016;149:1030–41.
45 Wong GWK, Li J, Bao Y-X, *et al*. Pediatric allergy and immunology in China. *Pediatr Allergy Immunol* 2018;29:127–32.
46 Mastrorilli C, Caffarelli C, Hoffmann-Sommergruber K. Food allergy and atopic dermatitis: prediction, progression, and prevention. *Pediatr Allergy Immunol* 2017;28:831–40.
47 Du Toit G, Roberts G, Sayre PH, *et al*. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803–13.
48 Westman M, Lupinek C, Bousquet J, *et al*. Early childhood IgE reactivity to pathogenesis-related class 10 proteins predicts allergic rhinitis in adolescence. *J Allergy Clin Immunol* 2015;135:1199–206.
49 Berings M, Karaaslan C, Altunbulakli C, *et al*. Advances and highlights in allergen immunotherapy: on the way to sustained clinical and immunologic tolerance. *J Allergy Clin Immunol* 2017;140:1250–67.

Associations between sensitization to allergens and allergic diseases: a hospital-based case-control study in China

Supplementary Method:

1. The definition of demographic, family history, and lifestyle factors

Age was calculated as the difference between the year of birth and the year of interview. Educational status was categorized into three levels: junior high school or lower, senior high school, and university or higher. The residential region was categorized into two groups: urban and rural. Marital status was also categorized into two groups: unmarried and married. Current smokers were defined on the basis of the World Health Organization criteria, as those who self-reported smoking every day for at least 6 months[9]. Regular alcohol drinkers were defined as drinking more than twice per week for at least one year. Classification of physical exercise (PE) was defined as followed:

We estimated PE condition of study participants using three variables of a structured questionnaire, exercise intensity (EI), exercise time (ET), and exercise frequency (EF) [1-4].

EI of study participants was classified into three groups, mild, moderate and strenuous exercise according to their exercise types. Value 1, 2 and 3 were assigned to the three groups respectively [5-8]. ET was measured by the hour. EF referred to how many times a week. We defined PE as

$$PE = \sum_{i=1}^{N} EI \times ET$$

Where N represented EF. If PE $\geq$ 2, PE was positive; PE was negative when PE $<$ 2. Therefore, as for a subject jogging (moderate exercise) 15 minutes 5 times a week, his/her PE was positive because PE $\geq$ 2 (PE = 5$\times$ 0.25 $\times$ 2 = 2.5).

2. The diagnostic criteria of atopic dermatitis, allergic asthma, and allergic rhinitis

2.1 Atopic dermatitis

The following diagnostic criteria for atopic dermatitis was developed by the American

Academy of Dermatology (AAD), which is based on age-specific clinical criteria that include pruritus and chronic or relapsing spongiotic dermatitis involving the face, trunk, and/or extensor extremities in infants, flexural surfaces like the wrists/ankles and antecubital/popliteal fossae in children, or the hands in adults[10].

Essential Features (both must be present):

1) Pruritus

2) Eczema (acute, subacute, chronic)

a. Chronic or relapsing history

b. Typical morphology and age-specific patterns

Infants: face, trunk (except "diaper area"), extensor extremities

Children: flexors (wrists, ankles, antecubital/popliteal fossae)

Adults: hands

All ages: sparing of the groin and axillary regions

Important Features (support the diagnosis and are observed in most cases of atopic dermatitis):

1) Early age of onset

2) Atopy

a. personal and/or family history; or

b. IgE reactivity

3) Xerosis

Associated Features (suggestive of atopic dermatitis, but too nonspecific to define or detect atopic dermatitis in research or epidemiologic studies):

1) Atypical vascular responses (eg, facial pallor, white dermatographism, delayed blanch response)

2) Keratosis pilaris, pityriasis alba, hyperlinear palms/ichthyosis

3) Ocular/periorbital changes (fissures, infraorbital folds)

4) Other regional findings (eg, perioral changes/periauricular lesions)

5) Perifollicular accentuation/lichenification/prurigo lesions

2.2 Allergic rhinitis

The diagnosis criteria for allergic rhinitis are as follows[11]:

1) Clinical history

Clinical history is essential for the accurate diagnosis of allergic rhinitis and the assessment of its severity as well as its response to treatment. The most frequent symptoms include sneezing, anterior rhinorrhea, bilateral nasal obstruction, and nasal pruritus in patients with allergic rhinitis. In addition, most patients with pollen-induced rhinitis have eye symptoms. It is also important to distinguish between allergy and nonallergy symptoms. Subjective assessment of symptoms of allergic rhinitis is generally based on 4 nasal symptoms (sneezing, rhinorrhoea, nasal itching, and nasal obstruction) and 2 ocular symptoms (ocular itching/grittiness/redness and ocular tearing). In China, VAS is most commonly used to quantify the above-mentioned assessments. VAS was used to quantify the above-mentioned assessments.

2) Nasal examinations

Anterior rhinoscopy and nasal endoscopy are the widely used approaches. The nasal examination should describe: 1) the anatomical situation in the nose (e.g. the septum, the size of the inferior turbinate, and if possible the structures in the middle meatus); 2) the color of the mucosa; and 3) the amount and aspect of the mucus. Endoscopic images of nasal mucosa in patients suffering from allergic rhinitis generally demonstrate pale and edematous nasal mucosa, watery nasal discharge, and swollen inferior turbinates.

3) Skin tests

Two methods of skin testing, including intradermal skin tests and skin prick tests (SPTs), are available in China. Skin tests should be read at the peak of their reaction by measuring the wheal and the flare approximately 15 minutes after the performance of the tests. For prick tests, when the control site is completely negative, wheals of >3 mm represent a positive skin response.

4) Serum specific IgE measurements

Enzyme-labeled anti-IgE measurement has been widely used in China. Results are expressed in terms of units of IgE (IU/mL, KU/L). The IgE level above 0.35 KU/L is usually testified as a positive result.

5) Differential diagnosis

In addition, it is necessary to differentiate allergic rhinitis from other diseases, such as vasomotor rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), infectious rhinitis, hormonal rhinitis, medicamentous rhinitis (rhinitis medicamentosa), aspirin intolerance triad, cerebrospinal fluid rhinorrhea, and so on.

2.2 Allergic asthma

The diagnosis criteria for allergic asthma are as follows[12]:

1) Clinical history

Wheezing, coughing, chest tightness

May only be present or worsened with exertion, upper respiratory infection, seasonal or perennial allergies

Nocturnal cough, particularly 2 AM to 4 AM

Need for short-acting β_2-agonist inhaler for relief of symptoms

Personal or family history of atopy

2) Spirometry

Airway obstruction evidenced by FEV_1: FVC ratio < lower limit of normal

Demonstrated reversibility of obstruction by increase in $FEV_1 \geq 200$mL and $\geq 12\%$ from baseline measure after inhalation of 2-4 puffs of short-acting β_2-agonist

Normal spirometry findings are not inconsistent with asthma

3) Bronchoprovocation with methacholine

20% or more decrease in FEV_1 with after inhalation of low concentration (< 4 mg/mL) of methacholine; used principally in patients with symptoms consistent with asthma but who exhibit normal pulmonary function tests

4) Impedance oscillometry

Elevated airway resistance at 5 HZ, elevated area of reactance, increased resonant frequency (Fres), reactance at 5 HZ more negative than predicted

5) Chest radiograph or CT scan of thorax

Usually normal but can exclude other diagnoses such as emphysema, lung cancer, infiltrative diseases, pneumonia

6) CBC

Eosinophilia, particularly > 300/μL; results can inform selection for mepolizumab or reslizumab therapy

7) Serum total IgE

Elevated in atopic asthma, not in nonatopic asthma; can inform selection of omalizumab therapy

8) Skin prick testing or serum-specific IgE for aeroallergens

Positive, particularly for perennial allergens, or seasonal allergens with corresponding seasonal variation in asthma symptoms; may be negative in nonatopic asthma; can inform omalizumab therapy

Positive testing can guide allergen avoidance strategies

9) Fractional excretion of nitric oxide

Intermediate level: 25-50 ppb in patients aged ≥ 12 y

High level: > 50ppb in patients aged ≥ 12 y

References

1. Schoenmakers, P., Reed, K., Van Der Woude, L., & Hettinga, F. J. High Intensity Interval Training in Handcycling: The Effects of a 7 Week Training Intervention in Able-bodied Men. Front. Physiol. 7, 638 (2016).
2. Tikkanen-Dolenc, H. et al. Frequent and intensive physical activity reduces risk of cardiovascular events in type 1 diabetes. Diabetologia doi: 10.1007/s00125-016-4189-8 (2016).
3. Mayer, J. M. et al. Effect of Lumbar Progressive Resistance Exercise on Lumbar Muscular Strength and Core Muscular Endurance in Soldiers. Mil. Med. 181, e1615- e1622 (2016).
4. King, A. C. et al. Preserving older adults' routine outdoor activities in contrasting neighborhood environments through a physical activity intervention. Prev. Med. 96, 87-93 (2016).
5. Parks, C. M. & Manohar, M. Distribution of blood flow during moderate and strenuous exercise in ponies (Equus caballus). Am. J. vet. Res. 44, 1861-1866 (1983).
6. Vijayaraghava, A., Doreswamy, V., Narasipur, O. S., Kunnavil, R. & Srinivasamurthy, N. Effect of yoga practice on levels of inflammatory markers after moderate and strenuous exercise. J. Clin. Diagn. Res. 9, CC08-12 (2015).
7. Wang, J. S. et al. Different effects of strenuous exercise and moderate exercise on platelet function in men. Circulation 90, 2877-2885 (1994).
8. Duzova, H., Karakoc, Y., Emre, M. H., Dogan, Z. Y. & Kilinc, E. Effects of Acute Moderate and Strenuous Exercise Bouts on IL-17 Production and Inflammatory Response

in Trained Rats. J. Sports Sci. Med. 8, 219-224 (2009).

9. WHO. Guidelines for the Conduct of Tobacco Smoking Surveys for the General Population. In Geneva, Switzerland: World Health Organization Document WHO/SMO/83 (1983).

10. Siegfried EC, Hebert AA. Diagnosis of Atopic Dermatitis: Mimics, Overlaps, and Complications. J Clin Med. 2015; 4(5): 884-917.

11. Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, Tan G, Tao Z, Wang D, Wen W, Xu R, Xu Y, Yang Q, et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. Allergy Asthma Immunol Res. 2018; 10(4): 300-353.

12. McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and Management of Asthma in Adults: A Review. Jama. 2017; 318(3): 279-290.

Supplementary Table:

Supplementary Table S1. Sixteen common allergens used in this study.

category	allergens			
indoor allergens	Dermatophagoides pteronyssinus	Cat and dog fur	Mould mixture [a]	
outdoor allergens	common ragweed and mugwort	German cockroach	Tree pollen mixture [b]	Hop
food allergens	Egg white/egg yolk	Blue mussel	Fish	Crab
	Mutton	Milk	Beef	Shrimp
	Wheat			

[a] Mould mixture is composed of Penicillium notatum, Cladosporium herbarum, Aspergillus fumigatus and Alternaria alternate.

[b] Tree pollen mixture is composed of Robur, Elm, London Plane, Willow and cottonwood.