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ORIGINAL RESEARCH

A Multicenter Study Assessing Risk Factors and Aeroallergens Sensitization Characteristics in Children with Self-Reported Allergic Rhinitis in China

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Background: Up to now, epidemiological studies on allergy rhinitis (AR) have primarily focused on determining the risk of disease in Chinese adults, with the majority of them designed by single centers, while cross-sectional and epidemiological data describing allergic sensitization in children with self-reported AR are scarce.

Objective: This study was estimating of the latest information about the sensitization patterns and risk factors of clinical AR to develop effective strategies for the prevention and treatment of AR.

Methods: We conducted a cross-sectional survey between January 2020 and June 2021 involving children from seven cities in China who reported AR. A total of 762 children participated in this survey. To evaluate the risk factors and specific sensitization patterns of clinical AR through questionnaires and specific immunoglobulin E to 11 aeroallergens.

Results: Of the 762 patients, 593 (77.8%) had at least one positive IgE level. Aged 7–14 years (OR 1.503, (95% CI 1.058–2.136), $P = 0.023$); With allergic conjunctivitis (OR 1.843, (95% CI 1.297–2.620), $P = 0.001$) and living in the Eastern (OR 1.802, (95% CI 1.263–2.573), $P = 0.001$) all elevated the risk of clinical AR associated with aeroallergens. The sensitization rates of *D. pteronyssinus* and *D. farinae* were higher than those of other allergens in the 0–6 and 7–14 years old age groups. The most common aeroallergens among self-reported children with AR in the eastern were *D. farinae* (74.9%) and *D. pteronyssinus* (74.3%), while in the western were mugwort (60.0%) and marguerite (56.6%). Majority of sIgE-positive subjects were sensitized to three or more of the tested pollen allergens in the Western (52.1%), compared with 5.7% in the Eastern.

Conclusion: There was an apparent geographic variation in childhood allergies in China. Age factors also had strong impacts on the allergen sensitization rate of children, but these impacts differed across regions.

Keywords: allergic rhinitis, specific immunoglobulin E, cross-sectional survey, aeroallergen, children

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Introduction

Allergic rhinitis (AR) is caused by immunoglobulin E (IgE)-mediated reactions to allergens,[1,2] affecting 10% to 40% of the population in the world.[3] Allergen sensitization is an important risk factor for AR,[4] which poses a substantial health risk to children and affects their quality of life.[5,6] Allergen sensitization in preschool and school-age children is closely related to allergen.[7] Exposures to aeroallergen may aggravate the symptoms of rhinitis[8–10] and asthma by promoting airway inflammation and airway hyperresponsiveness and airflow restriction.[11,12] The epidemiological investigation of

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allergic rhinitis is helpful to identify potential aeroallergen and assist clinicians in accurate diagnosis and treatment of the disease.

A series of studies have explored the prevalence of allergen sensitization in China, such as Li et al[13] assessed the prevalence of sensitizations by Skin prick tests (SPT) in patients with asthma and/or rhinitis in China from 2006 to 2007 and demonstrated significant differences in patterns of sensitizations from different geographical areas. However, in the vast territory of China, few multicenter studies have focused on sensitization to aeroallergens in children with AR. In addition, China's modernization, growing urbanization, changing lifestyles and climatic factors have further complicated geographical variations in the distribution of allergens. Sensitive patterns of the population are also evolving and need to be assessed regularly. Therefore, there is a strong need for a study to estimate the latest information about the sensitization patterns and risk factors of clinical AR to develop effective strategies for the prevention and treatment of AR in China, not just in a specific geographic region of China.

In this cross-sectional survey, we measured specific IgE to 11 aeroallergens in children with self-reported AR within China, analyzed the statistical variables of the patient population, allergen exposure, and serum-specific IgE sensitization, and then assessed the risk factors and sensitization characteristics of allergic rhinitis associated with aeroallergens.

Materials and Methods

Patients and Study Design

Research population: This cross-sectional (retrospective analysis) study was conducted in seven cities and nine centers, respectively, in eastern and western China between January 2020 and June 2021. These cities are Weifang in Shandong, Zhongshan in Guangdong, Suzhou in Jiangsu, Shijiazhuang in Hebei, Lanzhou in Gansu, Xijing in Shaanxi and Yinchuan in Ningxia in western China. Clinicians in nine centers collected medical history, questionnaires and serum examinations from children aged 0 to 14 who self-reported allergic rhinitis. There were 527 males and 235 females, with a median age (interquartile interval) of 7.00 (5.00, 10.0) years. According to their age, they were divided into two groups: 0–6 yr age group (n = 333) and 7–14 yr age group (n = 429). Classic symptoms of AR include sneezing, nasal congestion, rhinorrhea, and nasal pruritus, alongside ocular symptoms, such as redness and itching of eyes and lachrymation. NAR is a group of heterogeneous diseases, characterized by clinical nasal symptoms with negative specific allergen tests,[14] while Clinical AR with typical symptoms of AR and can be detected with IgE against relevant aeroallergens. The self-reported AR subjects were further divided into two groups: sIgE positive subjects were defined as clinical AR patients and sIgE negative subjects were defined as clinical NAR patients.

Questionnaire

The questionnaire used in the survey was adopted from the Chinese-translated version[15] of the questionnaire from International Study of Asthma and Allergies in Childhood Phase II,[16] and modifications were made according to the real situation of China. Questions about demographic characteristics; family history of allergic diseases; symptoms of rhinitis, wheezing, or coughing; burning or itchy eyes; and environmental exposure factors were asked. AR was diagnosed according to the criteria of 2010 aria guidelines,[17] if the subject had more than two of the following four typical rhinitis symptoms, he/she was defined as a self-reported AR patient. Such symptoms included sneezing, runny nose, nasal congestion and itching over the past 12 months, and excluded the effects of upper respiratory tract infection. All the selected patients signed a written informed consent in duplicate by themselves or their legal guardian before the study.

Blood Collection, Serum Processing and Storage

Serum samples from patients were obtained by 10-minute centrifugation at 3000g of venous blood collected with a separation gel containing vacutainer tubes. Aliquots of serum were stored at −80°C in AIR-SKLRD. The serum samples were analysed with the ALLEOS 2000^{TM} allergen detection system (Hycor Biomedical, USA). Allergic sensitization was defined as at least one positive sIgE. A positive result was defined as an IgE level of 0.35 kU/L or more for the specific allergen. The allergens tested were those known to be present in China. We grouped these allergens according to shared characteristics: pollens (birch, timothy, mugwort, marguerite, dandelion, plantain), animals (cat, dog, horse), mites (*D. pteronyssinus* and *D. farina*).

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Statistical Analysis

Data were analyzed using SPSS V.22 software package (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to study the demographic and general information of the study population. Geographical areas and age groups were treated as categorical variables. Chi-square analysis was performed to analyze the clinical evaluation and the sensitised allergens evidenced by sIgE. Univariate analysis was used, followed by multivariate logistic regression, to evaluate the associated factors of clinical AR and NAR. Both the OR and the 95% CI were measured. A value of $P < 0.05$ was considered to be significant. The differential variables with $P < 0.05$ were included in the model together with gender and disease. The correlation of different allergens was analyzed by Spearman's test.

Results

Characteristics Between Clinical NAR and Clinical AR

A total of 762 children were recruited for this study, including 527 males and 235 females. The mean age of the sample was 7.59 years (SD, 3.15); Table 1 shows the demographic characteristics of the study population, 593 (77.8%) sensitised to at least one aeroallergen. By univariate analysis, clinical AR in the 7–14 yr age group was higher than that in the 0–6 yr age group (41.1% vs 58.9%, $P = 0.008$); in the East was higher than that in the West (53.0% vs 47.0%, $P = 0.004$); Conjunctivitis was higher than that without conjunctivitis (57.3% vs 42.7%, $P = 0.001$). The above differential variables and the two confounding factors of gender and self-reported asthma were included in the logistic regression equation. The children aged 7 to 14 years (OR 1.503, (95% CI 1.058–2.136), $P = 0.023$); Children with conjunctivitis (OR 1.843, (95% CI 1.297–2.620), $P = 0.001$) and living in the eastern region (OR 1.802, (95% CI 1.263–2.573), $P = 0.001$) increased the risk of AR associated with inhaled allergens. As shown in Table 2, living in the eastern region, 7–14 years old and allergic conjunctivitis (AC) are independent risk factors for children with AR related to inhaled allergens.

The Patterns of Sensitization to Allergens in the Environment Differ Widely in Different Regions

As shown in Figure 1, the most common sensitising allergens were *D. farinae* (74.9%) and *D. pteronyssinus* (74.3%) in the Eastern, while in the Western were mugwort (60.0%) and marguerite (56.6%). There was a similar trend in the eastern sub-analysis of 0–6 years old, pollen sensitization was more common in the Western than in the Eastern ($P < 0.05$) (see Appendix 1). We also compared allergen exposure to plants and hairy animals in different regions, and found that people in the Western had more contact with plants than people in the Eastern (52.3% vs 47.7%, $P < 0.001$). After exposure to plants, people are more likely to develop nasal symptoms such as nasal itching, nasal congestion or sneezing (22.2% vs 42.5%, $P < 0.001$) and lung symptoms (10.10% vs 26.60% $P < 0.001$). There was no significant difference between eastern and western populations in contact with cat or dog, but people in the Western were more likely to develop nasal symptoms (29.4% vs 13.4%, $P < 0.001$) and pulmonary symptoms (23.5% vs 6.7%, $P < 0.001$). We also found that the use of air conditioners in the Eastern reached almost 99%, which was much higher than that in the Western (98.2% vs 38.9%, $P < 0.001$).

The Patterns of Sensitization to Allergens in Different Age Groups

Figure 2 shows the sensitization rate of mite was most common in both age groups. Prevalence rates for cat and dog, the 7–14 yr age group, were significantly higher than the 0–6 yr age group ($P < 0.05$ for each). A sub-analysis of tested patients residing in eastern indicated that those aged 0–6 years were less commonly sensitised to cat, horse or dog aeroallergens than patients aged 7–14 yr ($P < 0.05$ for each), however only cat sensitization in the 7–14 yr age group was higher than that in the 0–6 yr age group in the Western ($P = 0.001$) (Appendix 2).

Eastern and Western with Multi-Sensitization

Of the 762 patients who had undergone testing for all 11 allergen groups, 350 (13.8%) were only sensitised to the pollen allergen group, with Eastern and Western

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Table 1 Demographic and Clinical Characteristics of the Clinical NAR (N = 169) and Clinical AR (N = 593)

Characteristic		Self-Reported Allergic Rhinitis		Total (N=762)	*P*
		Clinical NAR	Clinical AR		
		n (%)[a]	n (%)[b]		
Region	Eastern	68 (40.2)	314 (53.0)	382 (50.13)	0.004
	Western	101 (59.8)	279 (47.0)	380 (49.87)	
Age (years)	0–6	89 (52.7)	244 (41.1)	333 (43.70)	0.008
	7–14	80 (47.3)	349 (58.9)	429 (56.30)	
Gender	Female	58 (34.3)	177 (29.8)	235 (30.84)	0.267
	Male	111 (65.7)	416 (70.2)	527 (69.16)	
Ethnic	Other	10 (5.9)	37 (6.2)	47 (6.17)	0.878
	Han	159 (94.1)	556 (93.8)	715 (65.88)	
Self-reported asthma	No	88 (52.1)	279 (47.0)	367 (48.16)	0.249
	Yes	81 (47.9)	314 (53.0)	395 (51.84)	
Allergic conjunctivitis	No	97 (57.4)	253 (42.7)	260 (34.12)	0.001
	Yes	72 (42.6)	340 (57.3)	502 (65.88)	
Skin allergy	No	90 (53.3)	291 (49.1)	381 (50.00)	0.337
	Yes	79 (46.7)	302 (50.9)	381 (50.00)	
Birth mode	Eutocia	93 (55.0)	351 (59.2)	444 (58.27)	0.333
	Cesarean	76 (45.0)	242 (40.8)	318 (41.73)	
Passive smoking	No	79 (46.7)	293 (49.4)	372 (48.82)	0.541
	Yes	90 (53.3)	300 (50.6)	390 (51.18)	
Family history	No	56 (33.1)	204 (34.4)	260 (34.12)	0.760
	Yes	113 (66.9)	389 (65.6)	502 (65.88)	
Location of the building	Urban	128 (68.1%)	404 (70.4%)	490 (69.82)	0.551
	Rural	60 (31.9%)	170 (29.6%)	272 (30.18)	
Residential floor	≤9 floors	118 (69.8)	372 (62.7)	490 (64.30)	0.090
	>9 floors	51 (30.2)	221 (37.3)	272 (35.70)	
Air conditioner	No	63 (37.3)	176 (29.7)	239 (31.36)	0.060
	Yes	106 (62.7)	417 (70.3)	523 (68.64)	
Using mattress	No	17 (10.1)	46 (7.8)	63 (8.27)	0.338
	Yes	152 (89.9)	547 (92.2)	699 (91.73)	
Q1	No	105 (62.1)	340 (57.3)	445 (58.40)	0.536
	Yes	44 (26.0)	173 (29.2)	217 (28.48)	
	Never contact	20 (11.8)	80 (13.5)	100 (13.12)	
Q2	No	129 (76.3)	409 (69.0)	538 (70.60)	0.141
	Yes	20 (11.8)	104 (17.5)	124 (16.27)	
	Never contact	20 (11.8)	80 (13.5)	100 (13.12)	
Q3	No	46 (27.2)	179 (30.2)	225 (29.53)	0.126
	Yes	8 (4.7)	52 (8.8)	60 (7.87)	
	Never contact	115 (68.0)	362 (61.0)	477 (62.60)	

(*Continued*)

Table 1 (Continued).

Characteristic		Self-Reported Allergic Rhinitis		Total (N=762)	*P*
		Clinical NAR	Clinical AR		
		n (%)[a]	n (%)[b]		
Q4	No	48 (28.4)	195 (32.9)	243 (31.89)	0.185
	Yes	6 (3.6)	36 (6.1)	42 (5.51)	
	Never contact	115 (68.0)	362 (61.0)	477 (62.60)	

Notes: [a]Self-reported AR subjects showing negative IgE. [b]Self-reported AR subjects with positive IgE. Q1: Symptoms of itching, stuffy nose or snorting after contact with grass, trees or flowers. Q2: Symptoms of dyspnea, wheezing, chest tightness, shortness of breath or cough after contact with grass, trees or flowers. Q3: Symptoms of itching, stuffy nose or snorting after contact with dogs or cats. Q4: Symptoms of dyspnea, wheezing, chest tightness, shortness of breath or cough after contact with dogs or cats. P value significant at <0.05.

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accounting for 100 (26.2%) and 250 (65.8%), respectively. There was a significant correlation between tree, grass and weeds. Among them, the correlation between mugwort and marguerite was the strongest (r = 0.893, $P < 0.05$), while timothy and mugwort was the weakest (r = 0.651, $P < 0.05$) (Table 3). Most of the patients in the Western showed sensitization to weeds (mugwort, marguerite, dandelion, plantain), birch and timothy. The majority of sIgE-positive subjects were sensitized to three or more of the tested pollen allergens in the Western (52.1%), compared with 5.7% in the eastern only. 95.4% (122/128) of patients with sensitization to timothy also had sensitization to weeds, and only 4.6% (6/128) were mono-sensitive to timothy in the Western (Figure 3A), while 17.6% (3/17) in the Eastern (Figure 3B). Of the 94 (24.7%) sensitised to birch in the Western, 94 (100%) were sensitised to both birch and weeds (Figure 3C); even a small number of birch sensitized patients in the Eastern, but 22.2% (4/18) patients were sensitised to birch only (Figure 3D). Of the 285 sensitised to marguerite, 2 (1.3%) was mono-sensitised to marguerite in the Western, while 21 (30%) in the Eastern; Among 60% (228/380) sensitised to mugwort in the Western, only 6.5% (15/228) were mono-sensitive to mugwort, 90.3% (206/228) also had sensitization to marguerite.

Table 2 Risk Factors (Odds Ratio (OR)) for Clinical AR

Factors	Clinical AR			
	β	*P*	OR	OR 95% CI
Male	0.184	0.332	1.202	0.829–1.743
Eastern	0.589	0.001	1.802	1.263–2.573
Age (7–14 years)	0.408	0.023	1.503	1.058–2.136
Self-reported asthma	0.216	0.230	1.241	0.872–1.766
Self-reported conjunctivitis	0.611	0.001	1.843	1.297–2.620

Notes: Two confounding factors of gender (female or male) and self-reported asthma (yes or no) were included in the logistic regression analysis.
Abbreviations: Clinical AR, Self-reported AR subjects with positive IgE; 95% CI, 95% confidence intervals; β, regression coefficient.

Discussion

We conducted an epidemiologic survey of self-reported AR and examined the sensitization rates against 11 aeroallergens by measuring the serum-specific IgE of 762 children in China.

Our results confirmed that the prevalence of clinical AR varied markedly between various regions and that this variation was more marked in the 7–14 age group. Inter- and intra-regional differences in climate, vegetation, air pollution levels, differences in lifestyle, pollen exposure, and genetic variability could be responsible for the variability. The current study showed that children with AC were 1.843 times more likely to develop clinical AR than those without AC (95% CI:1.297–2.620). Indeed, it has been found that AC occurs concomitantly with AR, which is consistent with current understanding.[18,19]

The study showed that the prevalence rates of sensitization to common inhaled allergens varied widely between regions. House dust mite (HDM) is the most important inhalant allergens in patients with self-reported AR in the Eastern, which is consistent with Li et al[13] or Zhang et al[20] previous studies in China.[21] Zhongshan and Suzhou were located in subtropical areas with high temperatures and humidity throughout the year, with suitable temperature and humidity for dust mites to live. Li et al[22] have reported that when the air conditioner is running, the mite allergens accumulate in the filter dust, increasing the allergic risk of rhinitis patients living in the room. Our data show that in the economically developed east, the air conditioning coverage rate reaches 99%, so insufficient ventilation for indoor activities may increase the sensitization

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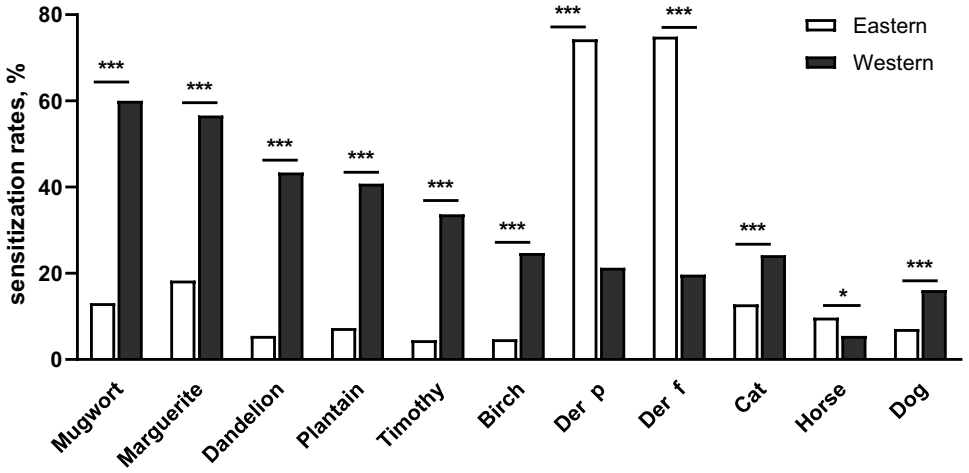

Figure 1 Prevalence (%) of allergic sensitization defined by specific IgE level of 0.35 kU/L or more by geographic areas (*P<0.05, ***P<0.01).

rate of HDM. Patients living in the arid western region were more sensitive to pollen, which is similar to the result of the increased susceptibility of plants in Sydney's inland areas far from the coast.[23]

There are also geographical factors affecting animal sensitization. For cats and dogs, the sensitization rate in the Western is higher than that in the Eastern. In agreement with a previous multicenter cross-sectional study in Europe, there are significant differences in Fel d 1 levels in mattress dust of 2800 families in 22 urban areas in Europe.[24] Also, children in the Western region were more likely to have nasal symptoms (29.4% vs 13.4%, $P < 0.001$) and pulmonary symptoms (23.5% vs 6.7%, $P < 0.001$) than in the Eastern. This may be related to the fact that most people in the Western are more sensitized after exposure to cats and dogs. It is obvious that the prevalence of sensitisation to dogs and cats varies by region and predisposition to atopy.

The Western pastoral area is dominated by plateaus and mountains, and the natural vegetation is dominated by grasslands and deserts. Affected by those natural conditions, the rate of horse ownership is high, and horse riding is more popular in the Western than in the Eastern. However, our data show that horse sensitization is surprisingly higher in the Eastern. Of 113 atopic people in Italian cities, 60 horse sensitised patients complained that they had no contact with horses.[25] This indicates that horse sensitization may also occur without significant direct or indirect contact with horses. We suspect that due to long-term contact with horses, immune tolerance is gradually established; thus, susceptible individual to horse is less common in the Western. What's more, people in the

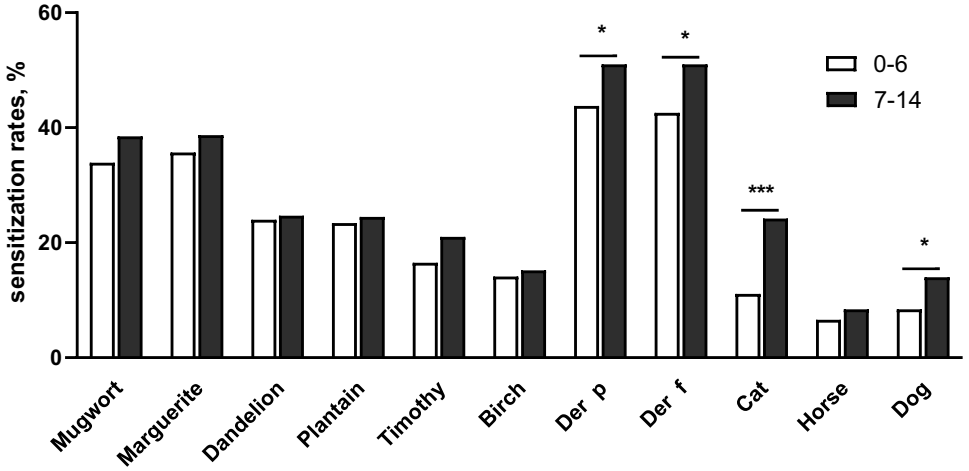

Figure 2 Prevalence (%) of allergic sensitization defined by specific IgE level of 0.35 kU/L or more by age (*P<0.05, ***P<0.01).

Table 3 Spearman Correlation Analysis of 6 Pollen Allergens IgE Concentrations

Allergen	Mugwort	Marguerite	Dandelion	Plantain	Timothy	Birch
Mugwort	1					
Marguerite	0.893*	1				
Dandelion	0.794*	0.863*	1			
Plantain	0.753*	0.783*	0.811*	1		
Timothy	0.651*	0.689*	0.702*	0.778*	1	
Birch	0.663*	0.695*	0.729*	0.808*	0.819*	1

Notes: *p<0.05. Spearman Correlation analysis showed that there was a significant correlation between birch, timothy grass and weeds. The depth of the color between two allergens represented the degree of relationship between them.

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eastern region may be indirectly exposed to serum albumin, an important panallergen involved in milk, meat and epithelia allergy, resulting in cross-reactivity. About half of the patients (45.1%) reacted with two or all three animals as specified, the result is similar to study in Austria.[26] To further verify cross-reaction and actual sensitization, it is necessary to develop allergen component detection in the future.

We also examined the role of age effects on the prevalence of aeroallergens. Subjects with self-reported aged 7 to 14 years were more sensitive to tested aeroallergens than aged 0–6 years. In a cohort of an urban population of the center of Italy, the positive rate of prick test increased by 11.6% after about 6–10 years of observation.[27] The sensitization to common aeroallergens increased over time, which could be related to children's increasing outdoor activities as they become older, increasing their chances of being exposed to inhaled allergens. On the one hand, our findings showed that the sensitization rate of preschool and school-age children to HDM was high, and paediatricians should give children effective dust mite intervention measures to reduce indoor dust mite allergen exposure. On the other hand, children with respiratory allergic diseases were more sensitive to pollen in the Western, especially those over 6 years old, corresponding preventive measures should be taken. To our knowledge, trends in peak pollen times are measured during the spring, summer and autumn, which depends on the allergen source (trees, grass, and weeds).[28] In China, birch tree pollen is one of the major portions in spring, while weed and grass pollen are the major portion in summer and autumn.[29] It is necessary to wear masks or reduce outdoor exposure time during pollen seasons as well as weed pollen season.

A new finding of this study is that the co-sensitization rate of patients sensitized to pollen varied widely between the geographic areas. The majority of sIgE-positive subjects were sensitized to three or more of the tested pollen allergens in the Western (52.1%), compared with 5.7% in the eastern only. This may be related to copious resources of vegetation in the western and arid, desert/steppe, cold arid climate, where pollens scattered with the wind and spread widely. In contrast, the eastern region is not conducive to the reproduction and spread of pollen, which is characterized by a single type of vegetation and high humidity. What's more, the high correlation and co-sensitization of pollens suggested another reasonable explanation, that is parallel sensitization or cross-reactivity between closely related allergens. Allergen components from different species may have the same functions.[30] The sensitization of highly cross-reactive allergens (such as profilin, calcium-binding protein or cross-reactive carbohydrate determinants) in distant relatives may be the reason for the common sensitization of different allergens. Martin Canis pointed out that trees and grasses are structurally similar allergens that can be classified as taxonomic allergens, and patients with a representative allergy (such as birch and timothy) may also respond to other sources of this class (such as hazelnut and rye).[31] Our data on 100% co-sensitization of birch sensitized patients with other pollen in the western region are consistent with this view. Thus, component-resolved diagnosis or molecular diagnosis is crucial to distinguish between cross-reaction and co-sensitization versus allergen immunotherapy decisions.

However, a major limitation of this study is the insufficient sample size. Affected by the epidemic of coronavirus disease 2019, number of outpatients has been greatly

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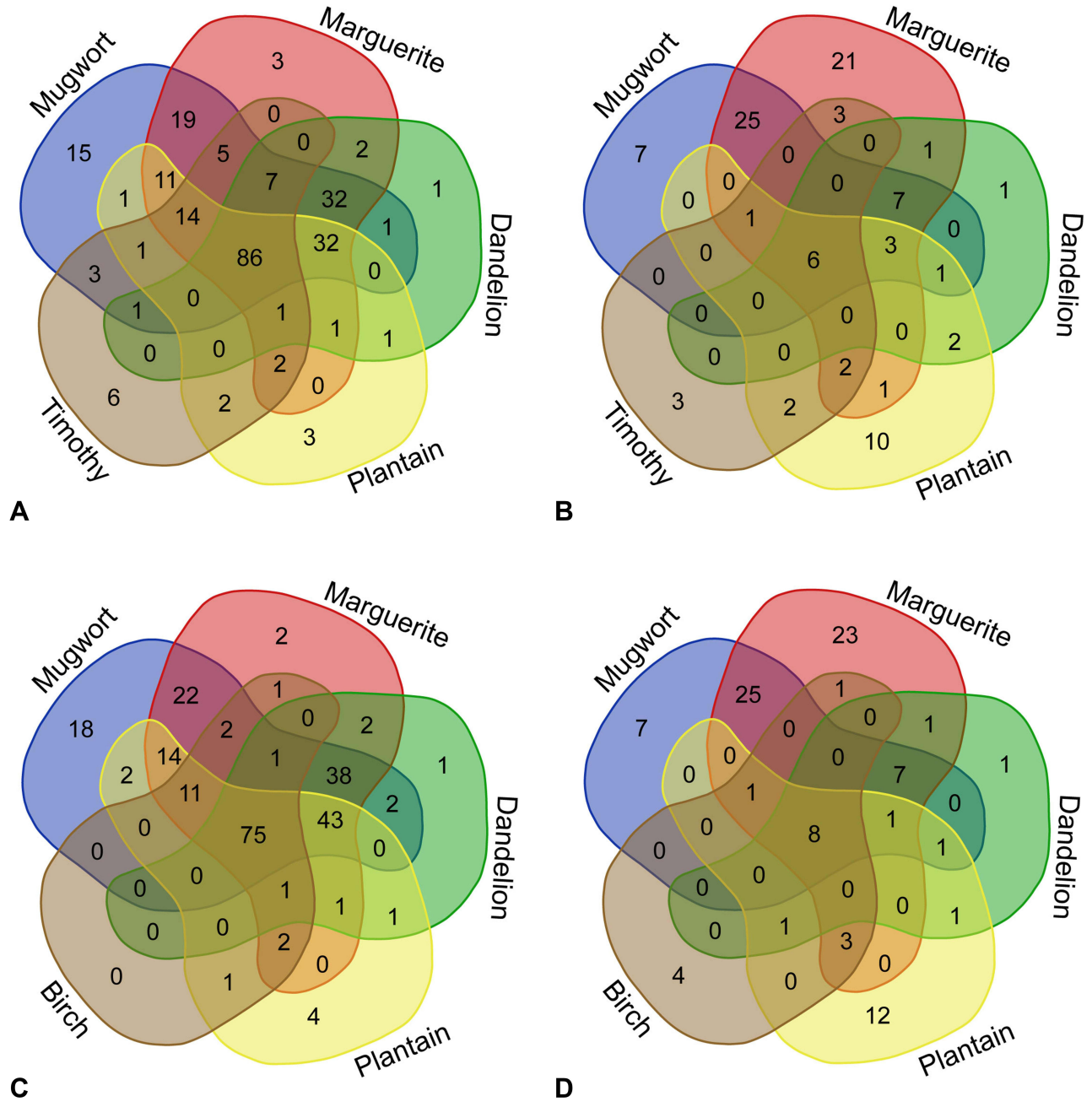

Figure 3 The co-sensitization between weeds pollen, timothy grass and birch. The Venn Diagram shows the number of patients what were co-sensitized. (**A**) The co-sensitization between timothy grass and weeds pollen in the Western. (**B**) The co-sensitization between timothy grass and weeds pollen in the Eastern. (**C**) The co-sensitization between birch and weeds pollen in the Western. (**D**) The co-sensitization between birch and weeds pollen in the Eastern.

reduced.[32] The other reason is that only the centers with developed economies were included in the survey, and there are no clinical data about primary hospitals. Therefore, further studies including more individuals or the inclusion of economically backward areas in the future can better guide local allergen detection. In particular, the difference between NAR and AR was based only on typical rhinitis symptoms and the presence of IgE, without data from SPT. In this respect, it is likely that the observed prevalence of NAR was higher than the actual prevalence. Self-described allergic rhinitis patients may not be sIgE positive caused by allergens, but we do not rule out non-sIgE-mediated allergic rhinitis. However, because allergic and non-allergic rhinitis have different origins and treatments, using sIgE to divide people into allergic and non-allergic rhinitis could yield interesting results.[33]

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Conclusions

In conclusion, the factors including age, geographical location and conjunctivitis were associated with AR related to inhaled allergens. Moreover, these risk factors interact with inhaled allergen sensitization rates. It provides an effective guiding basis for clinicians in the diagnosis and treatment of allergic diseases, and also provides reasonable health education materials for the prevention and treatment of allergic diseases in China.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki and approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (approval number: GYFYY-2017-18).

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Disclosure

The authors declare that they have no competing interests in this work.

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