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Article type : Letter to the Editor

Prevalence Patterns of Allergen Sensitization by Region, Gender, Age and Season among Patients with Allergic Symptoms in Mainland China: A Four-Year Multicenter Study

To the Editor,

The proportion of the population with allergic diseases has increased rapidly in recent decades¹.² In addition to affecting the quality of life, a significant economic burden of these diseases was transferred to society and the national health care system¹. China is a large country with a rapidly developing economy, wide geography, and diverse climate and lifestyles, which may lead to significantly regional differences in the distribution of allergens. Although a series of studies have explored the prevalence of allergen sensitization in China, the majority of them focus on one part of geography in China³⁻⁵. In 2009, a study⁶ was conducted to estimate the prevalence of common aeroallergens among patients with allergic asthma and/or rhinitis in mainland China. Although the study investigated the differences of the prevalence in different regions of China, it divided China into only four geographical regions, which may neglect detailed information about the

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characteristics of sensitization prevalence in different places in China. In that study, the skin prick test (SPT) was used to detect the sensitization to allergens. The method has low accuracy for positive results because it is heavily affected by certain factors, such as the skill of the tester, reagent used, interpretation of results and so on. Our research has the following different characteristics compared with previous studies: 1) covering a variety of allergic diseases, 2) exploring both aeroallergens and food allergens simultaneously, 3) including a large set of data from all the seven regions of mainland China, and 4) using an internationally recognized method of sIgE testing, ImmunoCAP, to detect sensitization. These advantages may help us obtain more accurate and reliable results and conclusions.

Here, we conducted a large multicenter study on the prevalence patterns of serum allergen-specific IgE (sIgE) sensitization to the four most common food allergens (i.e., egg white, cow's milk, crab, and shrimp) and five aeroallergens (i.e., house dust mite, German cockroach, tree pollen mix, mold mix, dog dander) among 44156 patients with allergic symptoms in 52 cities from 26 provinces of all the seven geographical regions in mainland China from July 2015 to June 2018. These patients were evaluated by the physicians in the hospital and those who were suspected to have allergic diseases were then referred to have an sIgE sensitization test conducted by a certified third-party laboratory service provider with uniform and standardized procedures. This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (Approval number: GYFYY-2017-18). Details about the methods were in the **supplementary materials**.

Our study showed that the overall prevalence of positive sIgE responses to the 9 allergens across mainland China from the highest to the lowest was 33.74% for house dust mites, 24.5% for cockroaches, 19.97% for shrimp, 17.31% for crab, 11.62% for cow's milk, 10.92% for egg white, 9.35% for tree pollen mix, 4.02% for dog dander and 3.92% for mold mix (**Table 1**). Our study

confirmed that an observation that the positive cases in sIgE fell mainly in the two low classes (i.e., classes 1 and 2) as shown in previous studies for certain specific areas in China³⁻⁵ was also held in all the seven regions in mainland China (**Table 1**).

Our study revealed the distinctive patterns in the prevalence of allergen sensitization by region, gender, age and season. Geographically, there is a significant difference in the prevalence among regions for all 9 allergens except for the mold mix (**Table S1**). House dust mites were the allergen with the highest prevalence of sensitization in all seven regions, with the highest in South China (40.79%) and the lowest in Northeast China (11.21%). Allergies to German cockroaches had a higher prevalence in southern regions (Southwest China, South China and East China) than in northern regions (North China and Northeast China). The prevalence of sIgE responses to dog dander was the highest in North China and was very close to each other in the southern regions. The prevalence of the egg white and milk in Central China, East China and South China was higher than in Southwest China, North China and Northeast China, which means that patients living in eastern, coastal and/or southern areas were more sensitive to egg white and cow's milk. The prevalence of crab and shrimp sensitization in Southwest China and South China was higher than that in the northern regions (North China and Northeast China). The difference in sensitization between crab and shrimp is small although people in different regions of China may have different preference in eating crab or shrimp (**Table S1**). The heatmap (**Figure 1**) displays the distribution of the prevalence of the sIgE response to allergens in different regions of mainland China.

The prevalence of sensitization to all nine allergens was higher overall in males than in females significantly (**Table 1** and **Figure S1**) although that may not be true in each age group for each allergen as shown in the forest plot in **Figure S1**. Our study showed that house dust mite, German cockroach, tree pollen, dog dander, crab and shrimp had a prevalence pattern by age that the

prevalence grows continuously as the age increases before and during the teenage period and then decreases continuously as the age increases after the teenage period ends whereas egg white and cow's milk had a pattern that the prevalence in the toddlers is the highest and then decrease continuously as the age increases (**Figure S2**). Mold had a pattern essentially from the mixture of these two patterns mainly caused by the different prevalence patterns in females and males (**Figures S2&S3**). Our study further showed that the peak of prevalence of house dust mite, German cockroach, tree pollen mix, dog dander, crab and shrimp moved roughly from late teenage to early teenage when middle/high sIgE classes (i.e., classes 3-6) instead of all classes (i.e., classes 1-6) were considered (**Figures S2&S4**). This move was clearer in females as compared to males (**Figures S3&S5**). **Figure S6** displays the prevalence pattern of allergens by month across years. The prevalence of dog dander and mold mix was very stable across months; however, the prevalence of other allergens fluctuated from January to December. The prevalence of house dust mites, German cockroach, shrimp and crab were higher in the summer months (from June to August) than in other months. The prevalence of tree pollen mix for classes 1-6 had two clearly high peaks in April and October, respectively; however, the peak in October disappeared when only classes 3-6 are considered.

We believe this is the first large study to investigate the prevalence of allergen sensitization in the patients with allergic symptoms from all the seven geographic regions of mainland China. Based on this study, we found that the prevalence of sIgE sensitization to allergens displayed distinctive patterns among regions, gender, age groups and seasons. The reasons for these patterns may include lifestyle factors, socioeconomic factors, genetic predispositions, climate, sexual hormones, cross-reactivity and so on^{3,4,6-9}. Please refer to **the supplementary materials** for the detailed discussion on the factors that influenced these variations. Our findings may help clinicians find effective individualized treatments for unique patient groups and direct researchers to conduct

further studies on the epidemiology of allergic diseases.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table 1. Overall prevalence of sIgE responses to 9 allergens and their proportion of each class as well as sIgE response to allergens in males and females

Allergens	German								
	House dust mite (d1)	cockroach (i6)	Tree pollen mix (tx4)	Mold mix (mx1)	Dog dander (e5)	Egg white (f1)	Cow's milk (f2)	Crab (f23)	Shrimp (f24)
Total cases (N)	31680	29343	9155	28746	31061	31109	31111	30830	30442
Positive cases	10690	7189 (24.5)	856 (9.35)	1126 (3.92)	1249 (4.02)	3396 (10.92)	3616 (11.62)	5336 (17.31)	6078 (19.97)
[n (%)]	(33.74)								
sIgE Class	class 1	2397 (22.42)	2232 (31.05)	471 (55.02)	533 (47.34)	711 (56.93)	1535 (45.20)	1411 (39.02)	1965 (36.83)
	class 2	3591 (33.59)	3571 (49.67)	282 (32.94)	408 (36.23)	424 (33.95)	1492 (43.93)	1708 (47.23)	2598 (48.69)
	class 3	2032 (19.01)	1240 (17.25)	64 (7.48)	149 (13.23)	89 (7.13)	308 (9.07)	436 (12.06)	670 (12.56)
	class 4	1197 (11.20)	134 (1.86)	17 (1.99)	29 (2.58)	17 (1.36)	49 (1.44)	46 (1.27)	80 (1.50)
	class 5	738 (6.90)	11 (0.15)	12 (1.40)	6 (0.53)	7 (0.56)	9 (0.27)	10 (0.28)	13 (0.24)
	class 6	735 (6.88)	1 (0.01)	10 (1.17)	1 (0.09)	1 (0.08)	3 (0.09)	5 (0.14)	10 (0.19)
Male	N	14340	13192	4070	12830	13988	14041	14066	13812
	n (%)	5252(36.62)	3469(26.3)	447(10.98)	612(4.77)	637(4.55)	1988(14.16)	2224(15.81)	2616(18.94)
female	N	16856	15702	4903	15404	16597	16599	16572	16498
	n (%)	5303(31.46)	3634(23.14)	398(8.12)	490(3.18)	599(3.61)	1364(8.22)	1342(8.1)	2659(16.12)
χ^2		92.07	38.26	21.07	46.7	17.23	274.96	439.37	41.48
p -value		8.4E-22	6.2E-10	4.4E-6	8.3E-1	3.3E-5	9.4E-62	1.5E-97	1.2E-1
				2				0	7

Note: A patient is tested positive in sIgE if the sIgE level ≥ 0.35 kUA/L. These sIgE positive patients are categorized further into six classes based on the absolute sIgE level in the unit of kUA/L: class 1 (0.35 ~ 0.70), class 2 (0.70 ~ 3.50), class 3 (3.50 ~ 17.50), class 4 (17.50 ~ 50.00), class 5 (50.00 to ~ 100.00) and class 6 (≥ 100.00). A small portion of participants had missing information on gender although they had valid sIgE test result. These participants were counted for the sIgE positive cases and class levels among

the total tested but not for the prevalence of male and female participants, leading to the result that the numbers of male and female participants did not add up to the total tested in the sIgE sensitization.

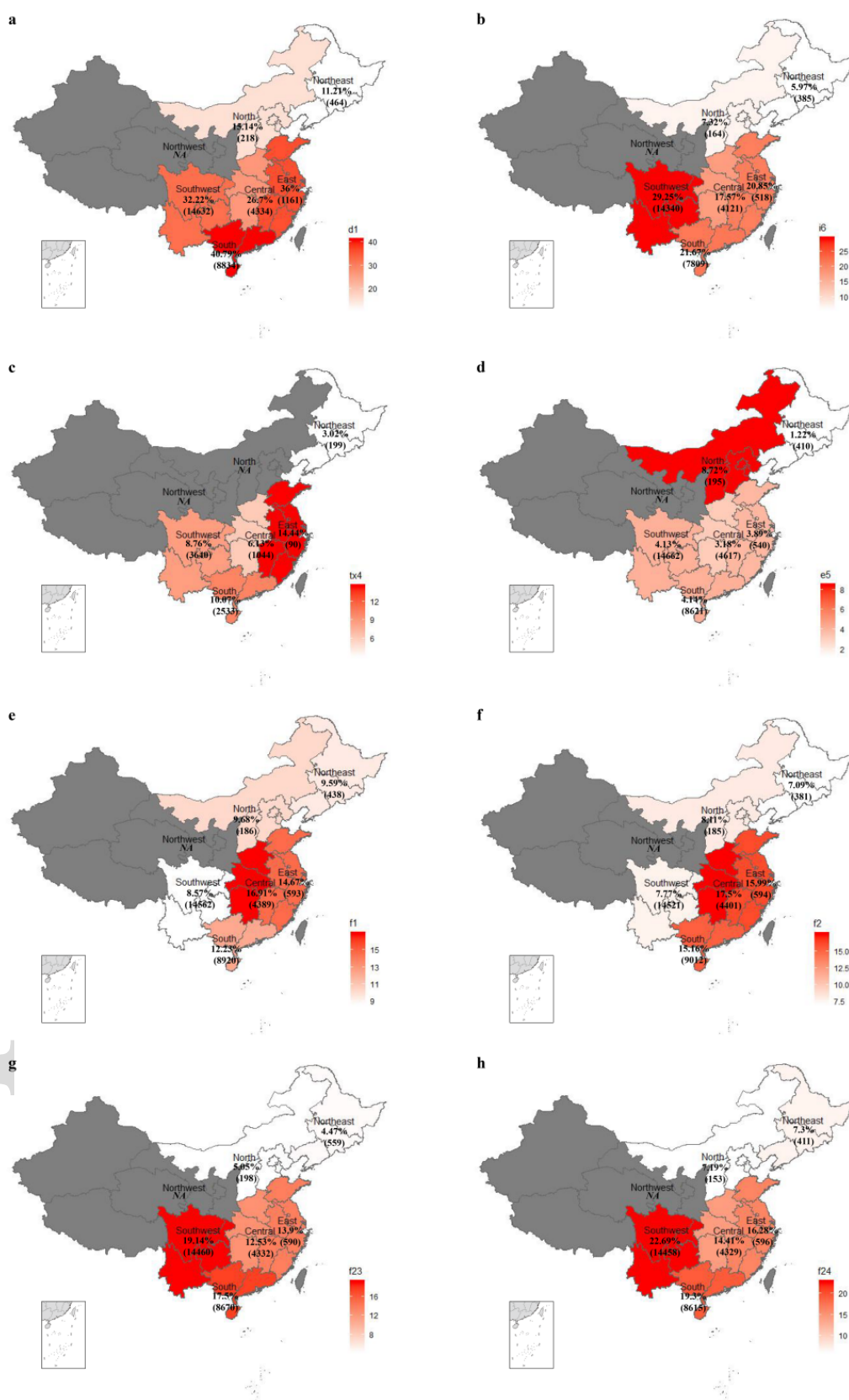
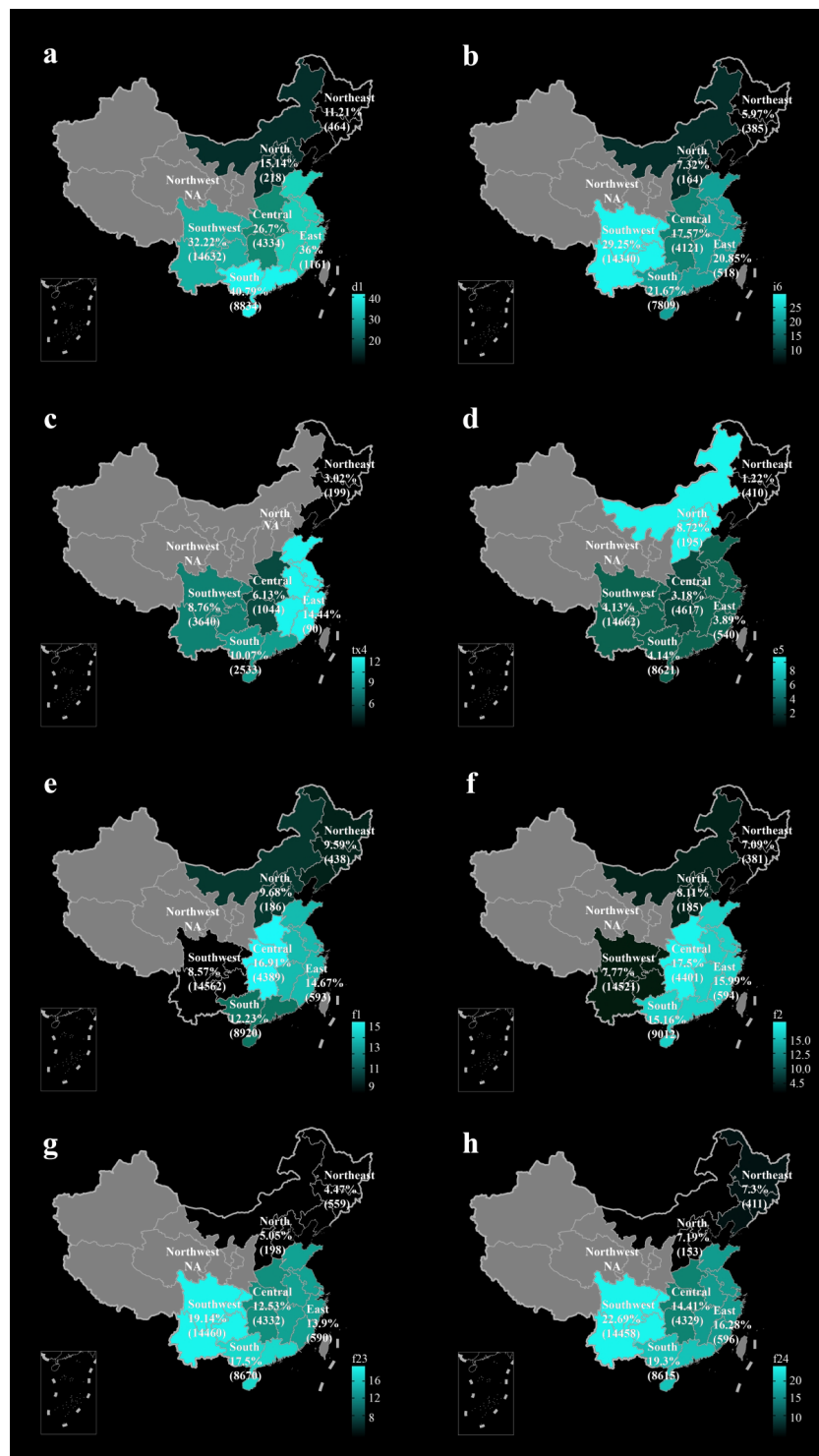
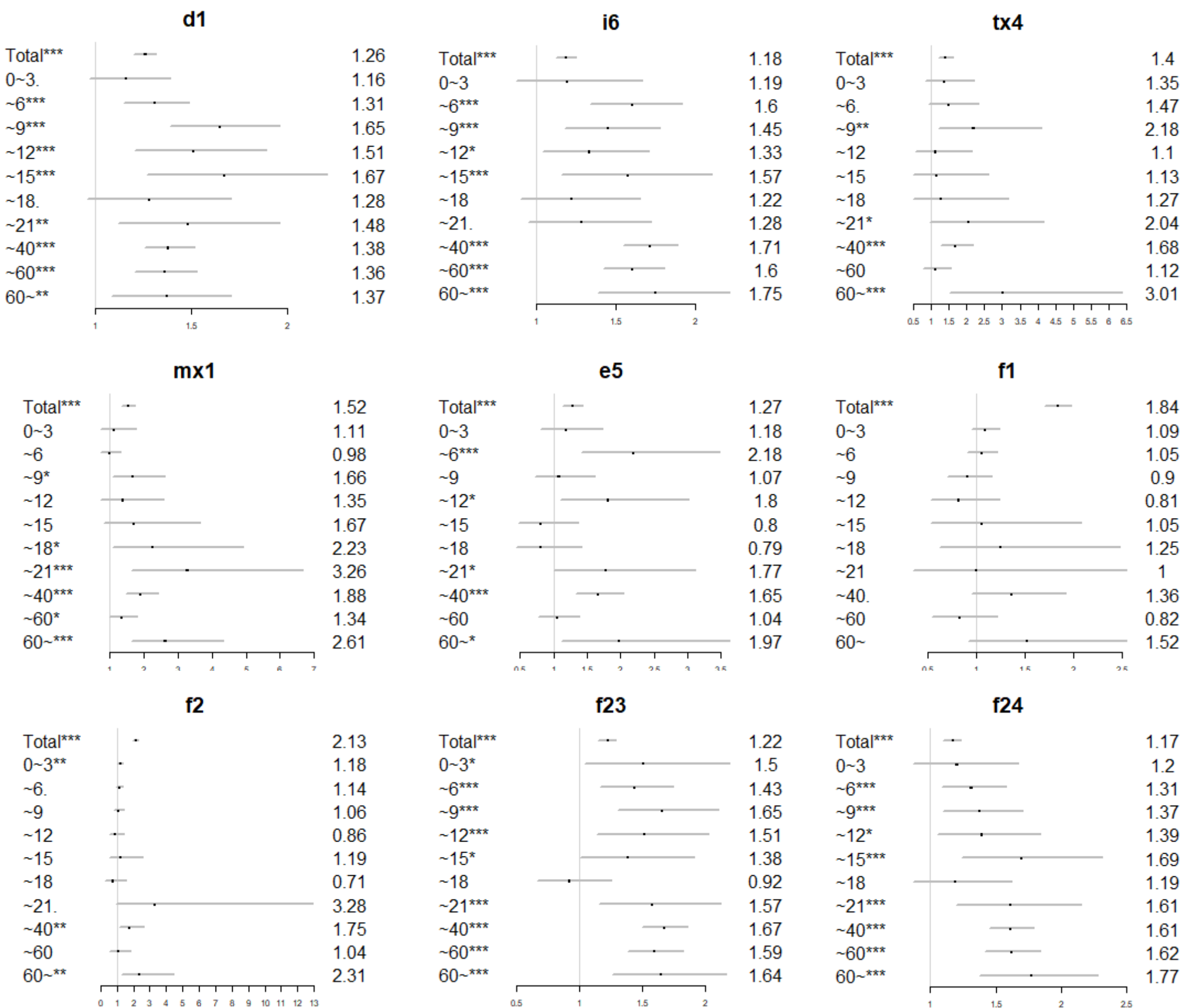


Figure 1. Heatmap for the prevalence of positive SIgE tests for d1:House dust mite (a), i6:German

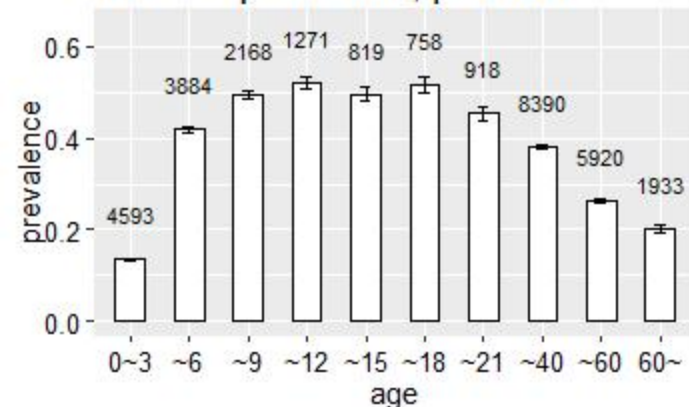
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cockroach (b), tx4:Tree pollen mix (c), e5:Dog dander (d), f1:Egg white (e), f2:Cow's milk (f), f23:Crab (g), f24:Shrimp (h) in different regions. The heatmap for the prevalence of sensitization to mold mix (mx1) is not shown here because the prevalence of mx1 sensitization is not significantly different in different regions (i.e., $p>0.05$). The prevalence (%) and total number of each region were marked. The prevalence for all 8 allergens in Northwest China and for tx4 in North Chain was treated as NA because their total numbers were all less than 50.

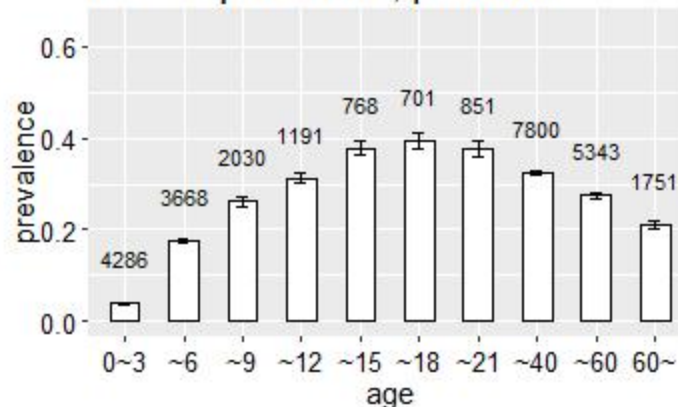




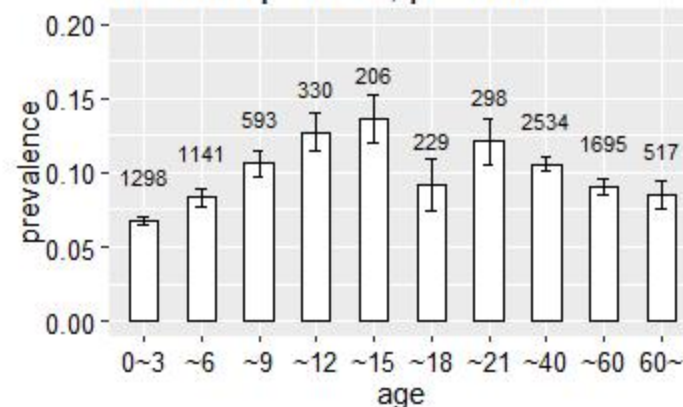
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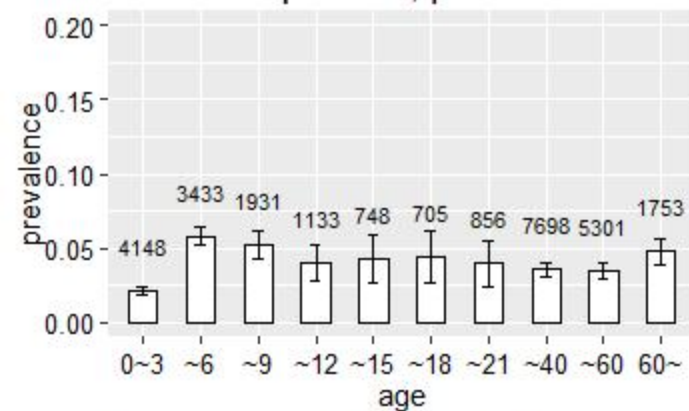
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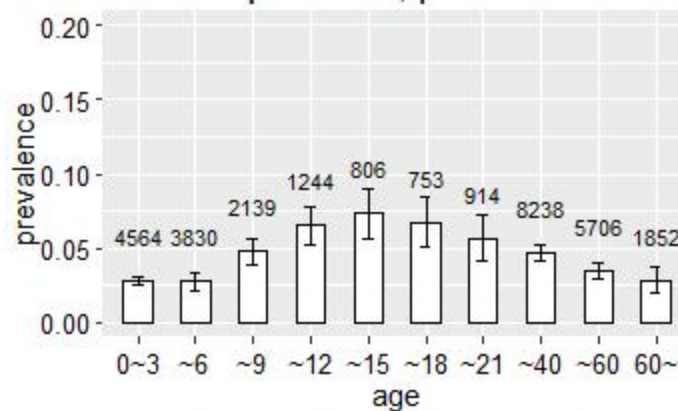
tx4: chisq=29.26, p<0.001



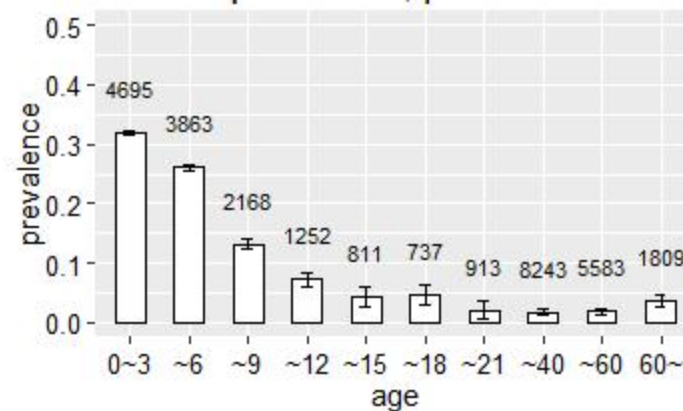
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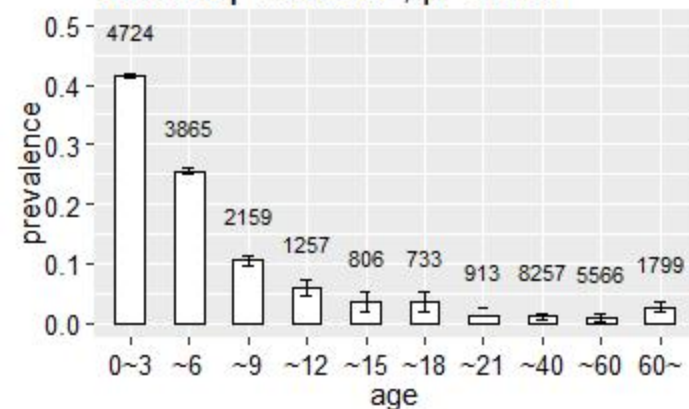
e5: chisq=122.18, p<0.001



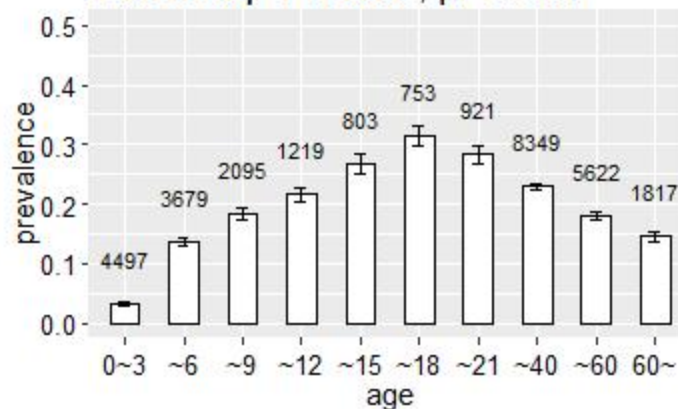
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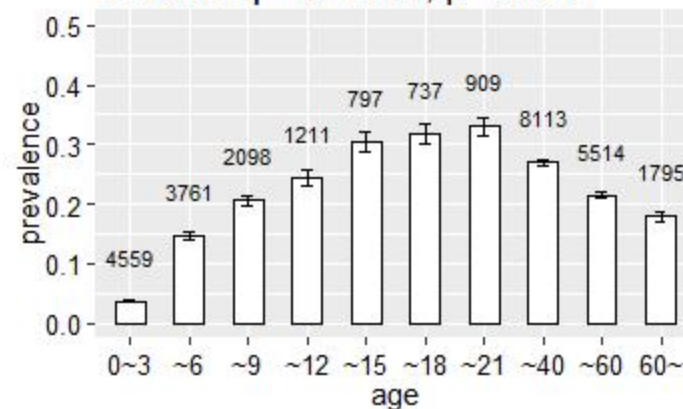
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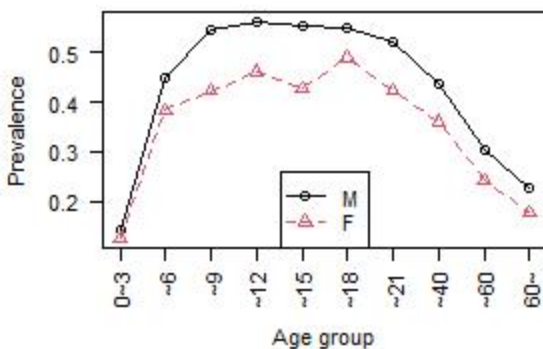
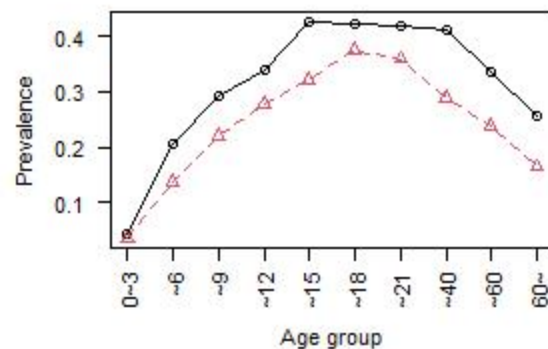
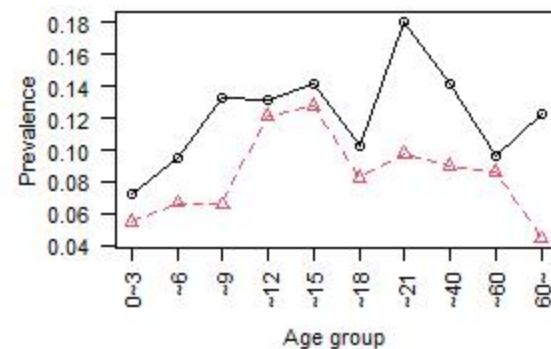
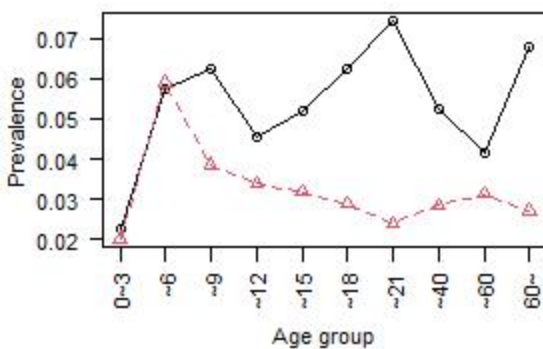
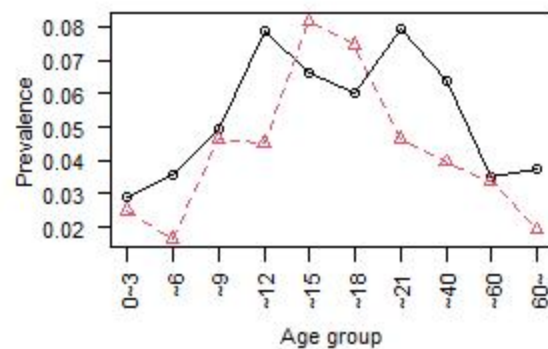
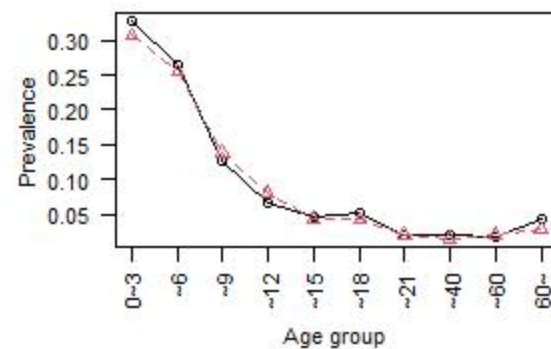
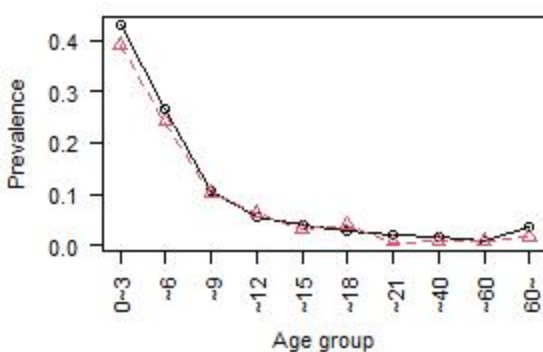
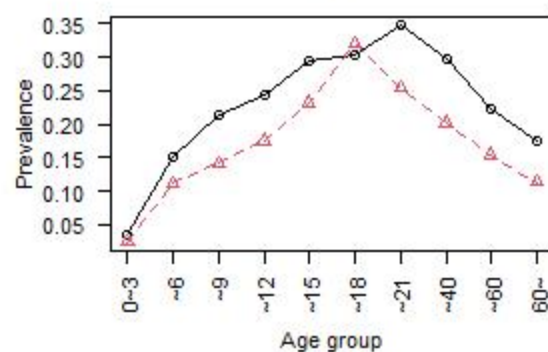
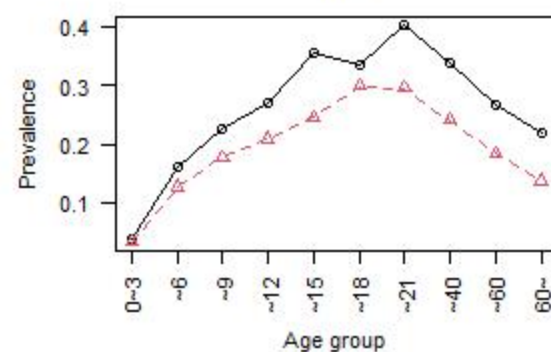


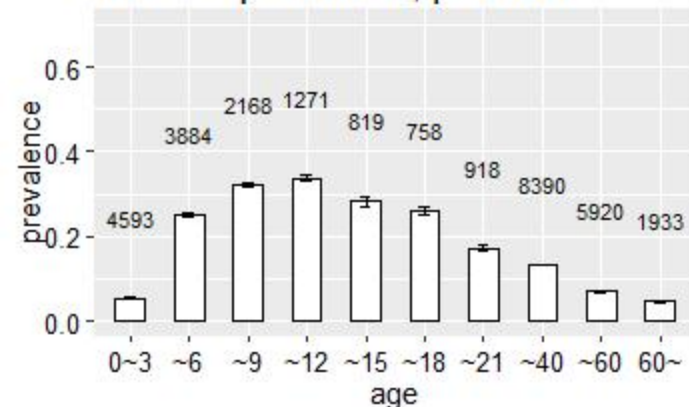
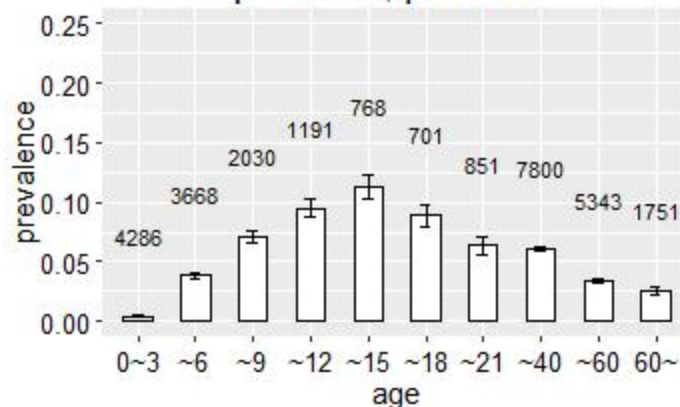
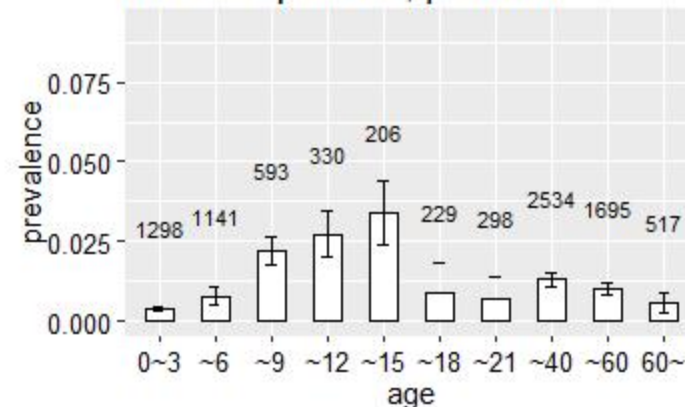
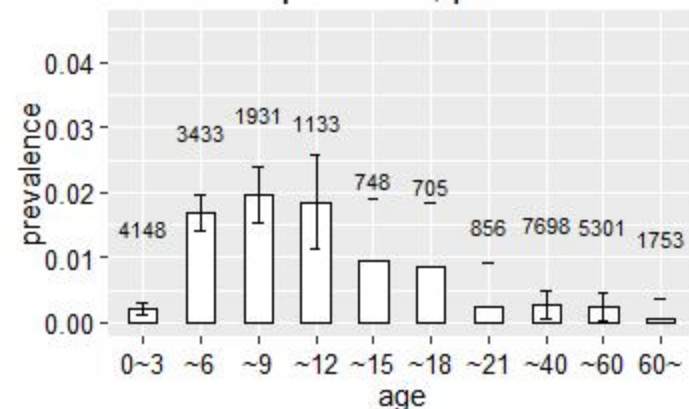
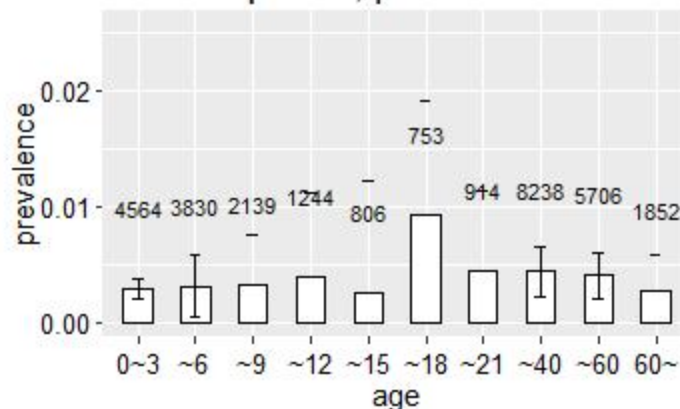
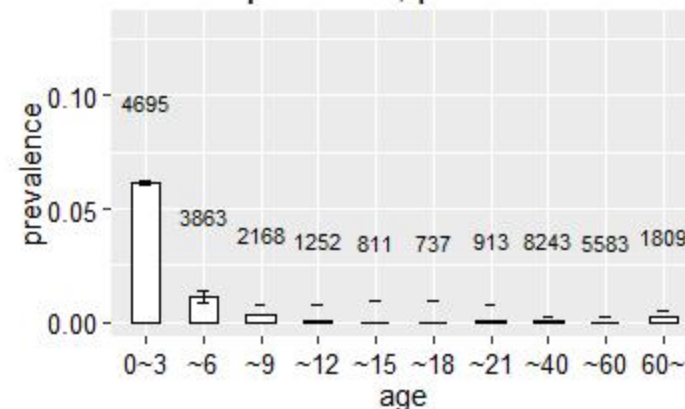
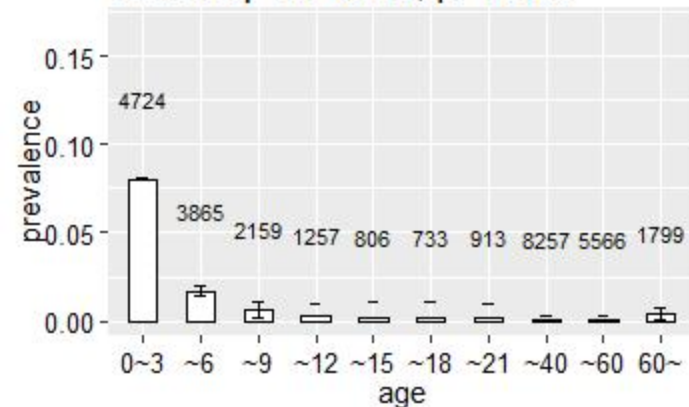
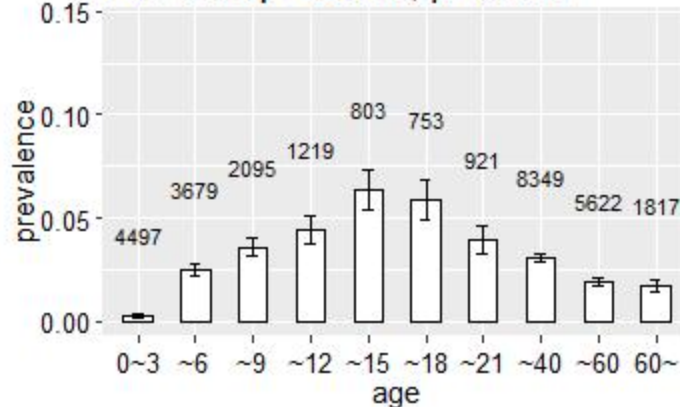
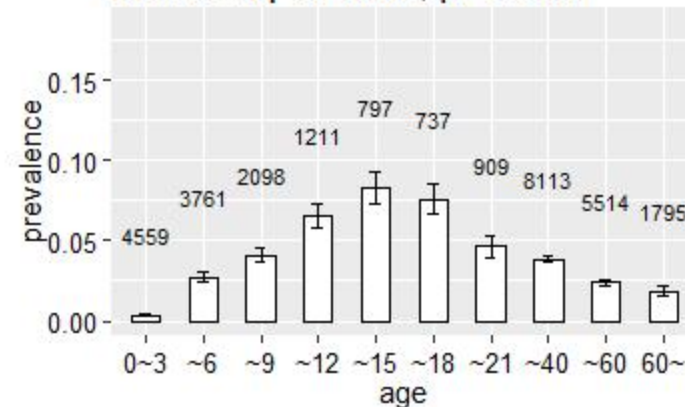
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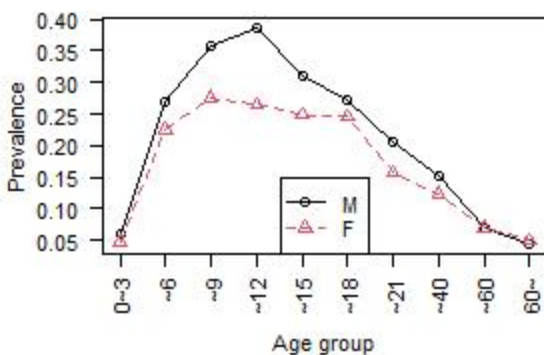
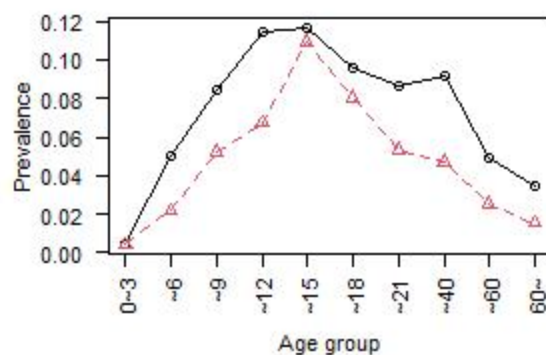
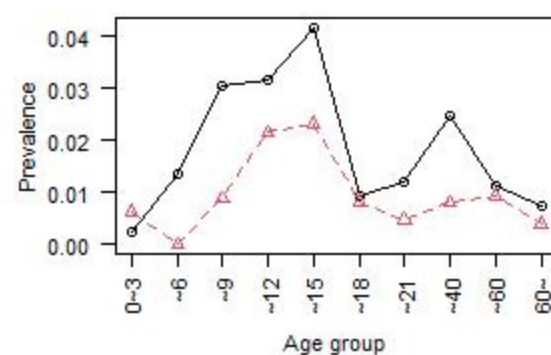
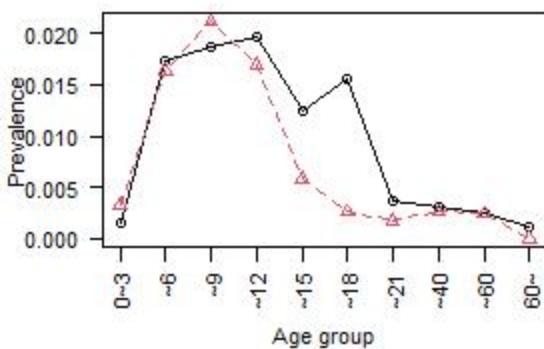
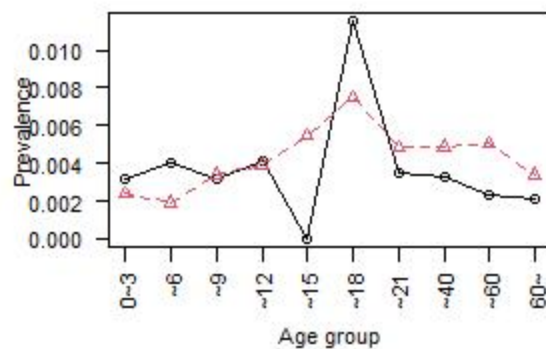
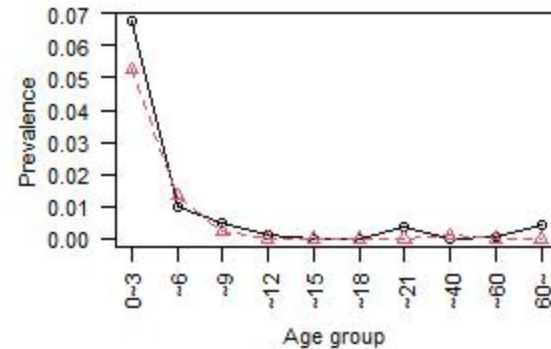
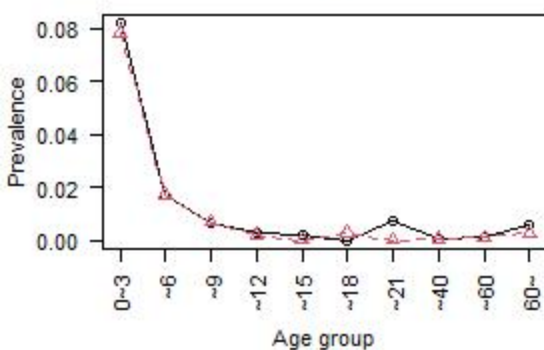
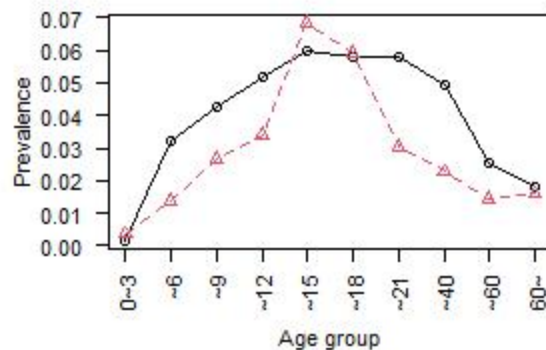
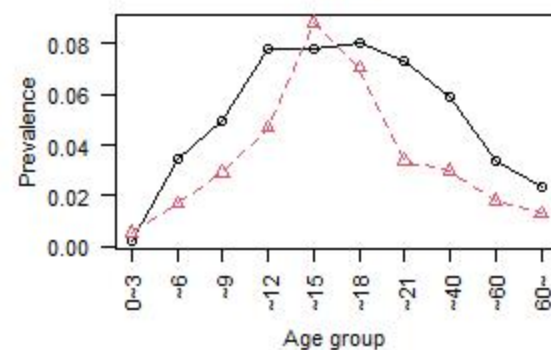


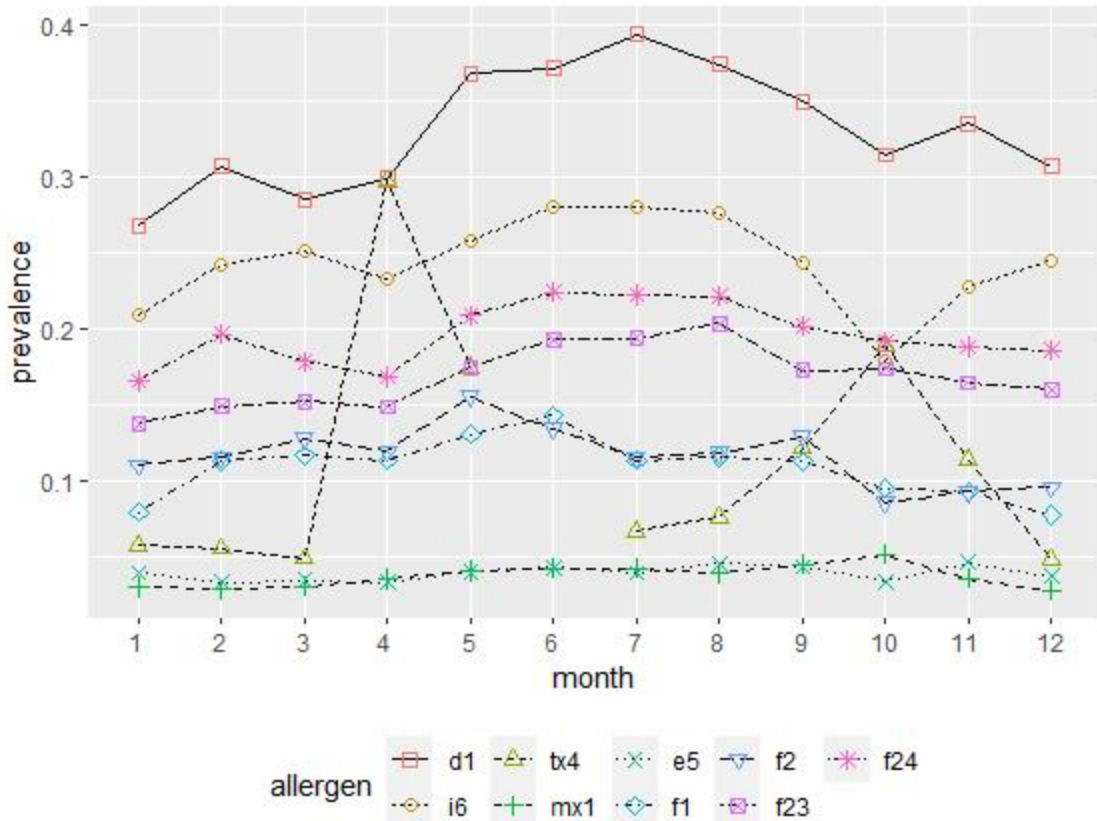
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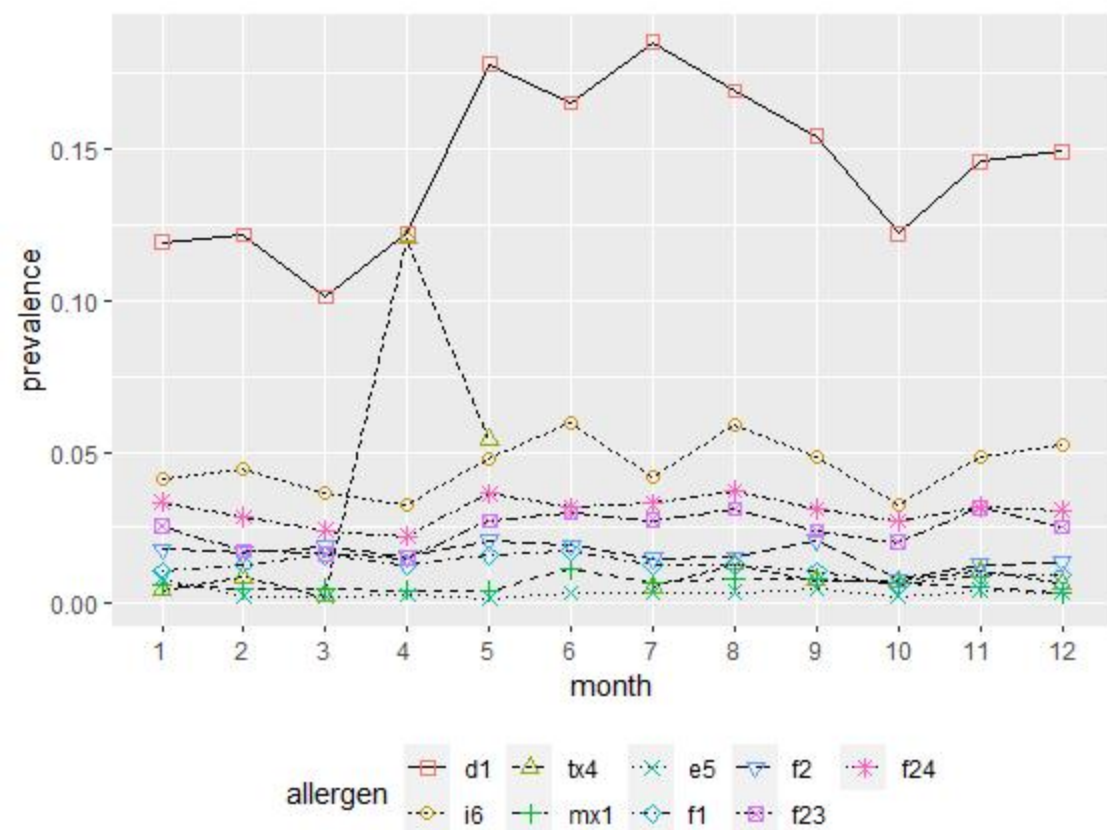


d1**i6****tx4****mx1****e5****f1****f2****f23****f24**

d1: $\text{chisq}=2174.39$, $p<0.001$ i6: $\text{chisq}=448.81$, $p<0.001$ tx4: $\text{chisq}=33.62$, $p<0.001$ mx1: $\text{chisq}=194.77$, $p<0.001$ e5: $\text{chisq}=9.57$, $p=0.387$ f1: $\text{chisq}=1237.2$, $p<0.001$ f2: $\text{chisq}=1526.87$, $p<0.001$ f23: $\text{chisq}=235.04$, $p<0.001$ f24: $\text{chisq}=329.22$, $p<0.001$ 

d1**i6****tx4****mx1****e5****f1****f2****f23****f24**





Supplementary Materials:

Prevalence Patterns of Allergen Sensitization by Region, Gender, Age and Season among patients with allergic symptoms in Mainland China: A Four-year Multicenter Study

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METHODS

Study population

This was a multicenter study covering 44156 patients with allergic symptoms (i.e., allergy clinic attendees) in 52 cities (from 26 provinces, 7 geographical regions) of mainland China from July 2015 to June 2018. The patients suffered from allergic symptoms were examined by the physicians in the participating hospitals, and those who were suspected to have allergic diseases were then referred to test their serum sIgE levels in one or more of the nine allergens and/or occasionally to other allergens using a uniform method in the same company. The suspected allergic diseases potentially leading to the allergic symptoms included allergic rhinitis (such as runny nose, sneezing, itching or nasal obstruction), skin allergy (such as rashes, wheal, or eczema), allergic asthma (such as wheezing, dyspnea, and/or cough not due to common cold) and so on. Patients with parasitic infections, immunodeficiency or under specific immunotherapy were excluded. The analyzed data covered the information on region, gender, age, month and sIgE levels for at least one of the nine allergens. In this study, among the 44156 participants, 39536 had valid sIgE test results in at least one of the nine allergens and 4620 did not. Among the 39536 subjects with valid sIgE test results, 38174 had complete information in gender, age and region and 1362 had missing information in gender, age or region. More detailed information is shown in **Table S2**.

Allergen-specific IgE detection

The serum sIgE samples of suspected allergic patients were collected and tested by a certified third-party laboratory service provider, KingMed Diagnostics, with uniform and standardized procedures.

A full-automated in vitro allergen detector, the ImmunoCAP 1000 system (Thermo Fisher Scientific Inc., California, USA), was used to detect allergen-specific sIgE in the sera, as described elsewhere^{1,2}. The sIgE levels for nine categories of allergens were evaluated in this study, including those for the house dust mite (d1: house dust mite; *Dermatophagoides pteronyssinus*), German cockroach (i6; *Blattella germanica*), tree pollen mix (tx4: *Quercus alba*, *Ulmus americana*, *Platanus acerifolia*, *Salix caprea*, *Populus deltoides*), mold mix (mx1: *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata*), dog dander (e5), egg white (f1), cow's milk (f2), crab (f23), and shrimp (f24). Positive reactivity was defined as an sIgE level ≥ 0.35 kUA/L (class 1 or above). According to the absolute sIgE levels, the reactivity was categorized into six classes: class 1 (≥ 0.35 to < 0.70 kUA/L), class 2 (≥ 0.70 to < 3.50 kUA/L), class 3 (≥ 3.50 to < 17.50 kUA/L), class 4 (≥ 17.50 to < 50.00 kUA/L), class 5 (≥ 50.00 to < 100.00 kUA/L), and class 6 (≥ 100.00 kUA/L)^{1,2}.

Geographical regions of mainland China

Based on natural and socioeconomic situations, the mainland China contains seven geographic regions, EC: East China, CC: Central China, NC: North China, NEC: Northeast China, NWC: Northwest China, SC: South China and SWC: Southwest China³.

Statistical analysis

The prevalence of positive sIgE tests for allergens was calculated as a proportion. Sex, age, region and month groups were analyzed as categorical variables. In general, the differences in the rates of sensitization between the variables were analyzed using the Fisher's exact test when the values in one or more cells were less than 5 (such as **Table S1**) and using the chi-square test otherwise. All data were transferred to and analyzed in R 4.0.2.

DISCUSSION

Based on this large study, the most common allergen for patients with allergic diseases in mainland China was house dust mites (**Table 1**). The results were consistent with those of previous studies⁴. Studies have also reported that house dust mites were the most common aeroallergen in many Asian countries^{5,6}. Another study also reported a high prevalence of 90% in Taiwan for house dust mite allergies. This is quite different from other continents of the world. For example, cat and dog allergies are the most common allergies in Europe and the United States^{5,7}, while in Africa, the most common allergies are cat and cockroach. Lifestyle and genetic differences may amount for some of these differences, despite similar longitudes and latitudes^{6,8}.

The statistical tests showed a significant difference in the prevalence of allergens among different regions for 8 allergens (except for mold mix) for sIgE classes 1-6 and for all 9 allergens for classes 3-6 (**Table S1**). The prevalence of the sensitization to house dust mite had an obvious geographical pattern in mainland China. The further south and the more coastal an area was, the higher the prevalence (**Figure 1**). This pattern may be caused by various factors such as humidity, temperature, heating condition, and so on, as described below. Humidity and temperature are the primary two determinant factors that affect dust mite reproduction and growth⁹. It is easy for dust mite to grow in warm and humidity places¹⁰. Regions in South and coastal have subtropical and tropical climates with higher temperature and relative humidity than other regions, leading to a higher prevalence of dust mite. In addition, people in the north in China are provided with heating for at least 5 months a year, which results in low indoor humidity. This lifestyle may also be the reason for the lower prevalence in the north. This is because in the regions other than the northern regions, which do not have heating supplies, people usually need long and thick carpets, blankets and quilts to keep warm indoors, all of which contribute to the proliferation of house dust mites¹¹.

German cockroaches were the second most common allergen affecting allergic patients in mainland China, with a prevalence of 24.5% (**Table 1**). Previous studies reported positivity rates of 11.5%-18.7%^{4, 12} for SPT and 20.9-26.5%² for sIgE. Cockroaches have been reported to be one of the most common indoor allergens worldwide¹³. Cockroach sensitization has been reported as 30% in Africa, 30% in India, and 6-29% in European countries. The high prevalence may be caused by immune regulation, genetic determinants¹⁴ and cross-reactivity between cockroaches and house dust mites¹². The prevalence in Southwest and Southern coast China was higher than those in the East and North China. However, Southwest China had higher prevalence than Southcoast. This was different from the prevalence pattern of house dust mite sensitization. The climate in the south may be more comfortable for cockroach growth than that in the north. However, compared with American cockroaches, German cockroaches are commonly found in dry and cold conditions¹⁵, which may be the reason for the higher prevalence in Southwest than in Southcoast China. Southcoast is more humid and hotter than west. The prevalence of tree pollen mix sensitization varied among regions. This may be attributed to different plant species in different regions¹⁶.

Among the four food allergens in our study, their prevalence fell into the range of 10%-20% (**Table 1**). The prevalence of cow's milk and egg white in North China was higher than those in other regions (**Figure 1**). Dietary patterns may also be one reason for variation in the prevalence of food allergens in different regions. Studies have concluded that infant diets with high levels of fruits, vegetables, and home-prepared foods are associated with fewer food allergies¹⁷. The high prevalence of cow's milk in East China may be caused by a family history of food allergies and atopy¹⁸. However, further evidence is required. Geographical variations in the patterns of aeroallergens also influence food allergy distributions where cross-reactivity exists between aeroallergen and food allergen components^{19, 20}. In our study, the prevalence patterns of crab and shrimp sensitization in all regions were quite similar to that of cockroaches, which could be caused by cross-reactivity. Different regions have different allergen sensitization patterns, which will provide a favorable basis for local allergen diagnosis and treatment.

Different regions of China may have different preference in eating crab and shrimp. For example, the people in East China are more likely to eat crab²¹ whereas those in Central China are more likely to eat shrimp²². Consider this fact, we tested the sensitization to crab and shrimp separately in our study with the intention to investigate whether there is any difference in the sensitization to crab and shrimp. The outcome of our study shows that the difference in sensitization between crab and shrimp is small (**Table 1**). This result should help the adoption of the strategies for the prevention and treatment of allergy to crab and shrimp in China.

Gender-based differences in the prevalence of allergies have long been recognized. However, conclusions about this topic are inconsistent among questionnaire studies and the detection of specific IgE antibodies or skin prick tests²³. In our study, the prevalence of all nine common allergens was significantly higher in males than in females (**Table 1 and Figure S1**). This suggests that being a male is one of the risk factors for allergen sensitization. Further studies need to be conducted to explain this observation.

Age had statistically significant influence on the prevalence of sensitization ($p < 0.001$) for all allergens (**Figure S2**). The prevalence by age had two major clear patterns. One pattern is that the prevalence grows continuously as the age increases before and during the teenage period and then decreases continuously as the age increases after the teenage period ends. Five of the nine allergens under study (house dust mite, German cockroach, dog dander, crab and shrimp) clearly had such a pattern and one allergen (i.e., mold) more or less had such a pattern (**Figure S2**). The other pattern is that the prevalence in the toddlers is the highest and then decrease continuously as the age increases. Two allergens (i.e., egg white and cow's milk) clearly had such a pattern. One allergen (i.e., tree pollen) had a pattern coming seemingly from the mixture of these two major patterns. Indeed, the dissection of the patients into males and females shows that females had the second pattern except that the toddlers had a low prevalence whereas males more or less had the first pattern in tree pollen (**Figure S3**). It is also interesting to see that, except mold, females had nearly the same prevalence pattern by age as males although females had a lower prevalence than males (**Figure S3**). These patterns by age were based on all positive sIgE classes (i.e., classes 1-6). Since a large portion of the positive sIgE patients fell in the low classes, it is worthwhile to explore the prevalence pattern by age and gender for the middle/high classes (i.e., classes 3-6). The analysis for classes 3-6 showed a move of the prevalence peak from the late teenage to early teenage age group, especially in females, for house dust mite, German cockroach, tree pollen,

dog dander, crab and shrimp (**Figures S4&S5**). The identification of prevalence pattern by age and gender for common allergens should help to improve the pertinence and accuracy of allergen detection for clinical diagnosis, which can reduce the burden of medical expenses for patients.

The peaks of prevalence in sensitization to German cockroach and house dust mite were both located in summer, which may be explained by the fact that house dust mites and cockroaches grow more easily and are more common in warm and humid conditions. The prevalence of sensitization to the tree pollen was significantly higher in April and October, which was consistent with the flowering seasons of most plants ¹⁶ (**Figure S6, left panel**). The prevalence of egg white and cow's milk sensitization was higher in spring, and crab and shrimp sensitization in summer (**Figure S6**), which might be influenced by seasonal differences in UVB exposure ²⁵. The analysis of prevalence by month for patients with the middle/high classes showed that the peak in October disappeared (**Figure S6, right panel**), indicating that tree pollen can hardly cause a high prevalence for the middle or high classes of allergy in October although it leads to a high prevalence in low classes of allergy in that month. There were differences in the distributions of allergen sensitizations in different seasons, which can be used for seasonal prevention and treatment of allergic diseases.

A previous study¹⁰ has also explored the sensitization of allergens in China in a similar way. Both articles found that house dust mite was the most common allergens and the positive cases in sIgE fell mainly in the two low classes (i.e., classes 1 and 2). However, there are differences between the former study and this study. At first, the former study only explored the patients with allergic symptoms in Guangzhou, a city in the South China whereas this study covered all the seven regions in mainland China. This study found distinctive patterns of sIgE response to allergens by region that the former study did not explore. This study showed higher positive rate in males than females for all the nine allergens, while the former study displayed statistically significant difference between males and females in cow's milk, crab and shrimp and no significant difference in house dust mite, German cockroach and dog dander. One reason for the different results of statistical significance on the three allergens may be the relatively smaller sample size in the former study as compared to this study. This study found distinctive patterns of sIgE response to allergens by month that the former study did not explore. Although the former study found peaks of the sIgE response in age groups for some allergens, the sensitization patterns were not as obvious as this study. This study also uniquely revealed the prevalence pattern by age in females and males separately in China and the prevalence pattern by age, gender and month for the middle/high sIgE classes.

It may be worth to note that among the 39536 subjects with valid sIgE test results, 68.17% did not show positive sIgE sensitization to any of the 9 allergens and the remaining 31.83% showed positive sensitization to at least one allergy. In more detail, 18.9% mono-sensitized, 8.86% 2-sensitized, 4.82% 3-sensitized, 7.42% 4-sensitized, 2.4% 5-sensitized, 0.76% 6-sensitized, 0.2% 7-sensitized, 0.1% 8-sensitized and 0.05% sensitized to all the 9 common allergens (**Table S3a**). The highest rate of mono-sensitization appears in house dust mite (**Table S3b**).

Finally, a note is that the results and conclusions in this article are based on clinical attendees with allergic symptoms that were suspected by the physicians to have allergic diseases and referred to test their serum allergen sIgE levels to one or more of the nine allergens and/or occasionally to other allergens. The study includes neither the people without allergic symptoms nor the people who have allergic symptoms but not attend the clinic. Considering that a large allergy study has yet to be conducted on the general population in China, further research in this area is needed.

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Table S1. The prevalence and sample size of allergen sensitization for the sIgE classes 1-6 and 3-6 respectively in each region.

Allergen		Region							<i>p</i> -value
		SC	SWC	CC	EC	NEC	NC	NWC	
d1	N	8834	14632	4334	1161	464	218	35	
	n1(%)	3603 (40.79)	4714 (32.22)	1157 (26.7)	418 (36)	52 (11.21)	33 (15.14)	3 (8.57)	0.0005
	n2(%)	1977 (22.38)	1723 (11.78)	465 (10.73)	220 (18.95)	21 (4.53)	18 (8.26)	0 (0)	0.0005
i6	N	7809	14340	4121	518	385	164	15	
	n1(%)	1692 (21.67)	4195 (29.25)	724 (17.57)	108 (20.85)	23 (5.97)	12 (7.32)	0 (0)	0.0005
	n2(%)	325 (4.16)	803 (5.6)	125 (3.03)	21 (4.05)	3 (0.78)	1 (0.61)	0 (0)	0.0005
tx4	N	2533	3640	1044	90	199	3	1	
	n1(%)	255 (10.07)	319 (8.76)	64 (6.13)	13 (14.44)	6 (3.02)	0 (0)	0 (0)	0.0015
	n2(%)	44 (1.74)	33 (0.91)	6 (0.57)	5 (5.56)	1 (0.5)	0 (0)	0 (0)	0.0005
mx1	N	7524	14046	4232	396	462	80	41	
	n1(%)	294 (3.91)	552 (3.93)	149 (3.52)	18 (4.55)	12 (2.6)	4 (5)	4 (9.76)	0.208
	n2(%)	41 (0.54)	110 (0.78)	15(0.35)	3 (0.76)	2 (0.43)	3 (3.75)	0 (0)	0.003
e5	N	8621	14662	4617	540	410	195	17	
	n1(%)	357 (4.14)	606 (4.13)	147 (3.18)	21 (3.89)	5 (1.22)	17 (8.72)	0 (0)	0.0005
	n2(%)	28 (0.32)	55 (0.38)	10 (0.22)	0 (0)	1 (0.24)	6 (3.08)	0 (0)	0.001
f1	N	8920	14562	4389	593	438	186	23	
	n1(%)	1091 (12.23)	1248 (8.57)	742 (16.91)	87 (14.67)	42 (9.59)	18 (9.68)	2 (8.7)	0.0005
	n2(%)	102 (1.14)	103 (0.71)	131 (2.98)	12 (2.02)	6 (1.37)	2 (1.08)	0 (0)	0.0005
f2	N	9012	14521	4401	594	381	185	18	
	n1(%)	1366 (15.16)	1128 (7.77)	770 (17.5)	95 (15.99)	27 (7.09)	15 (8.11)	2 (11.11)	0.0005
	n2(%)	187 (2.08)	123 (0.85)	147 (3.34)	13 (2.19)	1 (0.26)	1 (0.54)	0 (0)	0.0005
f23	N	8670	14460	4332	590	559	198	18	
	n1(%)	1517 (17.5)	2767 (19.14)	543 (12.53)	82 (13.9)	25 (4.47)	10 (5.05)	1 (5.56)	0.0005
	n2(%)	233 (2.69)	394 (2.72)	80 (1.85)	12 (2.03)	2 (0.36)	1 (0.51)	1 (5.56)	0.0005
f24	N	8615	14458	4329	596	411	153	17	
	n1(%)	1663 (19.3)	3281 (22.69)	624 (14.41)	97 (16.28)	30 (7.3)	11 (7.19)	1 (5.88)	0.0005
	n2(%)	261 (3.03)	522 (3.61)	96 (2.22)	19 (3.19)	1 (0.24)	1 (0.65)	0 (0)	0.0005

Note, N: the total number of patients who were tested for the sIgE to the allergen in a region, n1: the number of patients whose sIgE result was positive with classes 1 to 6 in a region, n2: the number of patients whose sIgE result was positive with classes 3 to 6 in a region, %: positive rate in percentage. d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp; EC: East China, CC: Central China, NC: North China, NEC: Northeast China, NWC: Northwest China, SC: South China, SWC: Southwest China. The *p*-value is from the Fisher's exact test because there are cells with a value less than 5.

Table S2. The frequency table for the patients with allergic symptoms by region, gender and age.

Gender	Age	Region							Total
		SC	SWC	CC	EC	NEC	NC	NWC	
Male	0~3	1568	1058	805	105	54	48	4	3642
	~6	1553	831	385	110	58	47	1	2985
	~9	822	501	218	75	36	27	1	1680
	~12	465	344	108	59	22	14	2	1014
	~15	240	243	74	25	7	10	2	601
	~18	192	187	74	21	5	6	1	486
	~21	171	175	30	19	8	2	1	406
	~40	1674	1258	214	162	32	41	11	3392
	~60	795	1249	280	255	42	46	5	2672
	60~	268	591	144	87	15	12	3	1120
Female	0~3	797	667	478	71	37	25	1	2076
	~6	969	612	270	78	76	22	3	2030
	~9	434	406	138	48	22	26	0	1074
	~12	231	262	76	32	13	16	0	630
	~15	155	223	45	22	3	6	1	455
	~18	173	244	54	21	7	8	1	508
	~21	282	383	63	27	10	6	1	772
	~40	3048	3064	754	276	83	82	7	7314
	~60	1218	2083	526	301	87	50	8	4273
	60~	253	530	135	88	26	8	4	1044
Total		15308	14911	4871	1882	643	502	57	38174

Note: In this study, there were 44156 participants with 39536 having valid sIgE test results in at least one of the nine allergens and 4620 not having any valid sIgE test results. Among the 39536 subjects with valid sIgE test results, 38174 had complete information in gender, age and region and 1362 had missing values in gender or age. EC: East China, CC: Central China, NC: North China, NEC: Northeast China, NWC: Northwest China, SC: South China, SWC: Southwest China.

Table S3. The number and percentage of mono- and poly-sensitized allergies and the number of patients with each combination of 8-sensitized allergies.

a: The number and percentage of patients with mono- or poly-sensitized allergies

Sensitized Type	0-sensitized	mono-sensitized	2-sensitized	3-sensitized	4-sensitized	5-sensitized	6-sensitized	7-sensitized	8-sensitized	9-sensitized	total
Number	26952	7473	3503	1904	2935	950	299	79	41	20	39536
Percentage	68.17	18.9	8.86	4.82	7.42	2.4	0.76	0.2	0.1	0.05	100

b: The number of patients for each mono-sensitized allergy

Mono-sensitized allergy	d1	i6	tx4	mx1	e5	f1	f2	f23	f24	Total
#Positive	3301	1118	197	227	80	878	1237	192	243	7473
#Patients tested	31680	29343	9155	28746	31061	31109	31111	30830	30442	NA
Prevalence	10.42	3.81	2.15	0.79	0.26	2.82	3.98	0.62	0.8	NA

Note, In Panel B, the comparison of the number of positive sIgE cases across allergens may be misleading because the total number of patients tested for each allergen differs; however, the prevalence is comparable across allergens because it is adjusted to the total number of patients tested for each allergen. d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: Mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp

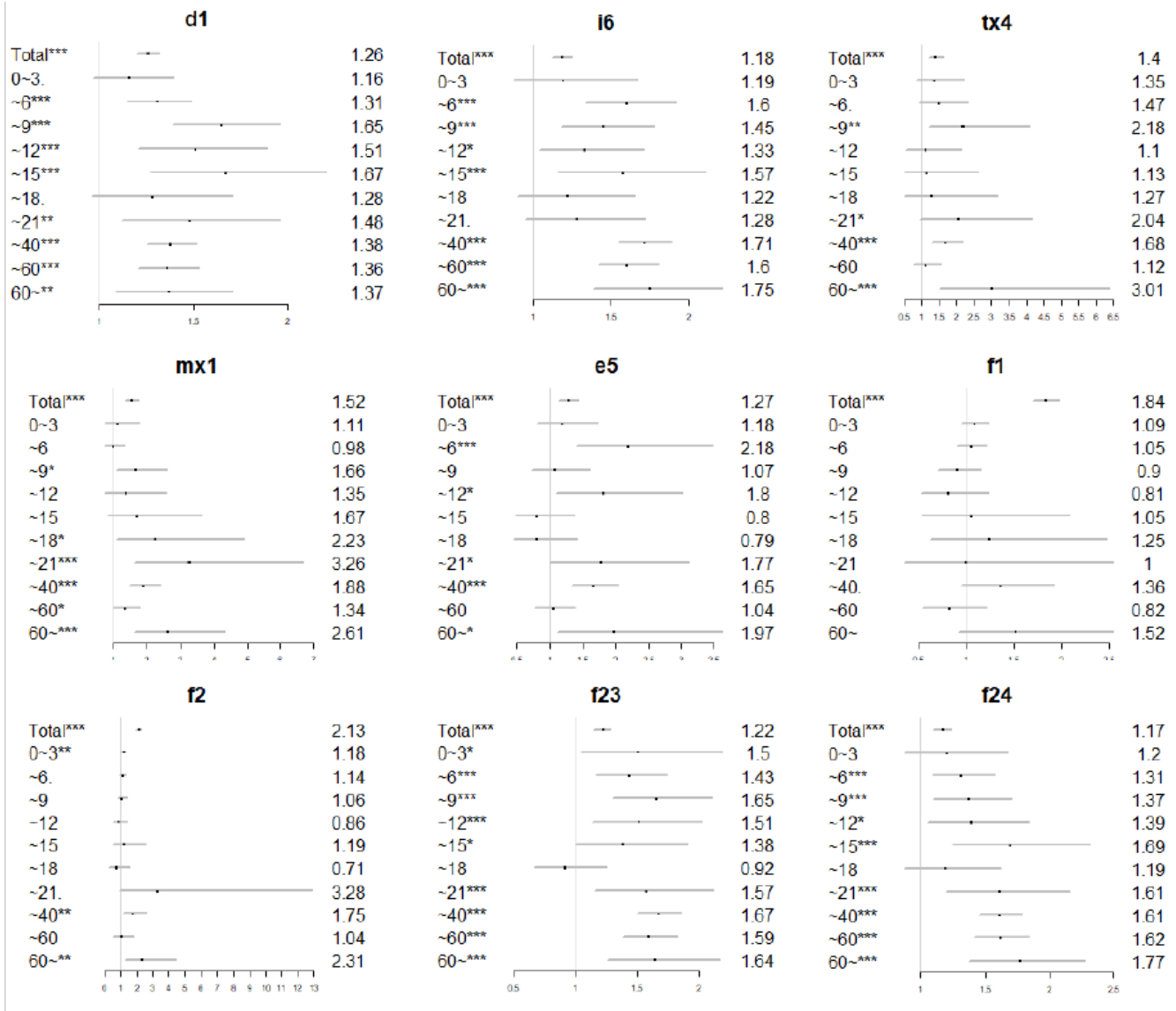


Figure S1. Forest plot for the OR of male to female subjects in each age group. (OR are displayed in the right column and age groups in the left panel for each allergen. *: p value < 0.05 , **: p value < 0.01 , ***: p value < 0.001 ; d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: Mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp)

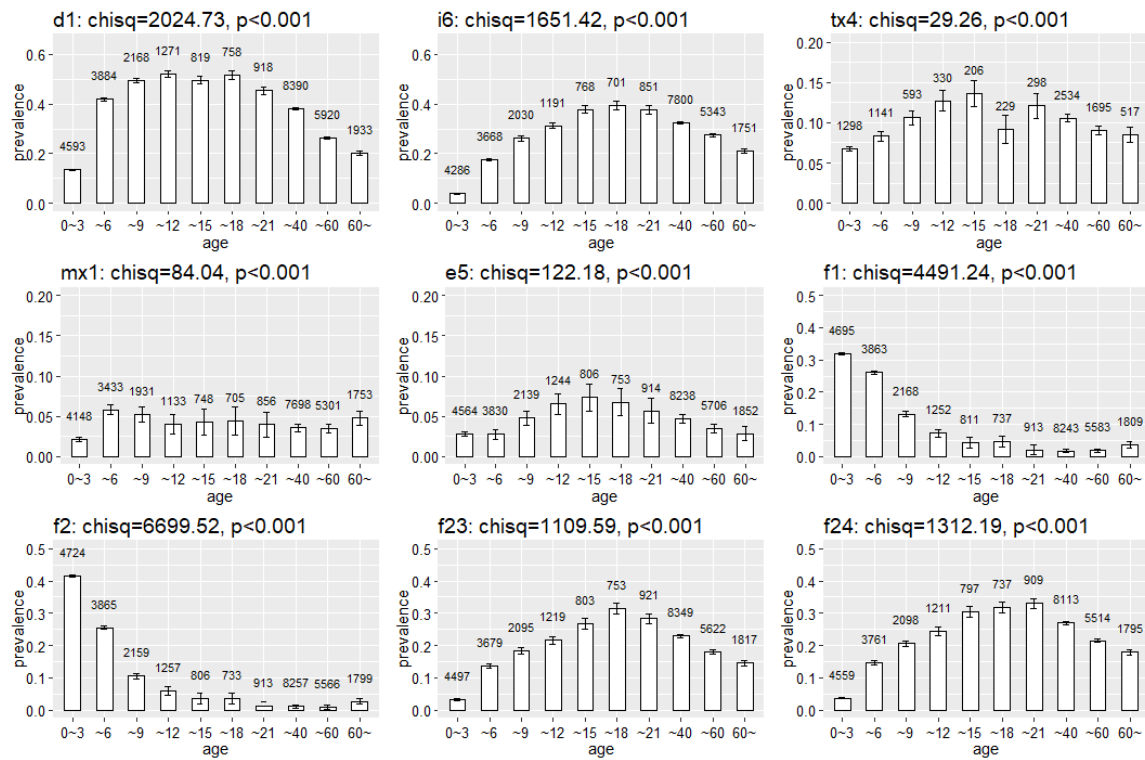


Figure S2. Prevalence of SIgE reactivity to allergens (including classes 1 to 6) in different age groups. (The total number of each case is labeled above the bars, and the X-squared and p values are also shown above the plots. d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: Mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp)

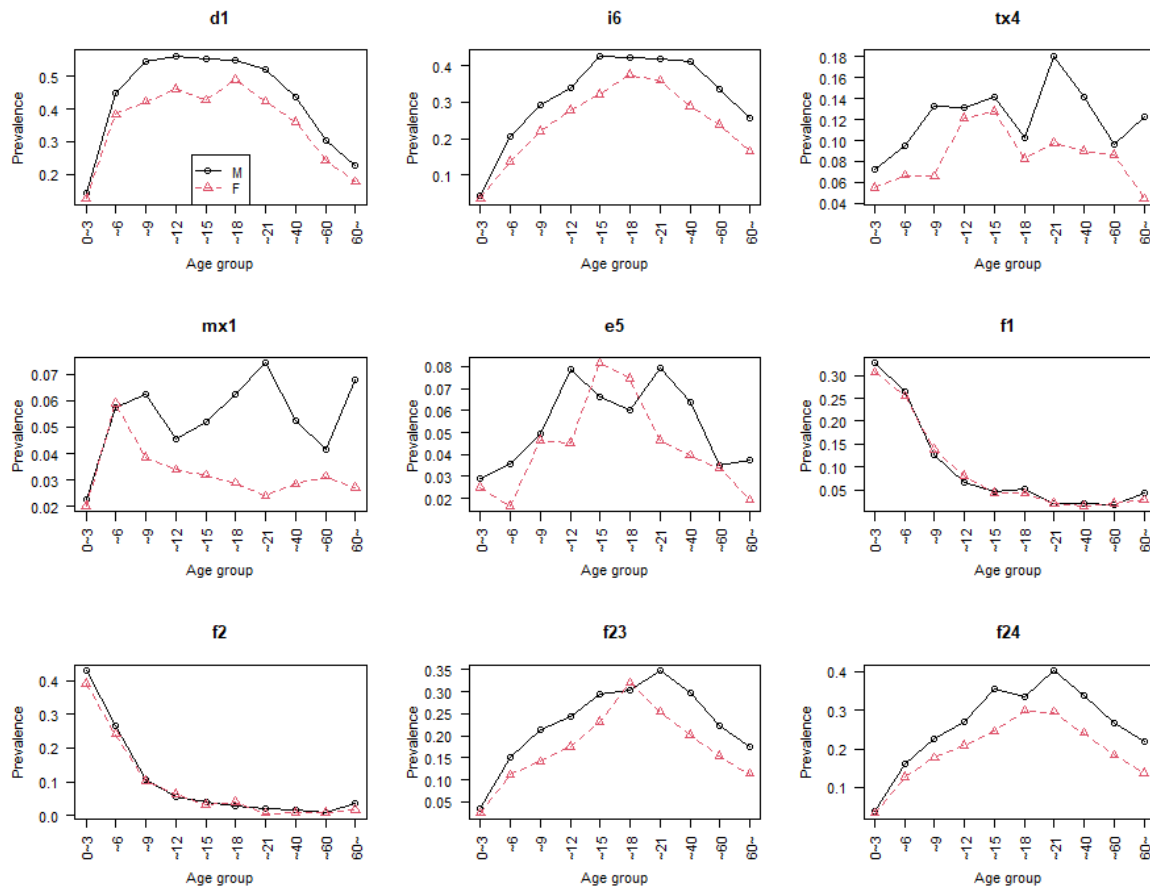


Figure S3. Prevalence of SIgE reactivity to allergens for classes 1-6 in different age groups and genders. d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: Mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp

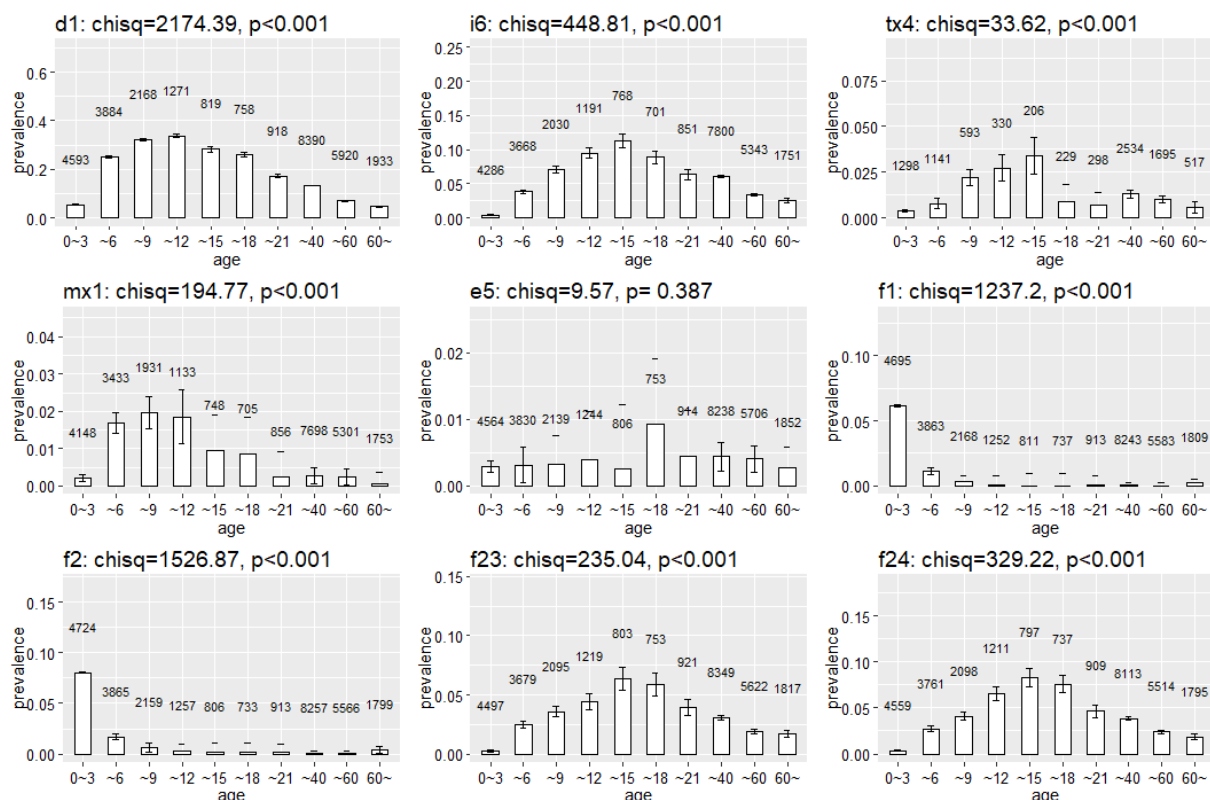


Figure S4. Prevalence of SIgE reactivity to allergens (including classes 3 to 6) in different age groups. (The total number of each case is labeled above the bars, and the X-squared and p values are also shown above the plots. d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: Mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp)

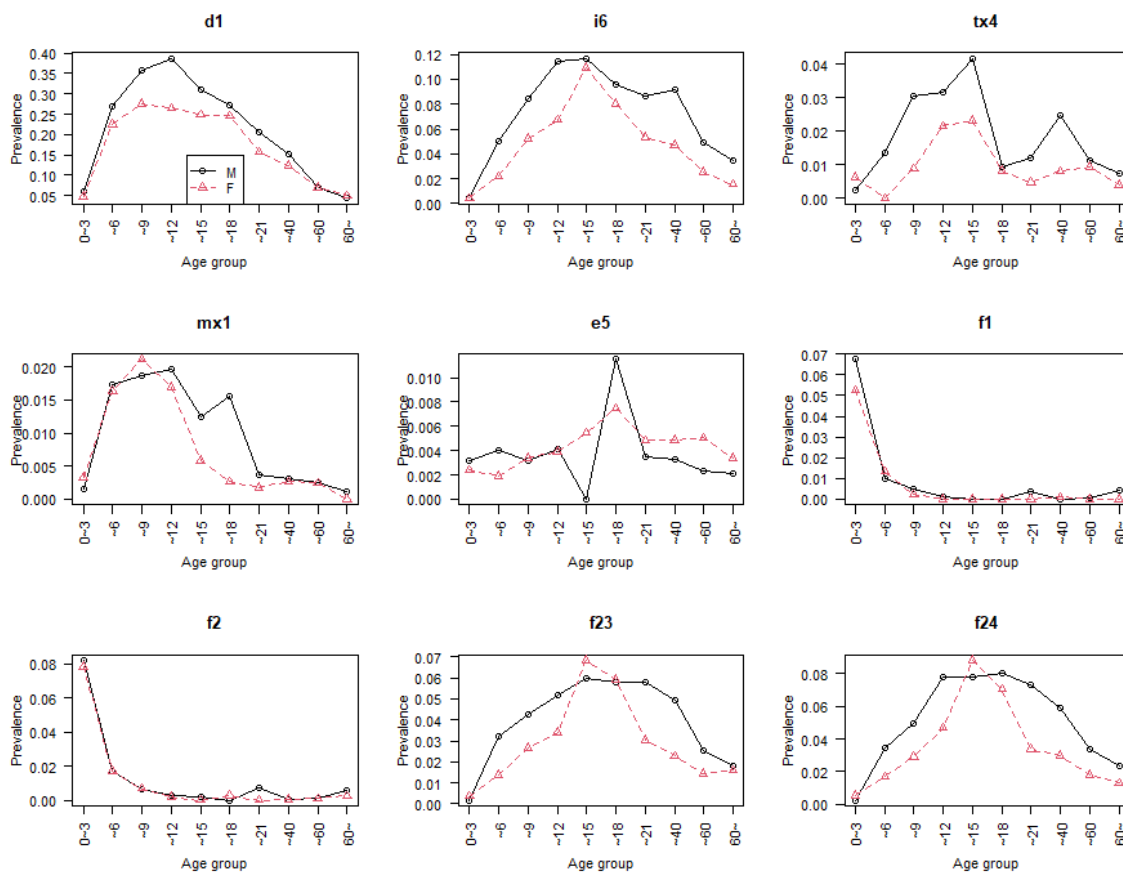


Figure S5. Prevalence of SIgE reactivity to allergens for classes 3-6 in different age groups and genders. d1: House dust mite, i6: German cockroach, tx4: Tree pollen mix, e5: Dog dander, mx1: Mold mix, f1: Egg white, f2: Cow's milk, f23: Crab, f24: Shrimp

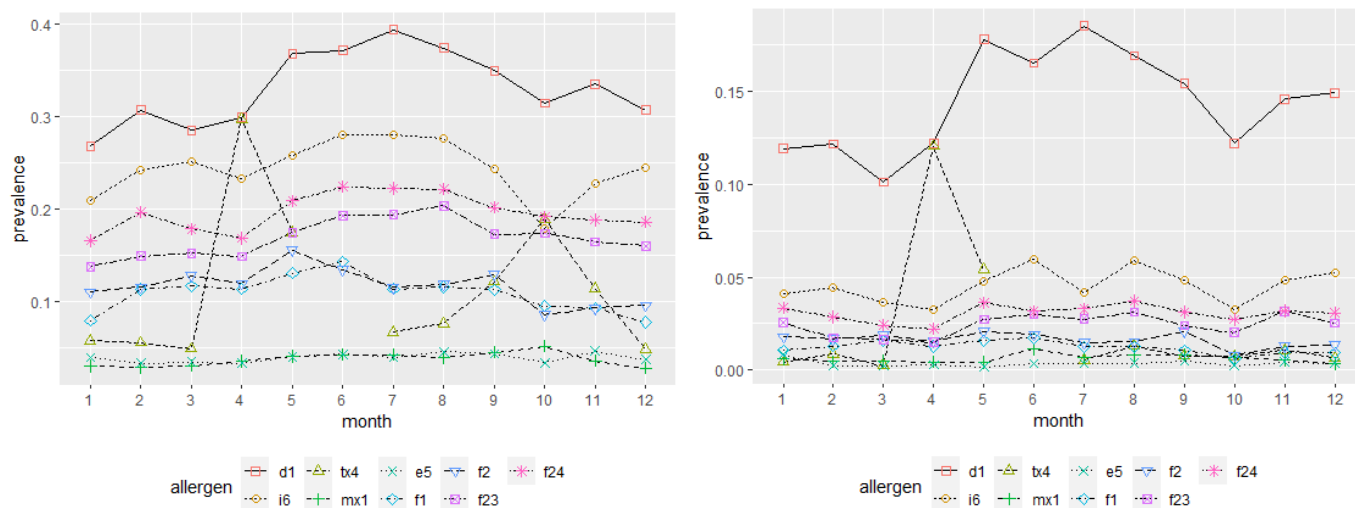


Figure S6. The prevalence of sIgE reactivities to allergens by month. Left Panel: for sIgE classes 1 to 6; Right Panel: for sIgE classes 3 to 6 (d1: House dust mites, tx4: Tree pollen mix, e5: Dog dander, f2: Cow's milk, f24: Shrimp, i6: German cockroach, mx1: Mold mix, f1: Egg white, f23: Crab; No data available in June for tx4)