Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI —WILEY— 589

DOI: 10.1111/all.14597

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 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, and interpretation of results. Our research has the following different characteristics compared with previous studies: (a) covering a variety of allergic diseases, (b) exploring both aeroallergens and food allergens simultaneously, (c) including a large set of data from all the seven regions of mainland China, and (d) 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 (ie, egg white, cow's milk, crab, and shrimp) and five aeroallergens (ie, house dust mite, German cockroach, tree pollen mix, mold mix, dog dander) among 44 156 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 Appendix S1.

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 (ie, classes 1 and 2) as shown in previous studies for certain specific areas in China[3-5] 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

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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	House dust mite (d1)	German 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)	31 680	29 343	9155	28 746	31 061	31 109	31 111	30 830	30 442
Positive cases [n (%)]	10 690 (33.74)	7189 (24.5)	856 (9.35)	1126 (3.92)	1249 (4.02)	3396 (10.92)	3616 (11.62)	5336 (17.31)	6078 (19.97)
sIgE Class [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)	2212 (36.39)
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)	2914 (47.94)
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)	837 (13.77)
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)	86 (1.41)
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)	16 (0.26)
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)	13 (0.21)
Male									
N	14 340	13 192	4070	12 830	13 988	14 041	14 066	13 812	13 721
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)	2934 (21.38)
Female									
N	16 856	15 702	4903	15 404	16 597	16 599	16 572	16 498	16 301
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)	3083 (18.91)
χ^2	92.07	38.26	21.07	46.7	17.23	274.96	439.37	41.48	28.22
P-value	8.4E−22	6.2E−10	4.4E−6	8.3E−12	3.3E−5	9.4E−62	1.5E−97	1.2E−10	1.1E−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.

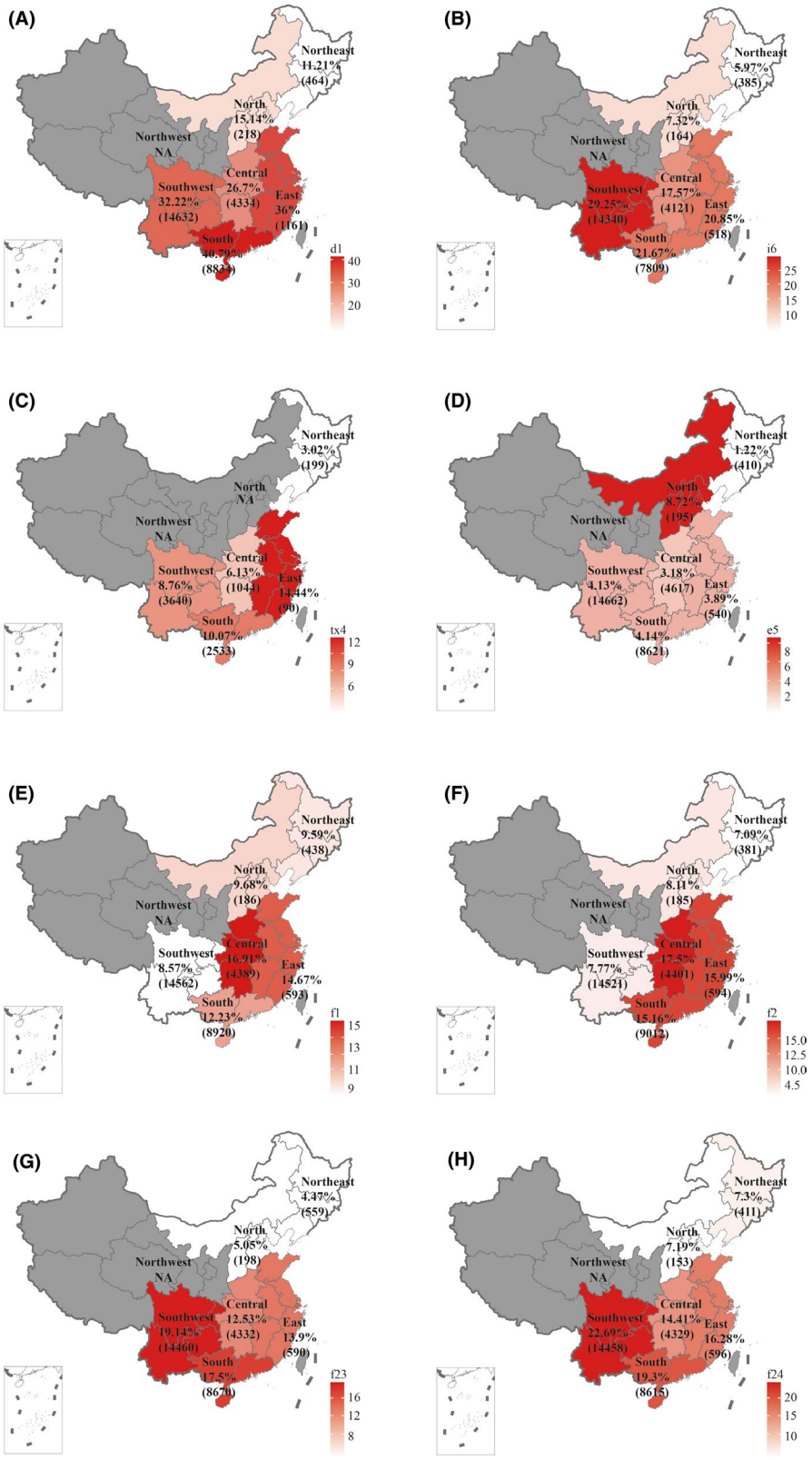

FIGURE 1 Heatmap for the prevalence of positive SIgE tests for d1:House dust mite (a), i6:German cockroach (b), tx4:Tree pollen mix (c), e5:Dog dander (d), f1:Egg white (e), f2:Cow's milk (f), f23:Crab (g), f24:Shrimp (h) in different regions. The heatmap for the prevalence of sensitization to mold mix (mx1) is not shown here because the prevalence of mx1 sensitization is not significantly different in different regions (ie, $P > .05$). 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

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 and 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 (ie, classes 3-6) instead of all classes (ie, classes 1-6) were considered (Figures S2 and S4). This move was clearer in females as compared to males (Figures S3 and 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, and cross-reactivity.[3,4,6-9] Please refer to the Appendix S1 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.

ACKNOWLEDGMENTS

This study was supported by the University of Macau (grant numbers: FHS-CRDA-029-002-2017, EF005/FHS-ZXH/2018/GSTIC and MYRG2018-00071-FHS), the Science and Technology Development Fund, Macau SAR (File no. 0004/2019/AFJ and 0011/2019/AKP), the National Natural Science Foundation of China (81802076 and 81871736), the National Key Technology R&D Program (2018YFC1311902), the Guangdong Science and Technology Foundation (2019B030316028), the Guangzhou Municipal Health Foundation (20191A011073), and the Guangzhou Science and Technology Foundation (201804020043). Dr Luo has nothing to disclose. Dr Wang has nothing to disclose. Dr Zhang has nothing to disclose. Dr Zheng has nothing to disclose. Dr Leng has nothing to disclose. Dr Li has nothing to disclose. Dr Liu has nothing to disclose. Dr Sun has nothing to disclose. Dr Zhang has nothing to disclose.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Ebert CS Jr, Pillsbury HC III. Epidemiology of allergy. *Otolaryngol Clin North Am*. 2011;44(3):537-548.
2. Lin J, Wang W, Chen P, et al. Prevalence and risk factors of asthma in mainland China: The CARE study. *Respir Med*. 2018;137:48-54.
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. *Multidiscip Resp Med*. 2014;9(1):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. *Sci Rep*. 2017;7(1):9593.
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*. 2016;78:105-112.
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*. 2009;64(7):1083-1092.

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*. 2002;57(2):137-142.
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. *Chin Med J*. 2010;123(24):3540-3544.
9. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy*. 2008;63(11):1418-1427.

SUPPORTING INFORMATION

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

DOI: 10.1111/all.14610

Treatment-emergent adverse events in dupilumab-treated patients with allergic diseases: A meta-analysis

To the Editor,

Allergic diseases such as asthma, chronic rhinosinusitis (CRS), atopic dermatitis (AD), allergic rhinitis, and eosinophilic esophagitis (EoE) affect more than 30% of the population,[1] with a dramatic increase[2] and a lack of effective treatments for recurrent or adverse effects of corticosteroids and immunosuppressants.[3,4] Dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha subunit and inhibits IL-4/IL-13 signaling, thus downregulating type-2 inflammatory responses.[5] Currently, dupilumab has proven effectiveness in patients with serious allergic diseases.[6-8] However, the evidence on safety of dupilumab is insufficient in allergic diseases. Therefore, we conducted a meta-analysis to assess the overall safety of dupilumab treatment by exploring the risk of treatment-emergent adverse event (TEAE) in patients with allergic diseases.

We carried out a systematic literature search of PubMed, Web of Science, EMBASE, and the Cochrane Library databases using the keywords such as "allergic disease," "dupilumab" to identify randomized controlled trials (RCTs) of dupilumab therapy in patients with allergic diseases from inception to June 2020. Seventeen RCTs with a total of 7578 participants were finally eligible for inclusion in this meta-analysis through our literature search strategy (Figure S1). The characteristics of the included studies are listed in Table S1. A quality assessment of the 17 RCTs was shown in Figure S2. In addition, the points in the funnel plot of the included RCTs were almost symmetrically distributed (Figure S3), and Egger's tests showed there was no statistical difference in publication bias among the RCTs ($P = .467$). Sensitivity analyses of any TEAE, any serious TEAE, and any TEAE by removing each RCT suggest that no single study had a significant impact on the results (Figure S4).

A pooled analysis showed that the incidence of any serious TEAE was 223 of 4923 (4.53%) patients receiving dupilumab treatment and 139 of 2401 (5.79%) patients receiving placebo. Treatment of patients with dupilumab was associated with a 32% lower risk of any serious TEAE than with placebo (RR = 0.68; 95% CI, 0.50-0.94; $P = .02$; $I^2 = 30.28\%$; Figure 1A). Furthermore, there was no evidence of a difference in risk for any TEAE leading to death between dupilumab (11/4557, 0.24%) and the placebo group (3/2303, 0.13%; RR = 0.95; 95% CI, 0.40-2.24; $P = .91$; $I^2 = 0.00\%$; Figure 1B). Data on the occurrence of any TEAE during dupilumab treatment showed that patients receiving dupilumab treatment (3809/5050, 75.43%) did not have a higher risk of any TEAE compared with those receiving placebo (1921/2528, 75.99%; RR = 0.99; 95% CI, 0.96-1.02; $P = .56$; $I^2 = 14.08\%$; Figure 1C). The risk of any leading to permanent treatment discontinuation in patients receiving dupilumab treatment was similar to that in patients receiving placebo (RR = 0.78; 95% CI, 0.53-1.16; $P = .23$; I2 = 32.37%; Figure 1D). In the 17 RCTs, 14 common TEAEs were reported following dupilumab treatment. A meta-analysis revealed lower risks of skin infections in patients receiving dupilumab treatment than in those receiving placebo (RR = 0.56; 95% CI, 0.45-71; $P < .01$; $I^2 = 0.00\%$; Table 1). In addition, the risk of other common TEAEs (headache, nasopharyngitis, bronchitis, upper respiratory tract infection, back pain, influenza, urinary tract infection, rash, 19 gastroenteritis, herpes viral infections) in patients receiving dupilumab treatment was similar to that in patients receiving placebo (all $P > .05$; Table 1). However, injection-site reactions (RR = 1.90; 95% CI, 1.50-2.40; $P < .01$; $I^2 = 37.69\%$), conjunctivitis (RR = 2.44; 95% CI, 1.82-3.26; $P < .01$; $I^2 = 0.00\%$), and eosinophilia ((RR = 5.85; 95% CI, 2.57-13.28; $P < .01$; $I^2 = 0.00\%$) were both associated with a higher risk in the dupilumab group than in the placebo group (Table 1).

We next analyzed whether dupilumab can reduce the risk of developing other allergic diseases in patients with allergic disease. The pooled data for the risk of developing asthma in patients with CRSwNP (2 RCTs) and AD (3 RCTs) demonstrated there was a 67% lower risk of developing asthma in patients that received dupilumab than in those that received placebo (RR = 0.33; 95% CI, 0.20-0.54; $P < .01$; $I^2 = 0.00\%$; Table 1). Meanwhile, among the five RCTs that included patients with allergic diseases such as asthma (3 RCTs) and AD (1 RCT), the risk of sinusitis was lower in patients that received dupilumab than in those that received placebo (RR = 0.60; 95% CI, 0.45-0.81; $P < .01$; $I^2 = 0.00\%$) (Table 1).

The present study examined the adverse events associated with dupilumab in various serious allergic diseases. Our result