Prevalence Patterns of Allergen Sensitization in Different Regions, Sexes, Ages and Seasons in Mainland China: A Four-year Multicenter Study

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To the Editor,

The proportion of the population with allergic diseases has increased rapidly in recent decades[1, 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 system[1]. 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 China[3-5]. In 2009, a study[6] 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 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 whites, 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. The sIgE sensitization was tested 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 whites, 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 shown in several

previous studies based on certain specific areas in China[3-5] that the positive cases in sIgE fell mainly in the two low classes (i.e., classes 1 and 2) 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 among regions, gender, age groups and seasons. 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 whites 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 whites 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 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 (**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, whereas the sensitization to egg whites and milk was the highest in children, the sensitization to other allergens tended to be the highest in teenagers and young adults (**Figure S2**). **Figure S3**displays he prevalence pattern of allergens by months 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 was much higher in April and October than in other months.

This should be 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 obvious and 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.

REFERENCES

1. Ebert CS, Jr., Pillsbury HC, III. Epidemiology of Allergy. *Otolaryngologic Clinics of North America* . 2011;44(3):537-548. doi:10.1016/j.otc.2011.03.001

2. Lin J, Wang W, Chen P, et al. Prevalence and risk factors of asthma in mainland China: The CARE study. *Respiratory medicine* . Apr 2018;137:48-54. doi:10.1016/j.rmed.2018.02.010

3. Sun BQ, Zheng PY, Zhang XW, Huang HM, Chen DH, Zeng GQ. Prevalence of allergen sensitization among patients with allergic diseases in Guangzhou, Southern China: a four-year observational study.*Multidisciplinary respiratory medicine* . Jan 15 2014;9(1):2. doi:10.1186/2049-6958-9-2

4. Zeng G, Luo W, Wu Z, et al. A cross-sectional observational study on allergen-specific IgE positivity in a southeast coastal versus a southwest inland region of China. *Scientific reports* . Aug 30 2017;7(1):9593. doi:10.1038/s41598-017-10109-3

5. Luo W, Huang H, Zheng P, et al. Major grass pollen allergens and components detected in a southern Chinese cohort of patients with allergic rhinitis and/or asthma. *Mol Immunol* . Oct 2016;78:105-112. doi:10.1016/j.molimm.2016.08.013

6. Li J, Sun B, Huang Y, et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. *Allergy* . Jul 2009;64(7):1083-92. doi:10.1111/j.1398-9995.2009.01967.x

7. Mihrshahi S, Marks G, Vanlaar C, Tovey E, Peat J. Predictors of high house dust mite allergen concentrations in residential homes in Sydney.*Allergy* . Feb 2002;57(2):137-42. doi:10.1034/j.1398-9995.2002.5720999.x

8. Sun BQ, Lai XX, Gjesing B, Spangfort MD, Zhong NS. Prevalence of sensitivity to cockroach allergens and IgE cross-reactivity between cockroach and house dust mite allergens in Chinese patients with allergic rhinitis and asthma. *Chinese medical journal* . Dec 2010;123(24):3540-4.

9. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions.*Allergy* . Nov 2008;63(11):1418-27. doi:10.1111/j.1398-9995.2008.01880.x

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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	Allergens	*House dust mite (d1)*	*German cock-roach (i6)*	*Tree pollen mix (tx4)*	*Mold mix (mx1)*	*Dog dander (e5)*	*Egg white (f1)*	*Cow's milk (f2)*	*Crab (f23)*
Total cases (N)	Total cases (N)	31680	29343	9155	28746	31061	31109	31111	30830
Positive cases [n (%)]	Positive cases [n (%)]	10690 (33.74)	7189 (24.5)	856 (9.35)	1126 (3.92)	1249 (4.02)	3396 (10.92)	3616 (11.62)	5336 (17.31)
proportion of Classi-fication [n_c (%)]	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	12084	10950	1866	10593	11742	11791	11815	11562
	n (%)	4547 (37.63)	3039 (27.68)	268 (14.36)	533 (5.03)	555 (4.73)	1732 (14.69)	1903 (16.11)	2310 (19.98)
female	N	14158	13011	2262	12707	13908	13907	13881	13800
	n (%)	4590 (32.42)	3180 (24.44)	245 (10.83)	420 (3.31)	496 (3.57)	1218 (8.76)	1136 (8.18)	2315 (16.78)
X^2	X^2	77.70	32.33	11.39	43.45	21.52	220.3	383.43	43.10
P	P	< 2.2e-16	1.3e-08	0.0007	4.4e-11	3.5e-06	< 2.2e-16	< 2.2e-16	5.2e-11

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: class 1 (0.35 ˜ 0.70 kUA/L), class 2 (0.70 ˜ 3.50 kUA/L), class 3 (3.50 ˜ 17.50 kUA/L), class 4 (17.50 ˜ 50.00 kUA/L), class 5 (50.00 to ˜ 100.00 kUA/L) and class 6 ([?] 100.00 kUA/L).

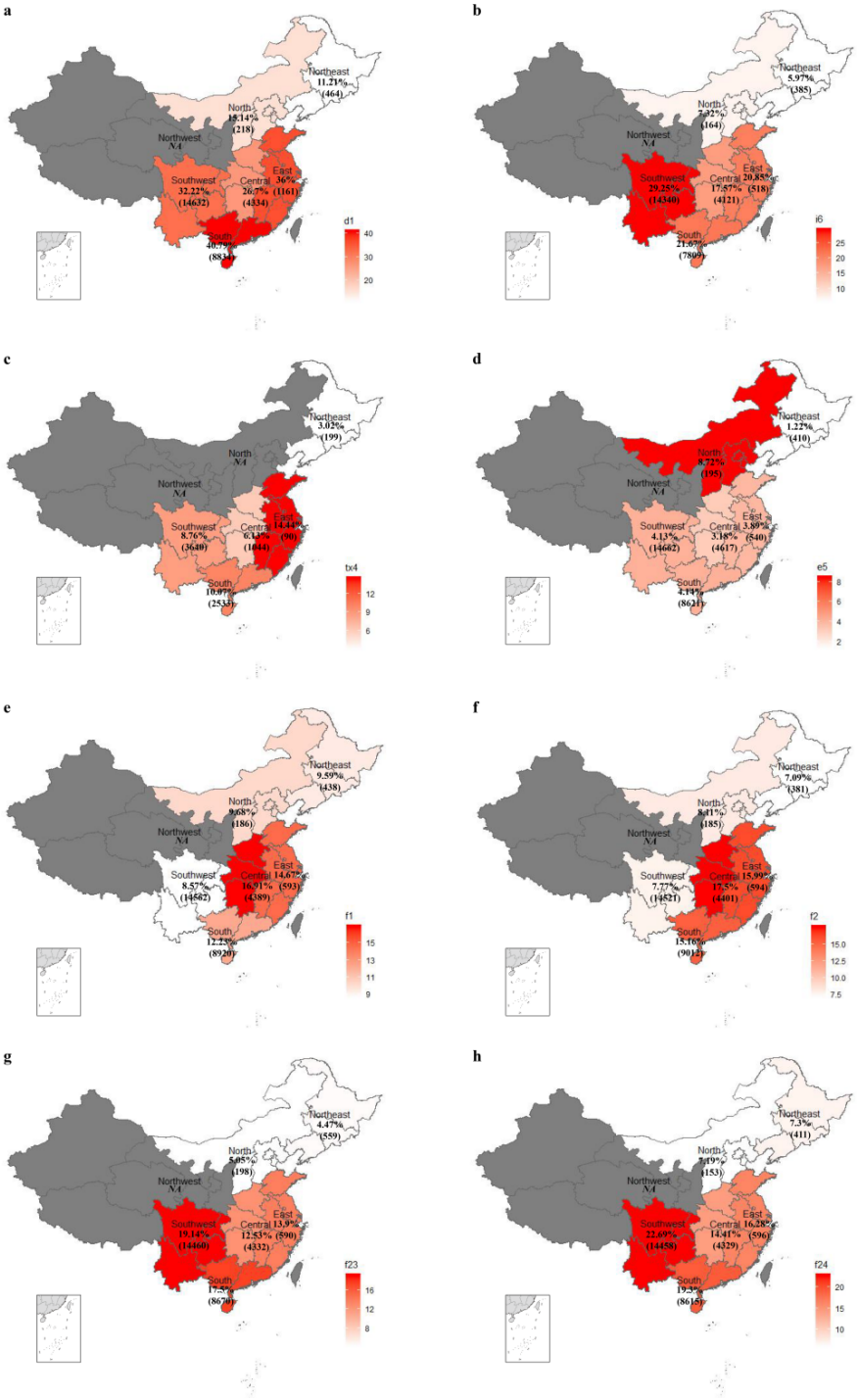

Figure 1. *Heatmap for the prevalence of positive SIgE tests for House dust mite (a), German cockroach (b), Tree pollen mix (c), Dog dander (d), Egg whites (e), Cow's milk (f), Crab (g), Shrimp (h) in different regions. The positive rate (%) and the total number of each case were marked. The total number of the cases in Northwest China for all 9 allergens and in North China for tx4 were less than 50, so the prevalence in those regions was not calculated (NA).*