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10 **Title:** Clinical characteristics of allergic rhinitis patients in 13 metropolitan cities of China

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72 MZ, XW, MW, WS, LC, ML, ZX, FM, LZ, LC, XL, XJ, DZ, GX, WW, WK, JC, ZT, YX, DW,
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To the editor,

As an international health problem, allergic rhinitis (AR) currently affects 10% to 40% of the global population.¹ Multicenter studies conducted in Europe and America have revealed the clinical features of pediatric, adolescent, and adult patients with AR, including the subtype percentages, common sensitizing allergens, frequent comorbidities, and methods of treatment;^{2,3} however, few studies have reported such information for children or the general population in the cities or provinces of China.^{4,5} Therefore, there remains an unmet need to acquire more reliable data concerning the manifestations of AR in China and the characteristics of Chinese AR patients. In this study, we conducted collaborative surveys to increase our knowledge about the clinical profiles of AR patients throughout mainland China and to determine how wide variations in the natural environment, economic and social conditions, and daily routines in different areas of China affect people's exposure to different types of allergens.

This study gathered information from 13 metropolitan cities located in 7 different geographic regions of China. Except for Urumqi, 12 major cities surveyed were located on the right side of the "Hu Line", consistent with the features of the geographical distribution of the Chinese population (Figure 1).⁶ All eligible AR patients (self-reported AR combined with positive skin prick tests [SPTs]) provided their written informed consent or the consent of their guardian for study participation and completed an electronic questionnaire designed to gather clinical data. Details regarding the choice of cities and patients, survey method, SPTs and questionnaire design are provided in the online repository (Methods, Tables and Figures). The study protocol was reviewed and approved by the Ethics Review Committee of Beijing Tongren Hospital (TREC2009-40).

A total of 6531 AR patients were recruited during a 1-year period. Among the enrolled patients, 2898 (44.4%) were female, 3633 (55.6%) were male, and a majority were in the 16-55 age group. Males were more common among patients < 35 years old, whereas females were slightly more common among patients > 35 years old; this difference was statistically significant ($X^2=94.78$, $p<0.01$, Figure S2). The proportions of AR patients classified as intermittent mild (IM), intermittent moderate-severe (IMS), persistent mild (PM), and persistent moderate-severe (PMS)

104 according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines¹ were 15.4%, 8.6%,
105 23.8%, and 52.2%, respectively, and the persistent and moderate-severe subgroups were more
106 common than the intermittent and mild subgroups. Meanwhile, when compared to mild AR cases,
107 moderate-severe cases were more predominant in the younger groups of patients ($X^2= 22.46$,
108 $p<0.01$, Figure S3). Among the enrolled patients, 31.1% only had a primary school or lower
109 degree, 17.8% had completed secondary school, 47.6% had a university degree, and 3.5% had
110 received postgraduate education. A further analysis showed that patients with a primary or
111 secondary school education suffered from moderate-severe AR (including IMS and PMS) more
112 often than did patients with a university or postgraduate degree ($X^2= 17.56$, $p<0.01$, Figure S4).
113 Consequently, AR patients with a lower education level were more likely to have ever or be
114 currently receiving allergen immunotherapy than were patients with a higher educational degree
115 ($X^2= 14.30$, $p<0.01$, Figure S5). The PMS subtype accounted for >40% of all subtypes in eleven
116 cities, with the highest percentage of that subtype being found in Taiyuan (91.9%) and the lowest
117 in Urumqi (25.8%) (Figure S6). A multinomial logistic regression analysis (Table 1) showed that
118 PM, IMS, and PMS AR patients were less likely to suffer from coronary heart disease than were
119 IM patients. The worse the subgroup of AR was, the lower the OR value was (OR: 0.45, 95% CI:
120 0.27-0.74; OR: 0.42, 95% CI: 0.22-0.80; OR: 0.30, 95% CI: 0.11-0.79, respectively). Moreover,
121 when the reference category was IM, the other three subtypes of AR patients were significantly
122 more likely to have atopic dermatitis (OR: 1.56, 95% CI: 1.01-2.43; OR: 1.53, 95% CI: 1.06-2.20;
123 OR: 1.62, 95% CI: 1.16-2.24, respectively). Both the IMS and PMS patients were more likely to
124 have concomitant allergic conjunctivitis (OR: 2.85, 95% CI: 1.42-5.75; OR: 2.38, 95% CI:
125 1.22-4.63, respectively) and a lower educational level (OR: 0.74, 95% CI: 0.59-0.93; OR: 0.76,
126 95% CI: 0.63-0.93, respectively) than the IM patients. Finally, when compared with IM patients,
127 the IMS patients more often had a family history of allergy (OR: 1.35, 95% CI: 1.06-1.71), and
128 PMS patients were less likely to be nonsmokers and more likely to have a drug allergy (OR: 1.19,
129 95% CI: 1.03-1.38; OR: 1.39, 95% CI: 1.03-1.88, respectively).
130 In most cities of China, the highest peak months of seeing a doctor for AR were August and
131 September. More than 45% of outpatient visits occurred during those two months, especially in the

132 cities of Changchun, Shenyang, and Taiyuan in northern China. Moreover, October was also the
133 peak month in Changsha, Shanghai and Hefei in southern China. The peak plateau period could
134 last from April to August in Urumqi. Finally, April, May, June, July and November were small
135 peak months in Beijing, Hefei, Guangzhou, Shanghai and Chengdu, respectively. In contrast, there
136 was greater variation in the months with lower incidences of visiting doctors in different cities,
137 such as February in Beijing and Chengdu, April to July in Taiyuan, June and July in Changsha,
138 September to December in Urumqi, October and November in Shenyang and November to April
139 in Shanghai (Figure 2). The survey used to collect information about therapy showed that 37.7%
140 of the patients seldom accepted the regular medication described by ARIA recommendations,
141 2.7% were prescribed medicine to take for an entire year, and 46.6% and 12.9% accepted their
142 prescribed medicine either when their AR symptoms were already present or when a specific time
143 period was approaching, respectively. Meanwhile, an evaluation of curative effects showed that
144 32.7% of all the recruited patients felt that their symptoms had disappeared, 2.3% felt that their
145 symptoms had worsened, 39.1% reported that their symptoms had improved, and 25.9% reported
146 that their symptoms remained unchanged. Finally, only 4.5% of the AR patients had ever or were
147 currently receiving allergen immunotherapy. Therefore, more patient education will be needed to
148 improve the poor adherence to medication regimens and the acceptance rate of immunotherapy in
149 the future. Table S1 shows that *Der p* and *Der f* were the most common inhalant allergens among
150 AR patients in most cities, except in the cities of Changchun, Taiyuan, and Urumqi, where
151 mugwort was the most frequent inhalant allergen in Changchun and Taiyuan, and *Chenopodium*
152 was more frequent in Urumqi. Positive reactions to at least 8 allergens (*Der f* (64.51%), *Der p*
153 (63.15%), mugwort (29.68%), animal hair (20.32%), ragweed (12.23%), *Blattella germanica*
154 (10.75%), *Aspergillus fumigatus* (3.51%), and *Alternaria alternata* (2.32%)) were consistently
155 detected in > 50% (seven) of the major cities. Consequently, the multi-sensitization and
156 co-exposure of dust mites and autumn pollens potentially contributed to the peak of seeing doctors
157 during the summer and early autumn in most cities of China.

158 In conclusion, this is the first extensive multicenter collaborative large-scale study of the clinical
159 characteristics of AR patients who visit clinics in China. It is true that we could not evaluate the

possible influence of the variation of pollen concentration on the change in number of outpatients because of the lack of pollen monitoring. However, this investigation still afforded an opportunity to improve our understanding of the correlations between age, gender, education, and AR, as well as the associations between different AR subtypes and chronic diseases and comorbidities. These results helped us to understand the previously unelucidated characteristics, including AR patients' peak periods of outpatient visits, the current situation of medical treatment and the characteristics of the sensitizing aeroallergens.

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Figure 1. Locations of the 13 metropolitan cities in mainland China.

Abbreviations: BJ = Beijing; CC = Changchun; CD=Chengdu; CS = Changsha; GZ = Guangzhou; HZ = Hangzhou; HF = Hefei; NJ = Nanjing; SH = Shanghai; SY = Shenyang; TY=Taiyuan; U = Urumqi; WH = Wuhan; HH = Heihe; TC = Tengchong.

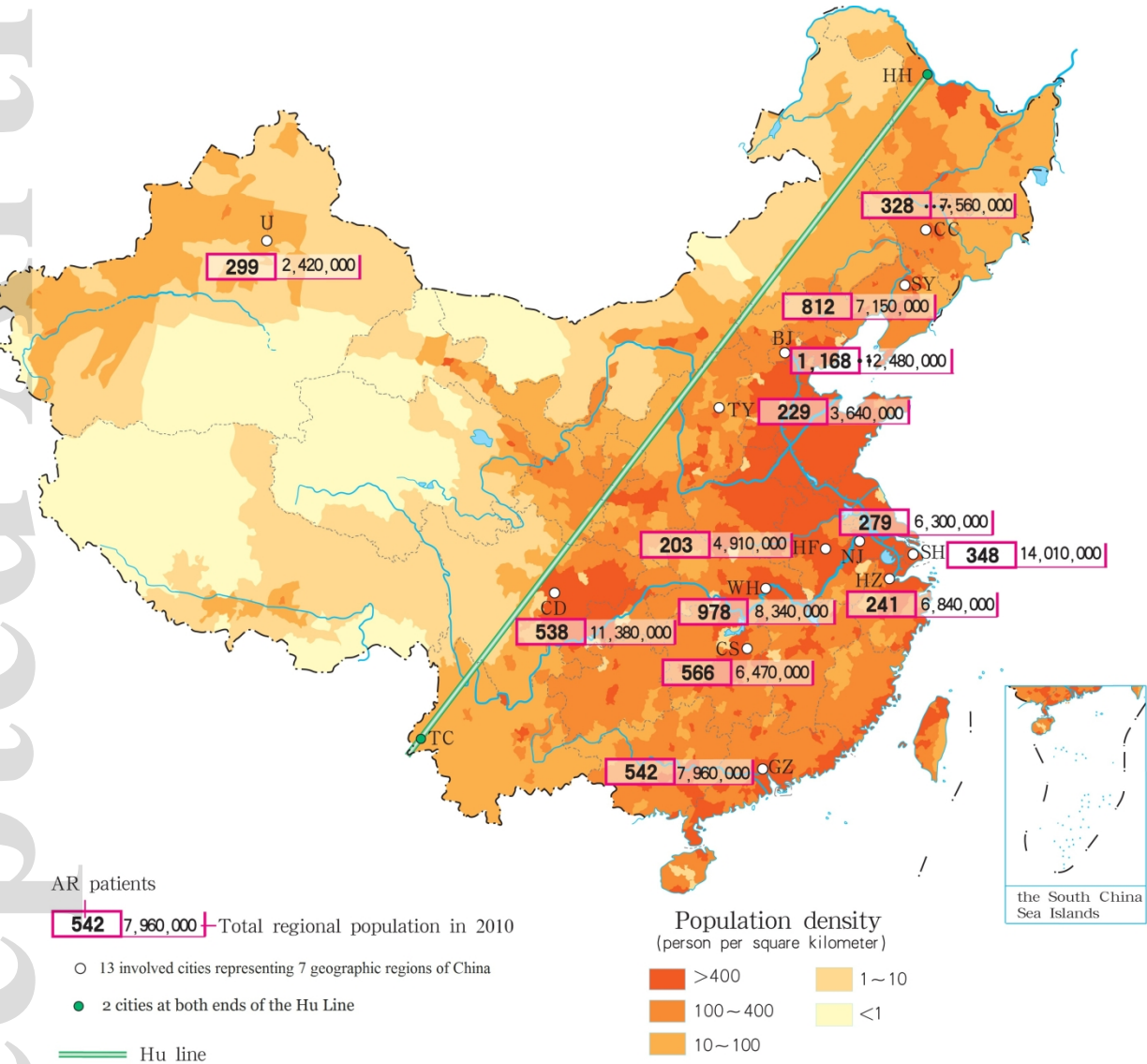


Figure 2. Distribution of outpatient visits for AR during the entire year.

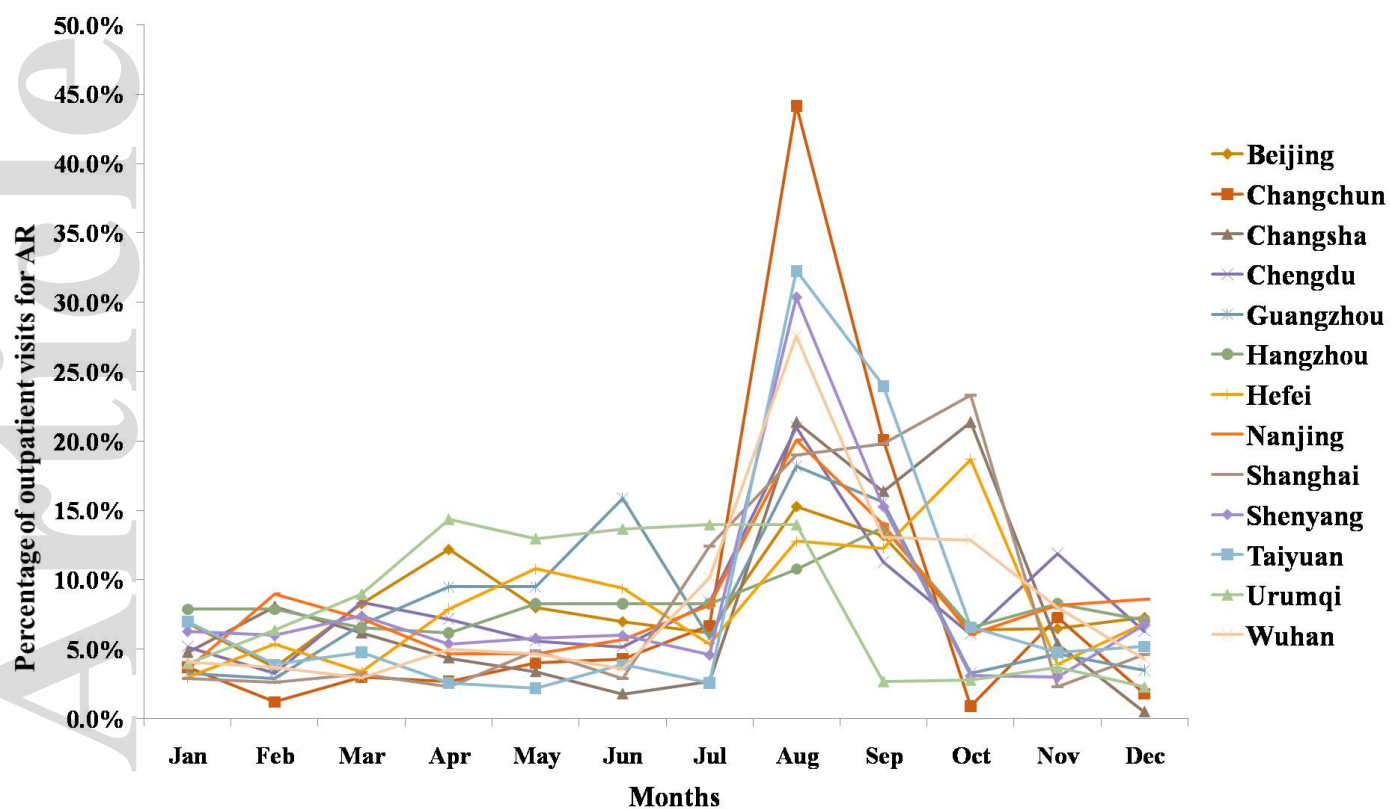


Table 1. The demographic characteristics, allergy histories, comorbidities, and chronic diseases among patients with various AR subtypes based on a multinomial logistic regression analysis.

Variables	PM vs. IM			IMS vs. IM			PMS vs. IM		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age group	0.97	0.88-1.06	0.48	0.90	0.83-1.02	0.34	0.95	0.89-1.01	0.11
Educational level	0.92	0.70-1.23	0.59	0.74	0.59-0.93	0.01*	0.76	0.63-0.93	0.01*
Gender	1.04	0.79-1.38	0.79	1.04	0.84-1.31	0.70	1.11	0.91-1.35	0.29
Smoking status	1.16	0.95-1.43	0.15	1.04	0.88-1.24	0.66	1.19	1.03-1.38	0.02*
Food allergy	1.05	0.53-2.08	0.88	1.19	0.70-2.04	0.52	1.49	0.93-2.40	0.10
Drug allergy	1.04	0.67-1.61	0.87	1.27	0.90-1.78	0.18	1.39	1.03-1.88	0.03*
Family history of allergy	1.28	0.95-1.73	0.10	1.35	1.06-1.71	0.02*	1.21	0.98-1.50	0.08
Asthma	0.66	0.44-0.98	0.04*	0.90	0.67-1.22	0.51	0.89	0.68-1.15	0.37
Atopic dermatitis	1.56	1.01-2.43	0.047*	1.53	1.06-2.20	0.02*	1.62	1.16-2.24	0.00*
Allergic conjunctivitis	2.29	1.00-5.25	0.051	2.85	1.42-5.75	0.00*	2.38	1.22-4.63	0.00*

Coronary heart disease	0.45	0.27-0.74	0.00*	0.42	0.22-0.80	0.01*	0.30	0.11-0.79	0.02*
Diabetes mellitus	1.14	0.20-6.45	0.88	1.47	0.41-5.23	0.55	1.23	0.39-3.90	0.72
Gastroesophageal reflux	0.90	0.44-1.84	0.76	1.49	0.88-2.51	0.14	1.14	0.71-1.85	0.59

*P<0.05

Title: Clinical characteristics of allergic rhinitis patients in 13 metropolitan cities of China

METHODS

Choice of cities

China has a tremendously large territorial area that comprises 7 geographic regions: Northeast, North, Northwest, Central, East, South, and Southwest. These regions include 32 municipalities, capital cities of provinces and autonomous regions. Thirteen cities were randomly selected from the abovementioned major cities by using the method of probability proportional to size. Among the chosen metropolitan cities, Beijing and Taiyuan are in northern China, Changchun and Shenyang are in northeastern China, Urumqi is in northwestern China, Wuhan and Changsha are in central China, Chengdu is in southwestern China, Guangzhou is in southern China, and Hefei, Nanjing, Shanghai, and Hangzhou are in eastern China. The “Hu Line” (Figure 1) shows that the percentage distribution of the Chinese population has been divided into two main geographical segments throughout history: a northwestern segment (left) and a southeastern segment (right). Only 6% of the general population lives in the northwestern segment, whereas the southeastern segment contains 94% of the population.^{1,2} Coincidentally, only one city included in this study (Urumqi) is located to the left of the “Hu Line,” and the remaining 12 cities are located in the southeastern portion of China.

Patient selection

This prospective study enrolled consecutive patients who had complained of at least two nasal symptoms (nasal obstruction, rhinorrhea, sneezing or nasal itching) during the preceding 12 months and had consulted a doctor with special training for this study at an otorhinolaryngology or allergy clinic of the designated large-scale comprehensive hospital in one of the selected cities during the

period of December 1, 2009, to November 30, 2010. Patients who showed a positive skin prick test (SPT) to at least one aeroallergen were recruited for this study. Patients with an evident nasal or sinus disease (e.g., nasal polyps, chronic sinusitis or severe deviation of the nasal septum), other limitations (mental abnormality, hypophrenia, dyslexia or illiteracy), and pregnancy were excluded from enrollment. Each eligible patient provided their personal written informed consent or that of a guardian (for patients < 16 years old) prior to enrollment in the study (Figure S1).

Survey methodology

All 18 hospitals in the cities selected for this project were members of the Chinese Allergic Rhinitis Collaborative Research Group. At each participating hospital, one doctor whose consulting hours were guaranteed for two half-day periods each week was recruited and given appropriate training before the study was initiated. All eligible AR patients were asked to complete a computer-based electronic questionnaire of identical content that was available at each research center. Each center supervisor was responsible for verifying the patient data obtained at his hospital. The study protocol was reviewed and approved by the Ethics Review Committee of Beijing Tongren Hospital.

SPT

Based on the practical needs of different centers, two standardized allergen extracts from Allergopharma (Allergopharma, Reinbeck, Germany) and ALK (Horsholm, Denmark) were used simultaneously in this study. The former extract consisted of a panel of standard allergen extracts and included animal hair, trees (mixed tree I, mixed tree II, pine, locust black), *Humulus*, *Chenopodium*, mugwort, ragweed, English plantain, grass pollen, cereals, dandelion, *Blattella germanica*, mites (*Dermatophagoides pteronyssinus*, *Der p* and *Dermatophagoides farinae*, *Der f*), and fungi (*Curvularialunata*, *Candidaalbicans*, *Penicillium notatum*, *Alternaria alternata* and *Aspergillus*

fumigatus). The latter extract consisted of the standard allergen extracts plus mites (*Der p*, *Der f* and *Blomia tropicalis*), animal hair, cockroach (American cockroach and *Blattella germanica*), mugwort, ragweed, mixed pollen I (spring pollen), mixed pollen IV (autumn pollen), a mixture of fungi I, and a mixture of fungi IV. A positive control agent (10 mg/mL histamine) and negative control agent (saline) were also included. SPT reactivity was expressed as the mean allergen to histamine wheal ratio (AHWR) and graded on a scale of 1+ to 4+. Thus, an AHWR ≥ 0.5 for a positive SPT to an allergen was defined as a grade 2+ reaction. Prior to testing, all outpatients seeing a doctor for AR were instructed to abstain from taking any antihistamines for at least 72 hours before the examination.

Questionnaire design

The questionnaire completed by each enrolled patient was designed to gather basic information, such as age, gender, time visiting the clinic, smoking status, family history of allergy, choice of medical treatment (regular medication recommended by ARIA, including intranasal glucocorticosteroids, oral/intranasal H1-antihistamines or a leukotriene antagonist), response to treatment, and education level. The questionnaire also asked the patient to classify their AR symptoms according to duration and severity as described in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines³; the classifications included intermittent mild (IM), intermittent moderate-severe (IMS), persistent mild (PM), and persistent moderate-severe (PMS). “Intermittent” was defined as symptoms occurring < 4 days/week or < 4 weeks/year, whereas “persistent” was defined as symptoms occurring ≥ 4 days/week and ≥ 4 weeks/year. “Mild” indicates that the symptoms caused no impairment of daily activities or sleep, while “moderate-severe” indicates that the symptoms impaired the patient’s daily activities or sleep. Moreover, the issues raised in the questionnaire also covered common comorbidities such as asthma, allergic conjunctivitis, and atopic dermatitis as diagnosed by a

physician, as well as chronic diseases such as coronary heart disease, diabetes mellitus, and gastroesophageal reflux. Finally, the number and types of sensitizing allergens were also listed after the SPT results for each AR patient.

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, Version 19.0 (IBM Corp, Armonk, NY, USA). Descriptive data are shown for the participants' characteristics. Comparisons between groups for each variable and correlations between different AR subtypes and related influencing factors were assessed by chi-square tests. A multinomial logistic regression analysis was performed to determine the associations between age group (7 subgroups: <16, 16-25, 26-35, 36-45, 46-55, 56-65, >65), educational level (primary or secondary school vs. university or postgraduate), gender (male vs. female), smoking status (nonsmoker, passive smoker, former smoker, current smoker), family history of allergies, comorbidities, chronic diseases, and the different AR subtypes. The IM subtype served as the reference category and represented the baseline levels of the four AR subtypes. All tests were two-tailed tests, and P-values < 0.05 were considered statistically significant.

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Table S1. Ranking of positive aeroallergens in 13 metropolitan cities based on SPT results

Cities	Positive aeroallergens																			
	Der p	Der f	Mugwort	Grass pollen	Chenopodium	Mixed tree	Mixed tree	Cereals	Ragweed	Animal	Blomia	Blattella	Pollen	Pollen	Alternaria	Aspergillus	Pine	Dandelion	Humulus	Plantain
						I	II			hair	tropicalis	germanica	I	IV	alternata	fumigate				
Beijing	1	2	3	4	5	6	7	8	9	10										
Changchun	4	3	1						2	6		8	5	7						
Changsha	2	1				9		6		5		3			7	4			8	
Chengdu	2	1		4		5	8	7		3					9	6				
Guangzhou	1	2	6						7	4	3	5	9	8	10					
Hangzhou	1	2	5						7	4		3				6				
Hefei	1	2	3			7				4		5				6				
Nanjing	2	1	9							4		6			7	3	5	8		
Shanghai	2	1	6						7	3		4			8	5				
Shenyang	2	1	3			6	8		4	5		7			9				10	
Taiyuan	2	3	1						6	5	4	7								
Urumqi	7	6	2		1	3	5		8											4
Wuhan	1	2	4				3		6	5		9			7	8				

The sensitization rates of the top three aeroallergens are listed below among 13 cities.

Beijing: *Der p*: 69.12%, *Der f*: 57.79%, Mugwort: 34.56%; Changchun: Mugwort: 57.41%, Ragweed: 35.98%, *Der f*: 26.77%

Changsha: *Der f*: 66.06%, *Der p*: 65.70%, *Blattella germanica*: 19.62%; Chengdu: *Der f*: 83.47%, *Der p*: 83.09%, animal hair: 26.49%

Guangzhou: *Der p*: 88.87%, *Der f*: 88.49%, *Blomia tropicalis*: 73.54%; Hangzhou: *Der p*: 86.61%, *Der f*: 81.61%, *Blattella germanica*: 8.39%

Hefei: *Der p*: 54.61%, *Der f*: 50.35%, Mugwort: 14.26%; Nanjing: *Der f*: 82.66%, *Der p*: 81.89%, *Aspergillus fumigatus*: 33.32%

Shanghai: *Der f*: 68.75%, *Der p*: 67.86%, Animal hair: 16.96%; Shenyang: *Der f*: 51.97%, *Der p*: 47.12%, Mugwort: 45.73%

Taiyuan: Mugwort: 55.92%, *Der p*: 55.26%, *Der f*: 54.61%; Urumqi: *Chenopodium*: 68.50%, Mugwort: 48.43%, Mixed tree I: 42.91%

Wuhan: *Der p*: 55.66%, *Der f*: 54.75%, Mixed tree II: 19.55%

Figure S1. Study flow chart

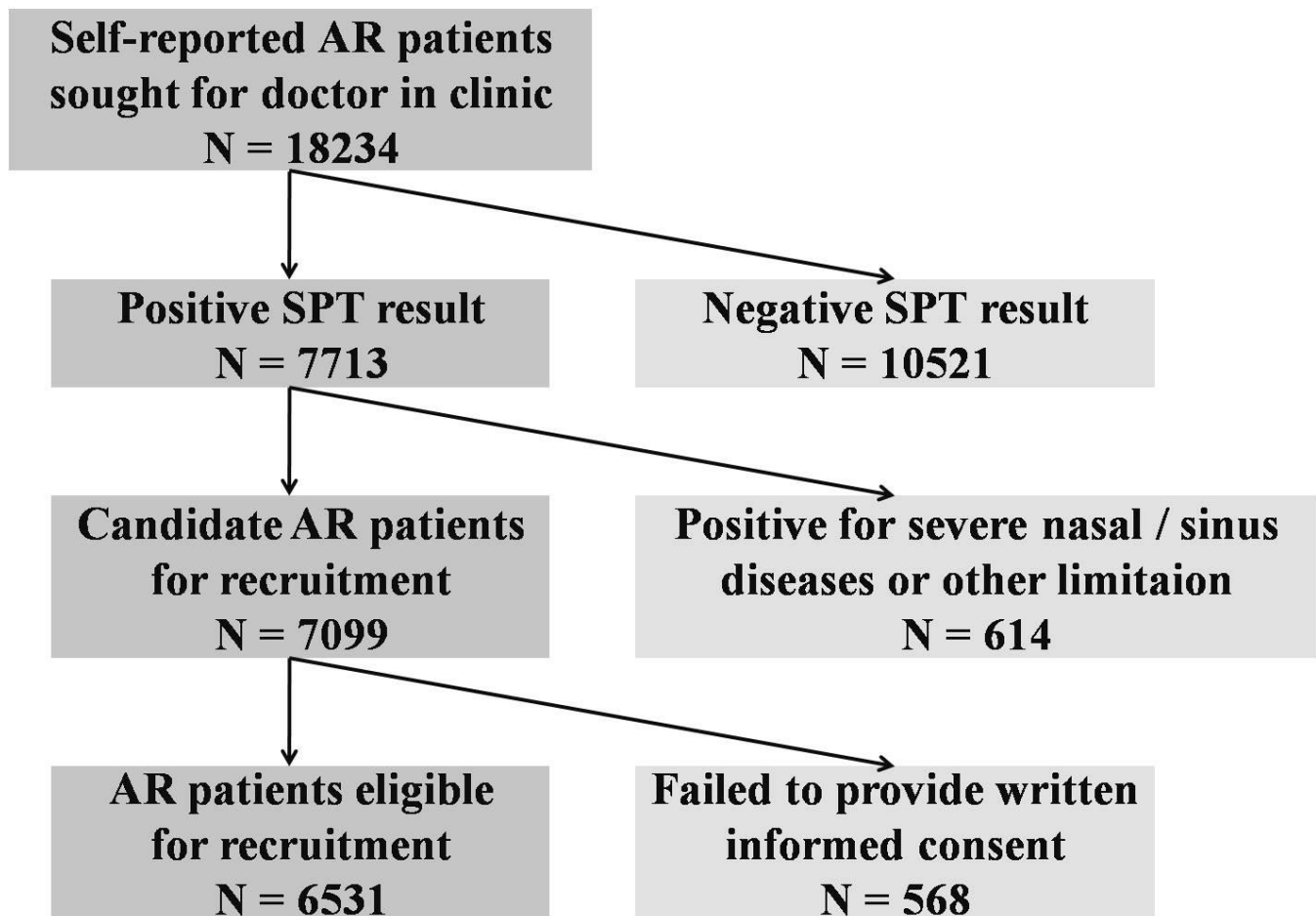


Figure S2. Gender of AR patients in the different age groups.

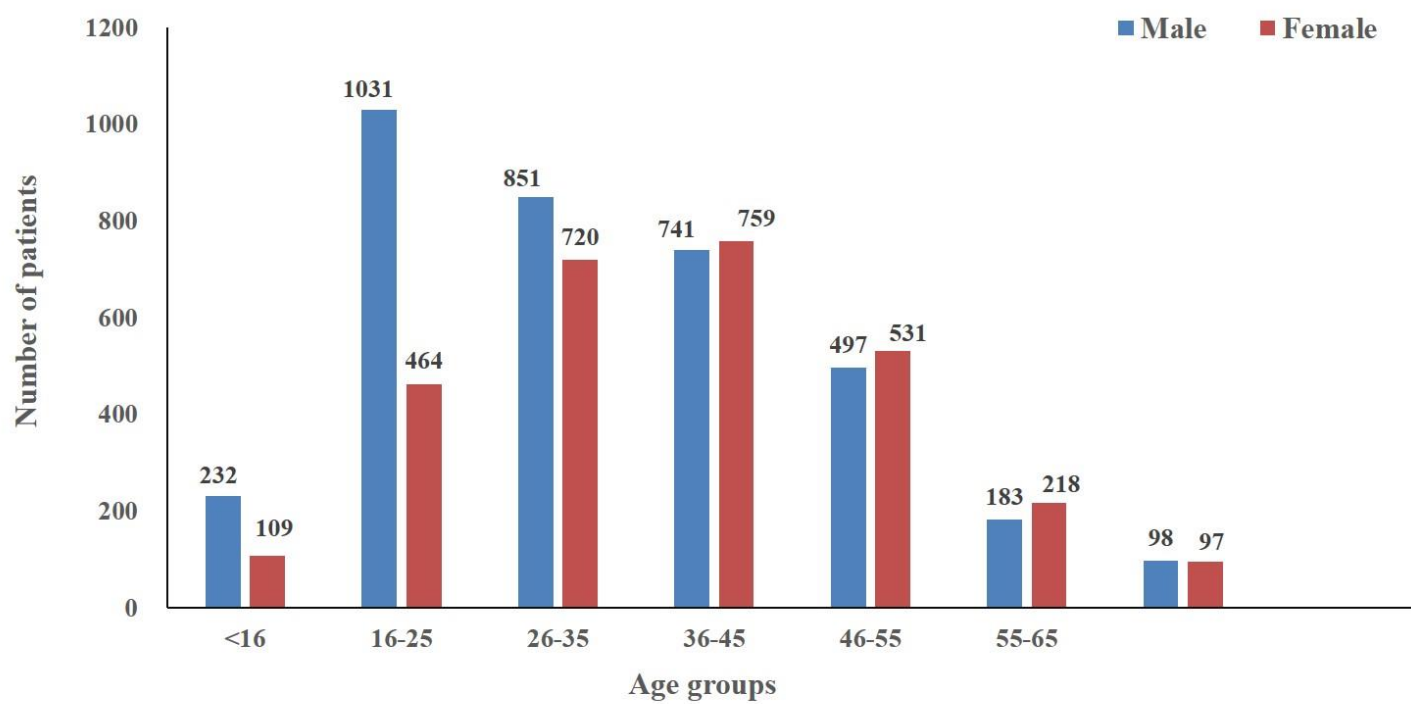


Figure S3. Comparison of AR severity in the different age groups

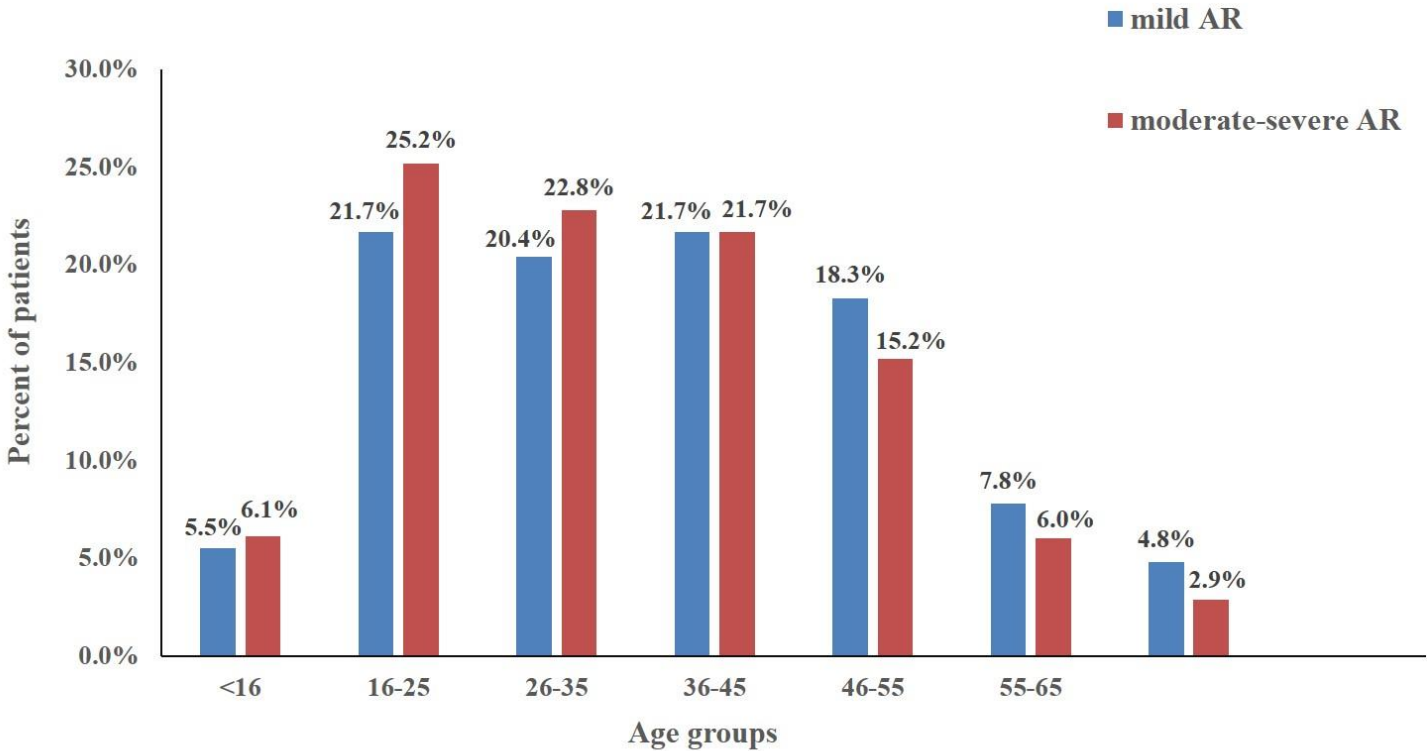


Figure S4. Comparison of the educational levels of patients with different AR subtypes

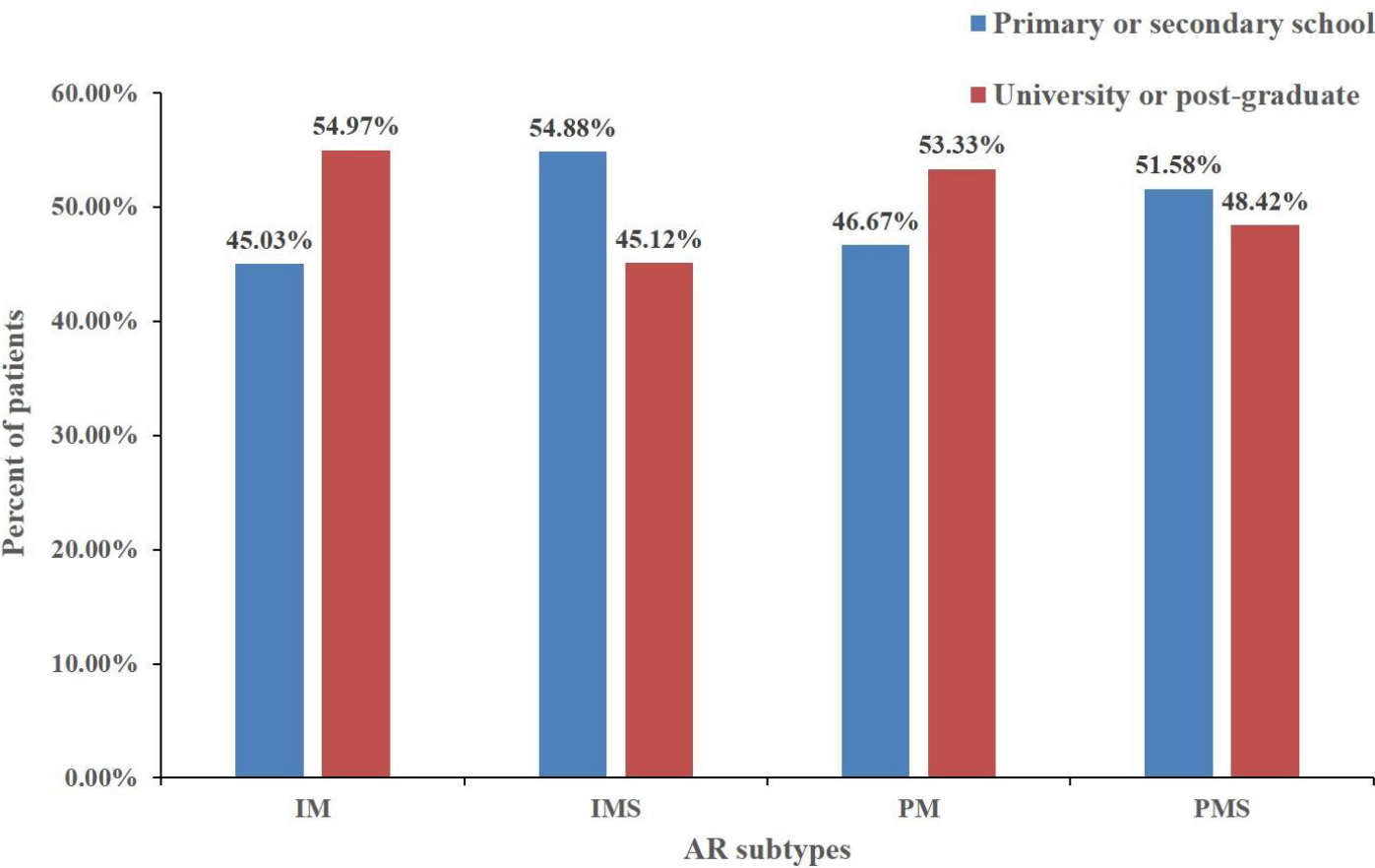


Figure S5. Comparison of acceptance of immunotherapy among AR patients with various levels of education

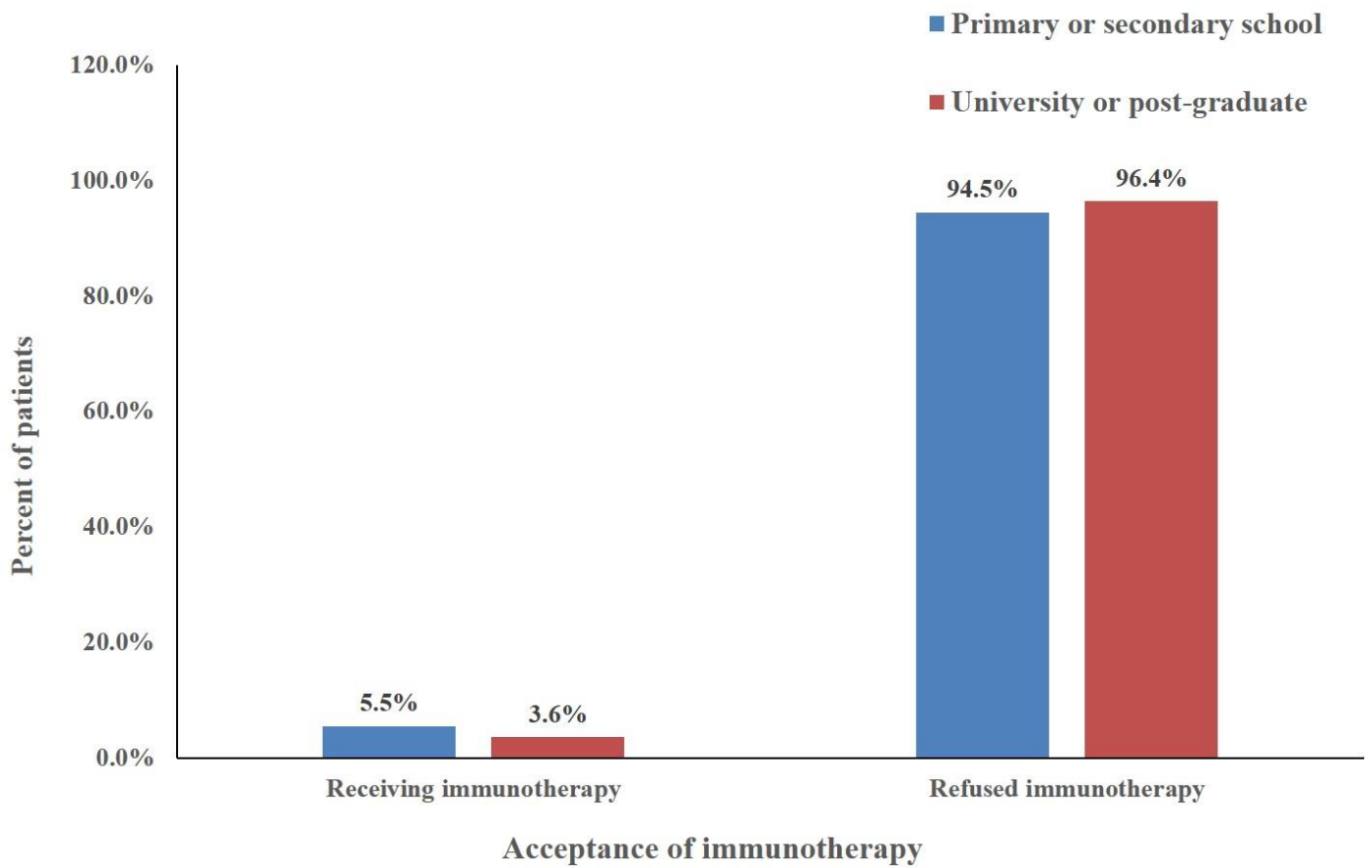


Figure S6. Percentages of AR subtype in different age groups and genders in 13 metropolitan cities.

