

Sensitisation of severe asthma in different occupations: A multicentre study in China

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Abstract

Objective: This was the first multicentre study assessing the sensitisation patterns in patients with severe asthma by different occupations as well as different regions of China, and aimed to provide evidence for the prevention of sensitised patients with severe asthma.

Methods: A total of 676 adults were included and assigned to three cohorts. Cohort A was comprised of severe asthma patients without smoking ($n = 454$), cohort B comprised severe asthmatic patients who were ex-smokers ($n = 149$), and cohort C comprised non-asthma individuals ($n = 73$). All study subjects underwent testing of serum sIgE level of house dusts mix (hx2), foods mix (fx5), moulds mix (mx2), tree pollen mix (tx4) and weed pollen mix (wx5) simultaneously.

Results: Overall, the positive rates of hx2, fx5, mx2, tx4 and wx5 were 37.6%, 11.9%, 16.6%, 9.0% and 9.5% in severe asthmatic patients, respectively. Comparing cohort A with cohort B, the hx2 positive rates in cohort A were higher in fulltime homemaker (30.0% vs. 0.0%) and medical staff (40.0% vs. 0.0%, $P < 0.05$). However, the mx2 positive rates in cohort B were higher in businessman (30.0% vs. 7.0%) and the tx4 positive rates in cohort B were higher in drivers (35.7% vs. 0.0%, $P < 0.05$). The optimal scale analysis showed that severe asthmatic patients who work indoor were more prone to be allergic to house dusts (Cronbach's $\alpha = 76.4\%$).

Conclusion: Patients with severe asthma in different occupations exhibited different sensitisation patterns. Avoid being contact with house dust and application of indoor air purifier should be considered for severe asthma patients.

KEYWORDS

allergen, multicentre study, occupation, severe asthma, sIgE

1 | INTRODUCTION

Asthma is a common disease characterised by airway inflammation with a high prevalence worldwide, about 300 million people suffering from the disease.¹ Among these patients, 5%–10% of them may have severe, unstable and uncontrolled

symptoms, which are defined as severe asthma by the World Health Organization.² These patients required hospitalisation more frequently due to acute exacerbation at night or with poor symptom control despite Step 4–5 treatment based on GINA guidelines, which seriously reduces their quality of life and constitutes heavy financial burden to their families.³

Clinically, it has been observed that patients with severe asthma may have breathing difficulty, wheezing and chest

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tightness during their rest. Particularly, among patients with atopy,⁴ attacks caused by allergens in the air occur more rapidly and unpredictable. Our previous study showed that the degree of atopy in patients with severe asthma was closely related to the environment where they worked and lived.⁵ Thus, it is necessary to investigate the occupation, region and lifestyle of patients with severe asthma and evaluate sensitisation among them. Unfortunately, it lacks research on sensitisation in patients with severe asthma from multiple regions of China, because of its wide distribution and the difficulty in recruiting patients.⁶ The China Biological Information Repository of Respiratory Diseases (CBIR-RD, Guangzhou, China) has become the largest biobank of asthma in China currently, which makes it possible to conduct multicentre research of sensitisation in patients with severe asthma.

Therefore, we recruited patients with severe asthma from 13 central cities in China. Their serum were obtained and transported to CBIR-RD for allergen detection, including hx2 (house dusts mix), fx5 (foods mix), mx2 (moulds and yeasts mix), tx4 (tree pollen mix) and wx5 (weed pollen mix), which are the common allergens screening in China. This was the first study to systematically assess the sensitisation of severe asthma patients between different occupations and regions, and we aimed to provide evidence for the prevention and control of severe asthma in China.

2 | MATERIALS AND METHODS

2.1 | Study design

The protocol for this multicentre cross-sectional study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (approval number GYFYY-2016-73).

In this study, a total of 676 adult subjects (age 18-75 years) were included and divided into three cohorts. Patients with severe asthma with no history of smoking ($n = 454$) were assigned to cohort A, while ex-smoker patients with severe asthma were assigned to cohort B ($n = 149$). Cohort C comprised non-asthma individual ($n = 73$). All study subjects came from different central cities in various regions of China, such as Beijing, Guangdong, Shanghai and Chongqing. The regional distribution of the participants is shown in Figure S1.

All patients diagnosed as severe asthma according to the criteria of this study were continuously recruited when they seek medical advice at local specialised hospitals from January 2016 to December 2018. The non-asthma individuals were recruited from physical examination centres. The serum samples and personal information, such as occupations, were collected if the patients met the inclusion criteria and agreed to participate in this study. All study subjects have signed informed consent form, there were 362 male and 314 female,

the average age was 36 ± 12 years old, part of patients with severe asthma did not test the forced expiratory volume in the first second (FEV₁) because of their poor physical condition, so the connection between sensitisation and FEV₁ were not analysed in this study. The study design flow chart was given in Figure S2. There was no significant difference in age and gender between different groups.

2.2 | Clinical diagnosis and exclusion criteria

Bronchial asthma was diagnosed according to the Global Strategy for Asthma Management and Prevention (GINA) guidelines.⁷ Severe asthma was defined as patients requiring moderate to high doses of inhaled corticosteroid and long acting β adrenoceptor agonist treatment to prevent it from being “uncontrolled” or asthma that remains “uncontrolled” despite this treatment. Non-asthma individual definition: normal parameters of clinical and laboratory tests of fitness, routine blood test and pulmonary function (FEV₁ $\geq$ 80% of the predicted); no asthmatic symptoms recorded in the clinical history such as dyspnoea, wheezing or chronic cough; and non-smoker, but cannot rule out all the diseases. Non-smokers referred to patients who smoked fewer than five packs – year. Patients were considered as ex-smoker if they smoked more than five packs – year before their first acute exacerbation.

Patients with cancer, immunodeficiency, gestation, parasitic infection, autoimmune diseases and other serious primary pulmonary diseases, especially pulmonary embolism, pulmonary hypertension and interstitial lung disease were excluded.

2.3 | Detection method

Eligible serum samples were obtained from venous blood collecting with separation gel containing vacutainer tubes by centrifuged at 3000g for 10 minutes at local hospitals of 13 central cities. Aliquots of serum were stored at -80°C and were transported to CBIR-RD via cold chain for specific IgE tests.

The serum IgE level of hx2 (house dusts mix: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blattella germanica*, etc), fx5 (foods mix: egg white, milk, fish, wheat, peanut, soybean), mx2 (moulds and yeasts mix: *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Setomelanomma rostrata*), tx4 (tree pollen mix: *Quercus alba*, *Ulmus americana*, *Platanus acerifolia*, *Salix caprea*, *Populus deltoides*) and wx5 (weed pollen mix: *Ambrosia elatior*, *Artemisia vulgaris*, *Chrysanthemum leucanthemum*,

Taraxacum vulgare, *Solidago virgaurea*) were detected using Phadia 1000 (Thermo Fisher Scientific, Sweden) by a single trained investigator (N Wei) who was blinded to the previous detection results of the samples. The sIgE level was expressed in kU/L and the level of sIgE ≥ 0.35 kU/L was considered as positive. The sIgE levels were classified according to the test results (class 0: <0.35 kU/L, class 1: ≥ 0.35 to <0.70 kU/L, class 2: ≥ 0.70 to <3.50 kU/L, class 3: ≥ 3.50 to <17.50 kU/L, class 4: ≥ 17.50 to <50.00 kU/L, class 5: ≥ 50.00 to <100.00 kU/L and class 6: ≥ 100.00 kU/L).

2.4 | Occupations

A total of 13 occupations were recorded in this study, including Office staff (white collars in companies), Fulltime homemaker (barely involved in any social works), Attendant (served in hotels and restaurants), Worker (blue-collar workers such as construction workers, railway workers and coal mine workers, etc), Civil servant (government employees dealing with government duties), Accountant (engaged in tax and financial work), Technician (personnel in non-biological laboratory, factory assembly lines or technical services of electric power, water conservancy, etc), School members (students and teachers), Farmer, Businessman (retail and salesmen), Driver (taxi and bus drivers), Medical staff (including all personnel working in hospital environment) and Unemployed (out of work currently, maybe due to the disease). All occupational information was self-reported by each patient according to their current situations and was recorded by local nurses.

2.5 | Statistical analysis

Non-normally distributed data such as the concentration of sIgE are presented as the median (interquartile range). Mann-Whitney *U* tests were used to compare the differences among three groups. Qualitative information such as positivity rate are presented as percentages or frequencies. Inter-group differences were assessed using the chi-squared test. Interrelationship between allergens was assessed via optimal scale analysis. Data analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Analysis items with $P < 0.05$ were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the entire study cohort

Among 676 adults, 603 had severe asthma and 73 were non-asthma individuals. Among patients with severe asthma,

TABLE 1 Characteristics of 676 adults included in the study with different occupations

Occupation (n, %)	Cohort A	Cohort B	Cohort C
Total	454	149	73
Office staff	59, 13.0%	0, 0.0%	0, 0.0%
Fulltime homemaker	40, 8.8%	4, 2.7%	1, 1.4%
Attendant	42, 9.3%	41, 27.5%	41, 56.2%
Worker	40, 8.8%	10, 6.7%	2, 2.7%
Civil servant	20, 4.4%	0, 0.0%	0, 0.0%
Accountant	19, 4.2%	0, 0.0%	0, 0.0%
Technician	30, 6.6%	19, 12.8%	1, 1.4%
School Members	29, 6.4%	0, 0.0%	0, 0.0%
Farmer	46, 10.1%	16, 10.7%	0, 0.0%
Businessman	43, 9.5%	20, 13.4%	3, 4.1%
Driver	21, 4.6%	14, 9.4%	0, 0.0%
Unemployed	53, 11.7%	23, 15.4%	5, 6.8%
Medical staff	12, 2.6%	2, 1.3%	20, 27.4%

Note: Cohort A: Non-smoking patients with severe asthma; Cohort B: Patients with severe asthma who had quit smoking; Cohort C: Non-asthma individual. There were no office staff, civil servants and accountant in cohorts B and C.

13.8% were attendants, 12.6% were unemployed, 10.4% were businessmen, 10.3% were farmers, 9.8% were office staff and 8.3% were workers. In cohort A, office staff accounted for the highest proportion (13.0%), followed by unemployed (11.7%) and farmers (10.1%). However, both cohorts B (27.5%) and C (56.2%) had the highest number of attendants (Table 1).

3.2 | Sensitisation in different cohorts

Overall, the positive rates of hx2, fx5, mx2, tx4 and wx5 were 37.6%, 11.9%, 16.6%, 9.0% and 9.5% in patients with severe asthma and were 19.2%, 2.7%, 1.4%, 4.1% and 2.7% in non-asthma individual, respectively. In cohorts A and B, the positive rates of hx2 were the highest (37.0% and 39.6%, respectively). Interestingly, there were only 10, 4 and 1 patient(s) in cohorts A, B and C with co-sensitisation to hx2, fx5, mx2, tx4 and wx5, respectively (Figure 1).

3.3 | Sensitisation of different cohorts by occupation

The positive rates of hx2, fx5, mx2, tx4 and wx5 in patients with severe asthma by occupations were shown in Figure 2. In cohort A, office staff had the highest positive rate of hx2 (54.2%), followed by unemployed (50.9%) and workers (42.5%). The highest positive rates of fx5, mx2, tx4 and wx5 occurred among students (24.1%), drivers (23.8%), technicians (16.7%)

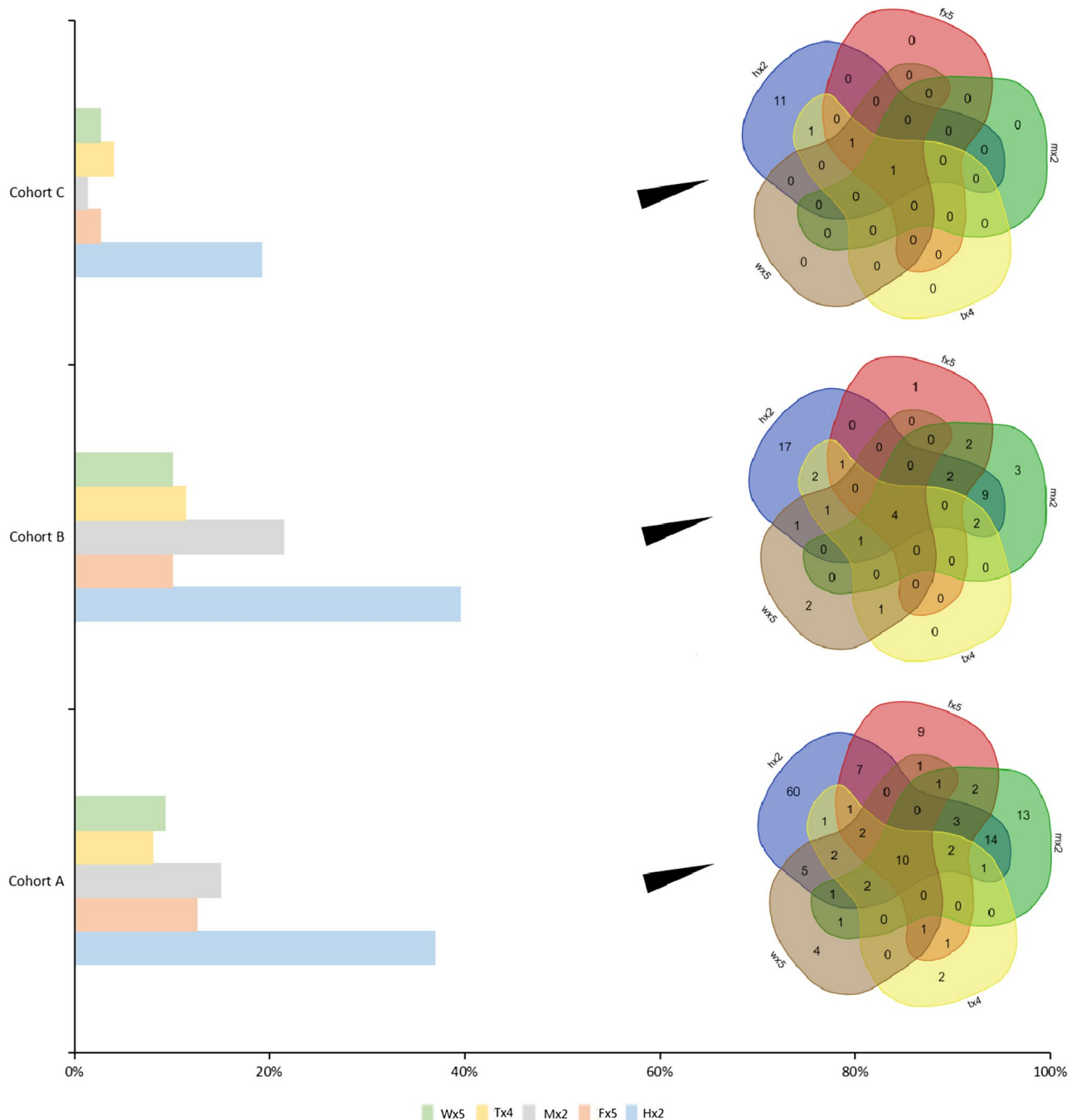


FIGURE 1 Co-sensitisation of adults in different cohorts. Cohort A: Non-smoking patients with severe asthma; Cohort B: patients with severe asthma who had quit smoking; Cohort C: Non-asthma individual; hx2: house dusts mix; fx5: foods mix; mx2: moulds and yeasts mix; tx4: tree pollen mix; wx5: weed pollen mix; In Cohort A, 37.0% of patients tested positive for hx2 and only 10 patients tested positive for hx2, fx5, mx2, tx4 and wx5 at the same time

and the unemployed (18.9%), respectively. In addition, the positive rates of hx2 among fulltime homemakers (30.0% vs. 0.0%, $P < 0.05$) and medical staff (40.0% vs. 0.0%, $P < 0.05$) in cohort A were higher than those in cohort B (Figure 2A). However, there were no significant differences in fx5 positivity between cohort A and B (Figure 2B). In cohort B, the highest positive rates of hx2 were workers (60.0%), followed by drivers

(50.0%) and businessmen (45.0%). The highest positive rates of fx5, mx2, tx4 and wx5 occurred among fulltime homemakers (25.0%), attendants (31.7%), drivers (35.7%) and workers (50%), respectively. Additionally, the positivity rates of mx2 among businessmen (30.0% vs. 7.0%, $P < 0.05$), tx4 among drivers (35.7% vs. 0.0%, $P < 0.05$) and wx5 among workers (50.0% vs. 5.0%, $P < 0.05$) in cohort B were higher than those

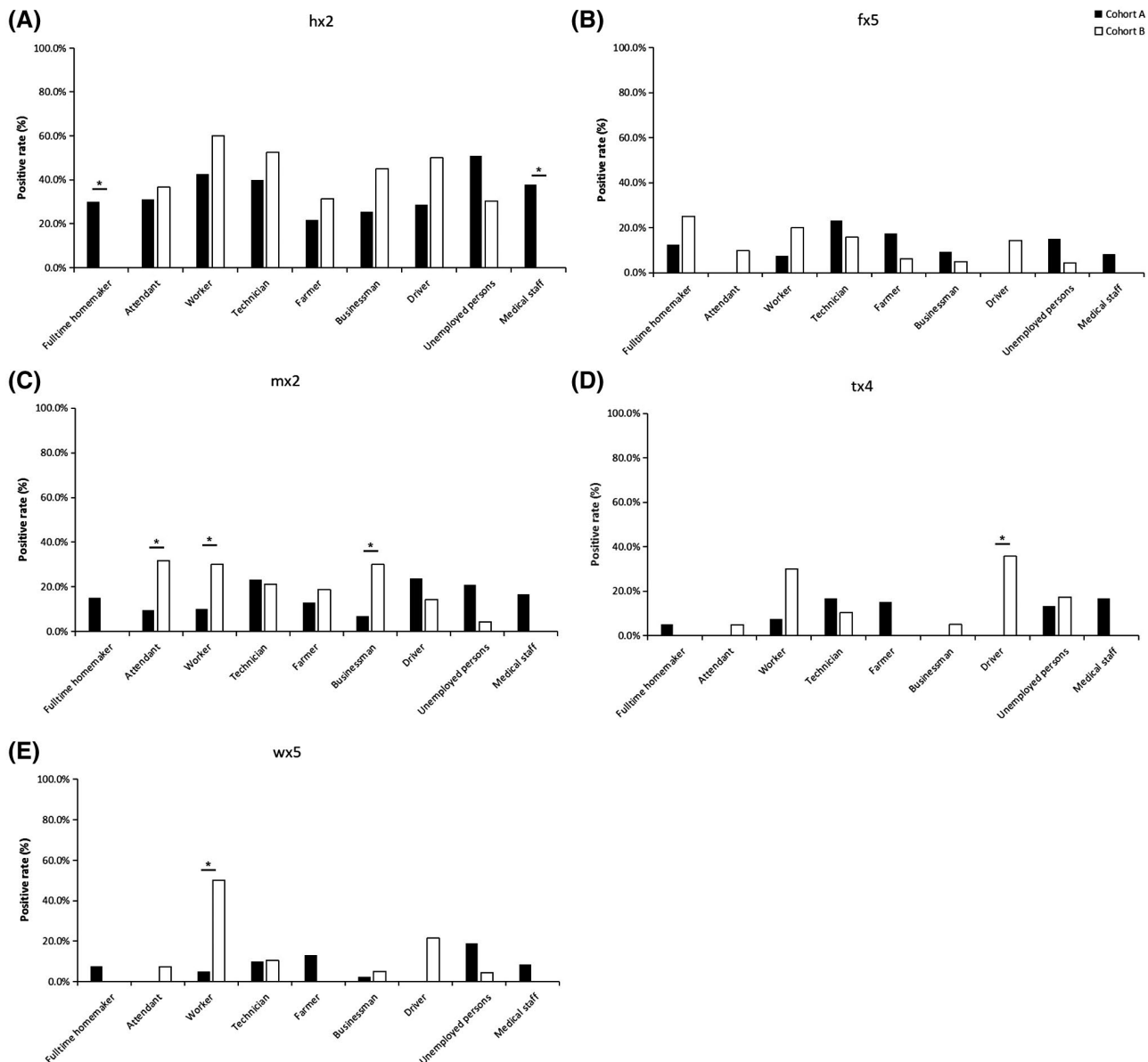


FIGURE 2 The sensitisation of patients with severe asthma by occupation. * $P < 0.05$, chi-square test; the sIgE positive rate of (A) hx2: house dusts mix; (B) fx5: foods mix; (C) mx2: moulds and yeasts mix; (D) tx4: tree pollen mix; and (E) wx5: weed pollen mix between different occupations in Cohort A: Non-smoking patients with severe asthma and Cohort B: patients with severe asthma who had quit smoking

in cohort A (Figure 2C-E). In cohort C, the unemployed shared the highest positive rate of hx2 (40.0%), whereas medical staff had the highest positive rate of fx5 (5.0%).

3.4 | Sensitisation of different cohorts by region

The positive rates of hx2, fx5, mx2, tx4 and wx5 in different regions among patients with severe asthma were shown in Figure 3. In cohort A, the highest positive rates of hx2 (55.6%), mx2 (44.4%), tx4 (44.4%) and wx5 (33.3%) occurred in Shandong, while the highest positive rate of fx5 occurred in Guangdong (28.3%) (Figure 3A). In cohort B, the positive rates

of hx2 in Guizhou, Shandong and Chongqing were all 100.0%. The highest positive rates of fx5 (20.5%), mx2 (38.6%) and tx4 (20.5%) were in Shanghai. However, the highest positivity rate of wx5 occurred in Beijing (18.2%) (Figure 3B). In cohort C, the highest positive rate of hx2 was in Chongqing (31.6%). The highest positivity rates of fx5 (20.0%), mx2 (20.0%), tx4 (20.0%) and wx5 (20.0%) occurred in Yunnan.

3.5 | Sensitisation level of patients with severe asthma

The sIgE levels of hx2 in cohort A [7.35 kU/L (1.56, 30.48)] were significantly higher than those in cohort B [1.36 kU/L

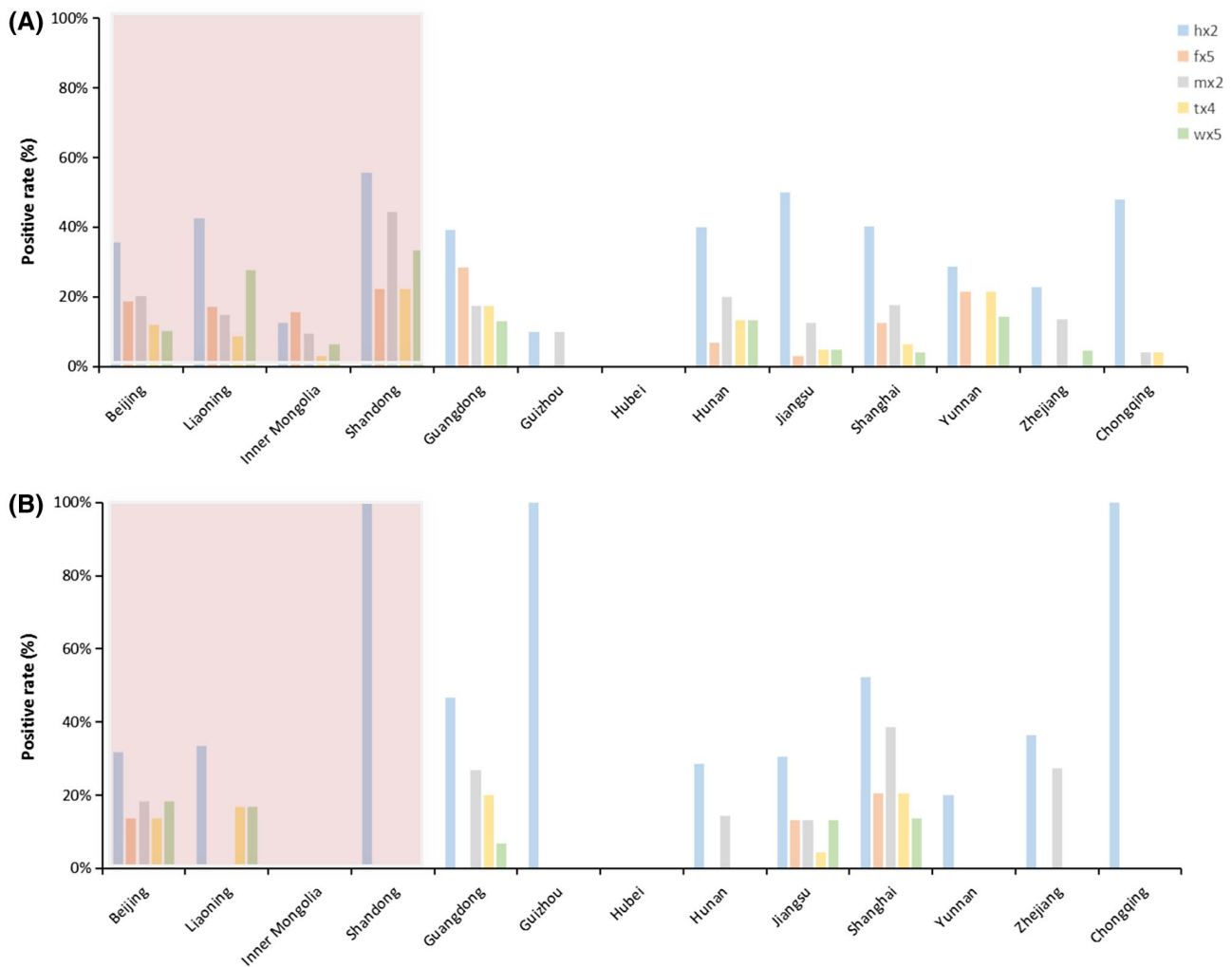


FIGURE 3 The sensitisation of severe asthma patients between different cities. The sIgE positive rate of hx2: house dusts mix, fx5: foods mix, mx2: moulds and yeasts mix, tx4: tree pollen mix and wx5: weed pollen mix between different cities in (A) Cohort A: Non-smoking patients with severe asthma and (B) Cohort B: patients with severe asthma who had quit smoking. The cities from Northern China was shown in the red box and the other cities was from Southern China

(0.66.10), $P < 0.05$] (Figure 4A), while the sIgE levels of fx5 (Figure 4B), mx2 (Figure 4C), tx4 (Figure 4D) and wx5 (Figure 4E) showed no significant differences between these two cohorts. Notably, patients with severe asthma who worked indoors were more likely to have positive result of hx2 (Cronbach's alpha = 76.4%) (Figure 4F). In addition, there were nine patients with considerably high (sIgE > 7.35 kU/L), six of them (66.7%) were from cohort A and three (33.3%) were from cohort B (Table 2).

4 | DISCUSSION

Smoking, respiratory infections, air pollution and allergens are important causes of severe asthma.⁸ Regarding the allergen aspect, our results showed that 37.6% of severe asthmatic patients were sensitised to house dust allergen, which contains *D pteronyssinus*, *D farinae* and *B germanica* that can easily

cause bronchial asthma and aggravate coughing or breathing symptoms. We have previously reported that avoiding house dust allergen was necessary for people with chronic respiratory diseases⁹ and therefore, keeping low levels of house dust allergens (*D pteronyssinus*, *D farinae* and *B germanica*, etc) in the air does matter for severe asthmatic patients as they were suggested to minimise exposure to house dust and get their living environment clean. With the help of air purification technology,¹⁰ the application of ventilation systems in hospital wards or patients' living environment, which are able to filter most of the house dust allergens may greatly reduce the risk of attack and deterioration of severe asthma.

In addition, we found that more than 80% of severe asthma patients with atopic were positive for house dust allergens, although some of them were co-sensitised to foods, moulds, tree pollen or weed pollen allergen. This was partly inconsistent to our previous epidemiological study results that pollen was the main allergen in northern China,¹¹ while mites and cockroaches

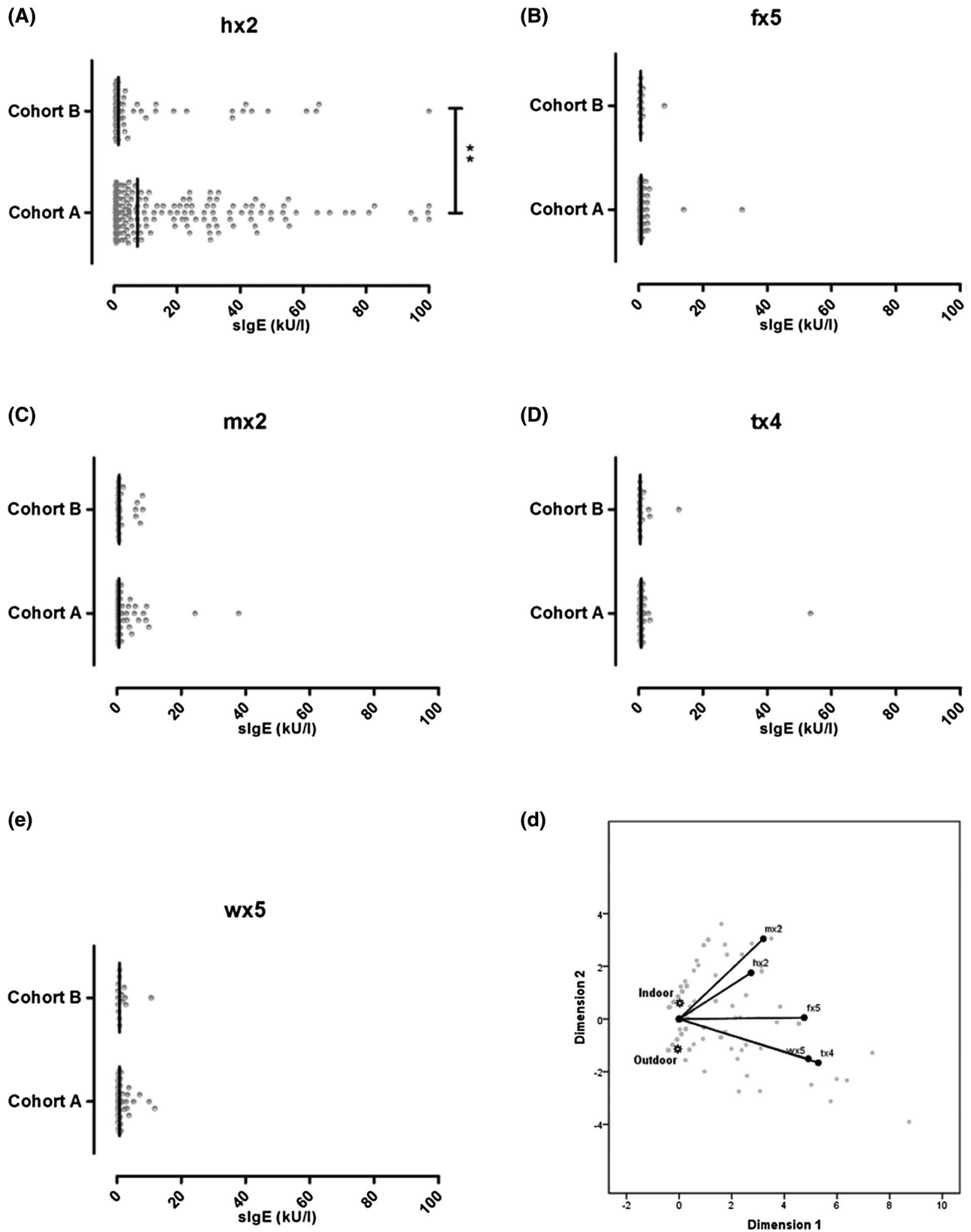


FIGURE 4 The sensitisation level of severe asthma patients. $**P < 0.001$, Mann-Whitney U tests; the sIgE level of (A) hx2: house dusts mix; (B) fx5: (C) foods mix; (D) mx2: moulds and yeasts mix; (E) tx4: tree pollen mix and (F) wx5: weed pollen mix between Cohort A: Non-smoking patients with severe asthma and Cohort B: patients with severe asthma who had quit smoking. (F) In the optimal scale analysis, the closer of the points, the stronger the correlation between them (Cronbach's alpha = 76.4%)

TABLE 2 Characteristics of severe asthma patients with high mx2 level

No. (kU/L)	Occupation	City	Cohort	hx2	fx5	tx4	wx5	mx2
1.	School members	Shanghai	A	1.23	1.03	1.57	0.25	37.80
2.	School members	Shanghai	A	0.79	1.04	0.91	0.14	24.30
3.	Technician	Liaoning	A	2.58	0.58	1.07	0.83	9.97
4.	Technician	Liaoning	A	4.01	0.63	0.99	0.82	9.23
5.	Accountant	Zhejiang	A	36.90	0.10	0.25	0.11	9.08
6.	Office staff	Shanghai	A	11.10	0.54	0.12	0.05	8.31
7.	Driver	Shanghai	B	3.37	1.04	1.64	1.68	8.15
8.	Attendant	Shanghai	B	3.49	0.17	0.29	0.23	7.95
9.	Technician	Shanghai	B	1.36	0.96	0.38	0.89	7.38

Note: Cohort A: Non-smoking patients with severe asthma; Cohort B: patients with severe asthma who had quit smoking; hx2: house dusts mix; fx5: foods mix; mx2: moulds and yeasts mix; tx4: tree pollen mix; wx5: weed pollen mix. There were nine patients with considerably high mx2 level (sIgE > 7.35 kU/L), six of them (66.7%) were from cohort A and three (33.3%) were from cohort B.

are the major allergens in southern China.¹² As located in sub-tropical or tropical area, with high temperature and humidity, the climate in southern China is very suitable for the reproduction of mites or other microorganism in house dust. Unlike the south, northern China has a warm climate and is covered by lots of grassland rich in plant species and thus, the content of pollen in the air is higher than most other places.^{13,14} The change in major allergens in the northern asthmatic population was possibly due to the smog caused by air pollution, as the urbanisation accelerated, especially in northern China. Exposure to smog may be linked to respiratory problems such as asthma, and increase the serum sIgE level of house dust allergens in patients.

We also found that severe asthma patients with different occupations had different sensitisation patterns. Among severe asthma patients who did not smoke, office staff had the highest house dust allergen positive rate (54.2%), followed by the unemployed (50.9%). These patients usually had indoor activities for a long time where the ventilation was poor, and thereby the components of house dust, such as debris and excreta of mites or cockroaches, can easily drift into the air and be inhaled by them, causing serious allergic reactions.¹⁵ Among severe asthma patients who smoked, however, workers had the highest positive rates to house dust allergen (60.0%), followed by drivers (50.0%). Patients with these two occupations had a higher chance of exposure to air pollutants such as automobile exhaust during their outdoor activities. The combined effect of smoking and outdoor polluted air may be an exacerbating factor of asthma.^{16,17} Nevertheless, whether smoking increase the risk of allergy to house dust and the underlining mechanisms required further investigation in future studies.

Interestingly, among the severe asthma patients who did not smoke, Shandong had the highest rate of sensitisation to all tested inhaled allergens, which were house dust (55.6%), moulds (44.4%), tree pollen (44.4%) and weed pollen (33.3%). Studies have shown that humid environment can lead to allergen sedimentation and not easy to be inhaled by asthmatic patients, while allergens in arid areas are more likely to spread in the air

and cause sensitisation.^{18,19} Shandong province is located in the northeast of China, with a temperate monsoon climate. It is usually dry and windy, with less precipitation in springs and falls, which allows pollens to spread and in summers, it becomes hot and humid, providing conditions for moulds' reproduction. Thus, those aeroallergens could be much easier to be inhaled under such climate condition and the inhalation sensitisation may be associated with regional air humidity.

Overall, this was the first multicentre study assessing the sensitisation patterns of severe asthma patients in different regions of China. We analysed the patterns in patients with different occupations and found that the majority severe asthma patients were attendants, the unemployed and businessman. This reflected the real world situation, as the individuals were recruited by local respiratory specialists and their occupation information was not informed prior to inclusion in this study. In addition, there were nine patients with high sIgE of mx2, who might develop Allergic bronchopulmonary aspergillosis. We need to pay more attention to severe asthma with fungal sensitisation in clinical practice, which is a newly described entity of worse controlled asthma.^{20,21} The main limitation of the study was that sample size needed to be increased and the prevalence of sensitisation was too low (except for hx2) to permit a reliable analysis of relationships between sensitisation, regions and any effect of smoking. However, it is not easy to recruit patients with severe asthma because of not only the dependent of patients' compliance, but also the strict exclusion criteria, particularly in patients with complications. Besides, some rare allergens not included in this study may also play an important role in the development of severe asthma, which needs further study in the future.

5 | CONCLUSIONS

In our study, house dust was the most popular allergens in China. Patients with severe asthma in different occupations

exhibited different sensitisation patterns. Therefore, the diagnosis and prevention strategies of severe asthma need to be improved based on regions in the future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval was obtained from the ethic committee of The First Affiliated Hospital of Guangzhou Medical University (Reference number: GYFYY-2016-73). Everyone has written informed consent.

CONSENT FOR PUBLICATION

No additional data available.

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COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Baoqing Sun conceived and designed the experiments. Haisheng Hu wrote the main manuscript text. Mingshan Xue and Huimin Huang prepared figures and tables. Nili Wei, Peiyan Zheng and Nairui An performed the measurements. All authors reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The data that support these findings are available on reasonable request from the corresponding author BS. Data are not publicly available due to concerns regarding research participant privacy.

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SUPPORTING INFORMATION

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

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Supplementary File



Fig S1. Distribution of 676 patients included in the study from different cities

Cohort A: Non-smoking patients with severe asthma; Cohort B: Severe asthmatic patients with quit smoking; Cohort C: Non-asthma individual; In 90 patients from Beijing, there were 65.6% belong to Cohort A.

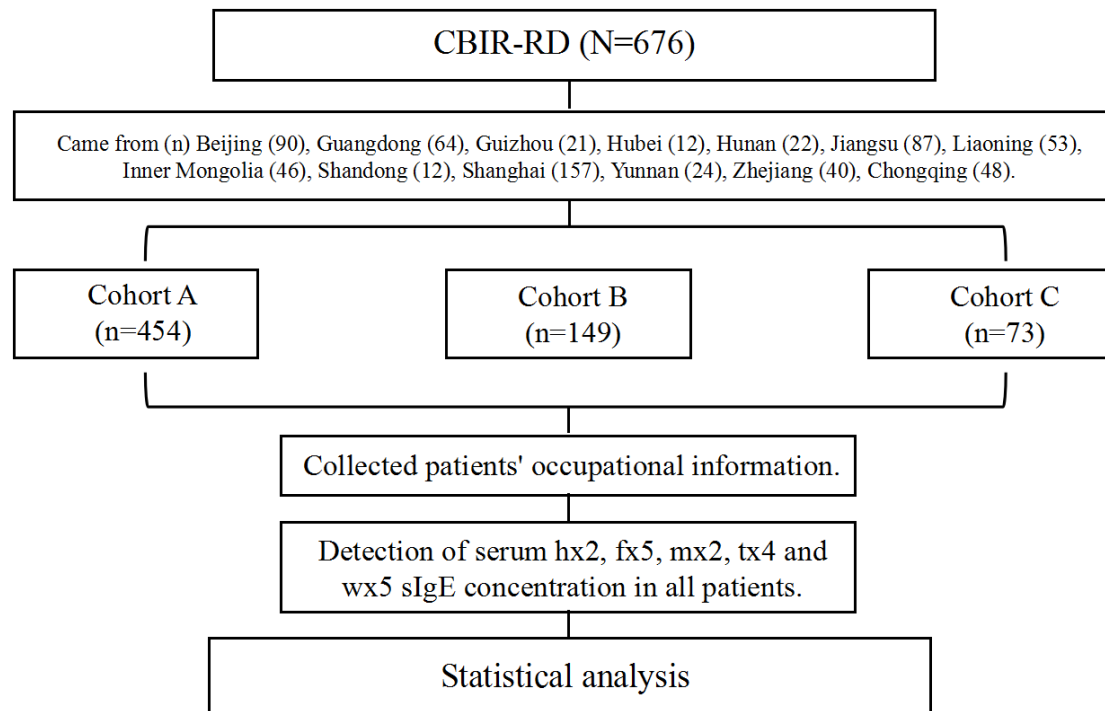


Fig S2. Study design

Cohort A: non-smoking patients with severe asthma; Cohort B: patients with severe asthma who had quit smoking; Cohort C: healthy controls; hx2: house dusts mix; fx5: foods mix; mx2: molds and yeasts mix; tx4: tree pollen mix; wx5: weed pollen mix; A total of 676 adults from 13 central cities in China were included in this study.