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Original Article

Geographic and demographic variations of inhalant allergen sensitization in Koreans and non-Koreans

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MAST multiple allergen simultaneous test
JCP Japanese cedar pollen

ABSTRACT

Background: To diagnose and treat respiratory allergic diseases, it is important to identify the specific allergens involved. Many differences exist between common inhalant allergens depending on the residential environment and demographic factors. This study aimed to compare common inhalant allergens between Koreans and non-Koreans according to their residential region, age, and sex.

Methods: This study evaluated 15,334 individuals who underwent serum tests for multiple allergen-specific immunoglobulin E at a tertiary academic medical center between January 2010 and December 2016. The individuals included 14,786 Koreans and 548 non-Koreans. The AdvanSure™ Allostation assay (LG Life Science, Korea) was used to test for 33 inhalant allergens.

Results: The house dust mite (HDM) was the most common allergen in both Koreans and non-Koreans, although the proportion of individuals with HDM sensitization was greater among Koreans. High sensitization rates for various pollen types were detected among Koreans in Gangwon region, whereas Japanese cedar pollen was unique among Koreans in Jeju region. Grass pollen and animal dander were relatively common among individuals from the Americas, whereas weed and grass pollen accounted for the 10 most common allergens for individuals from Central Asia. The total sensitization rate, sensitization to HDM, and sensitization to animal dander peaked among adolescents and young adults, then subsequently decreased with age.

Conclusions: This large-scale study demonstrates that various regional and age-related differences exist in the allergen sensitization rates of Koreans and non-Koreans. These data could be useful for development of avoidance measures, immunotherapy for causative allergens, and policymaking regarding allergic diseases.

Introduction

Allergen sensitization is an important risk factor for the development of respiratory allergic diseases; thus, the identification of an individual's allergen sensitization is essential for the diagnosis and treatment of diseases.[1,2] *In vitro* serum allergen-specific immunoglobulin E (IgE) tests are widely used to detect sensitized allergens because their results are not affected by drug history

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(e.g., antihistamine treatment) and are highly allergen-specific. These tests are relatively rapid and safe compared to *in vivo* skin prick tests, which allows them to be used for infants and patients with severe skin diseases.[3] The multiple allergen simultaneous test (MAST) is commonly used in the clinical setting because it is a simple, low-cost, and convenient way to simultaneously detect dozens of allergens using a small amount of blood.[4] The recently introduced AdvanSure™ system can simultaneously detect 90 allergen-specific IgEs using only 250 μL of serum.[5]

The pattern of inhalant allergen sensitization is affected by environmental factors (e.g., geographical area) and demographic factors, including age and sex.[6–9] Several studies have evaluated allergen sensitization rates in individual countries.[8,10–13] However, no large-scale studies have compared inhalant allergen sensitization according to country and demographic factors among Koreans and non-Koreans. Previous Korean studies included a relatively small number of allergens and patients.[11,14] In addition, a recent multicenter study had limitations due to confounding factors from using different allergen extracts and allergen test panels among the different institutions.[15] Furthermore, an increasing number of non-Koreans are being evaluated at Korean hospitals. Therefore, the present study aimed to examine the overall inhalant allergen sensitization rates among Koreans and non-Koreans who were evaluated using the same equipment at a single institution. A detailed analysis was also performed according to the individuals' residential region, age, and sex.

Methods

Study population

The present study evaluated 15,334 individuals with suspected respiratory allergic diseases (e.g., allergic rhinitis, asthma) during their first visits to Yonsei University Severance Hospital, a tertiary academic medical center in Korea, between January 2010 and December 2016. The individuals included 14,786 Koreans (mean age: 35.8 years, range: 1–94 years) and 548 non-Koreans (mean age: 33.1 years, range: 1–71 years). All individuals were classified into five groups according to age (Table 1). Allergen sensitization can be affected by an individual's residential environment; hence, all subjects were classified based on chart reviews and telephone surveys according to their area of birth for long-term residents or area of prolonged residence (>4 seasons) for migrants. Patients were not simply classified by nationality or address in the document. Non-Koreans were defined as individuals who were visiting Korea, including for medical purposes. We excluded non-Koreans who were currently residing in Korea or had resided in Korea for >4 seasons.

The prevalence of allergen sensitization was compared between Koreans and non-Koreans. Korean individuals were assigned to one of eight administrative areas: Seoul, Incheon Gyeonggi, Busan Gyeongnam, Daegu Gyeongbuk, Honam, Chungcheong, Gangwon, or Jeju district (Fig. 1). The residential areas were also categorized as either urban areas (metropolitan cities and cities with a population of >100,000) or rural areas (including locations defined as a *gun* [county], *eup* [town], or *myeon* [township]).[9] Non-Koreans were assigned to one of nine regions: East Asia, South Asia, Central Asia, Russia, Europe, the Americas, Middle East, Oceania, or Africa. The countries included in each international region are listed in Supplementary Table 1.

Table 1
Demographic characteristics of the study participants.

	Koreans	Non-Koreans
Number (persons)	14,786	548
Sex		
Male	8561 (57.9%)	336 (61.3%)
Female	6225 (42.1%)	212 (38.7%)
Age (years), mean ± SD	35.8 ± 21.5	33.1 ± 17.6
Age distributions (years)		
0-12 (children)	2745 (18.6%)	97 (17.7%)
13-18 (adolescents)	1110 (7.5%)	38 (6.9%)
19-30 (young adults)	2984 (20.2%)	107 (19.5%)
31-50 (adults)	3446 (23.3%)	203 (37.0%)
≥51 (middle-aged and older)	4501 (30.4%)	103 (18.8%)
Total allergen sensitization	7505 (50.8%)	278 (50.7%)

Assessments

Blood samples were analyzed using the AdvanSure™ Allostation MAST assay (LG Life Science, Korea), which detects 33 inhalant allergens from seven groups: house dust mite (HDM), tree pollen, grass pollen, weed pollen, animal dander, fungi, and insects. The indoor allergens included HDM (*Dermatophagoides farinae* [*Der f*] and *Dermatophagoides pteronyssinus* [*Der p*]), animal dander (cat and dog), and insects (cockroach mix). The outdoor allergens included tree pollen (acacia, ash mix, birch alder mix, hazelnut, Japanese cedar, oak, pine, poplar mix, sallow willow, and sycamore mix), grass pollen (Bermuda grass, orchard grass, reeds, rye grass, sweet vernal grass, and timothy grass), weed pollen (dandelion, goldenrod, Japanese hop, mugwort, oxeye daisy, ragweed, Russian thistle, and pigweed), and fungi (*Alternaria, Aspergillus, Cladosporium*, and *Penicillium*).

The test results were classified into seven levels, ranging from class 0 to class 6. A positive test result (i.e., allergen sensitization) was defined as grade 2 or higher.[3,5] Individuals with ≥1 positive allergen were considered to be allergen sensitized. The sensitization rates for each allergen were investigated.

Statistical analysis

All statistical analyses were performed using IBM SPSS software (version 23.0; IBM Corp., Armonk, NY, USA). Intergroup differences in the allergen sensitization rates were evaluated using the Chi-square test and Cochran-Armitage trend test. A p-value of <0.05 was considered to be statistically significant.

Ethical considerations

This study was conducted according to the principles expressed in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) of Yonsei University College of Medicine (IRB No. 4-2017-0520). The requirement for written informed consent was waived. Patient anonymity was preserved using methods approved by the Ethics Committee.

Results

Comparing the prevalence of allergen sensitization among Koreans and non-Koreans

Among the 14,786 Koreans, 7505 individuals were sensitized to ≥1 allergen (50.8%). Among the 548 non-Koreans, 278 individuals were sensitized to ≥1 allergen (50.7%). The most common allergen in both groups was HDM, although Koreans had a greater proportion of sensitization. Among Koreans, the most common allergens were *Der f* (36.5%) and *Der p* (32.3%); the other allergens had positive rates of <7%. Among non-Koreans, *Der p* (25.2%) and *Der f* (22.6%) were also the most common allergens; however, sensitization rates of >10% were observed for several pollen types and animal dander allergens, including timothy grass (14.4%), orchard

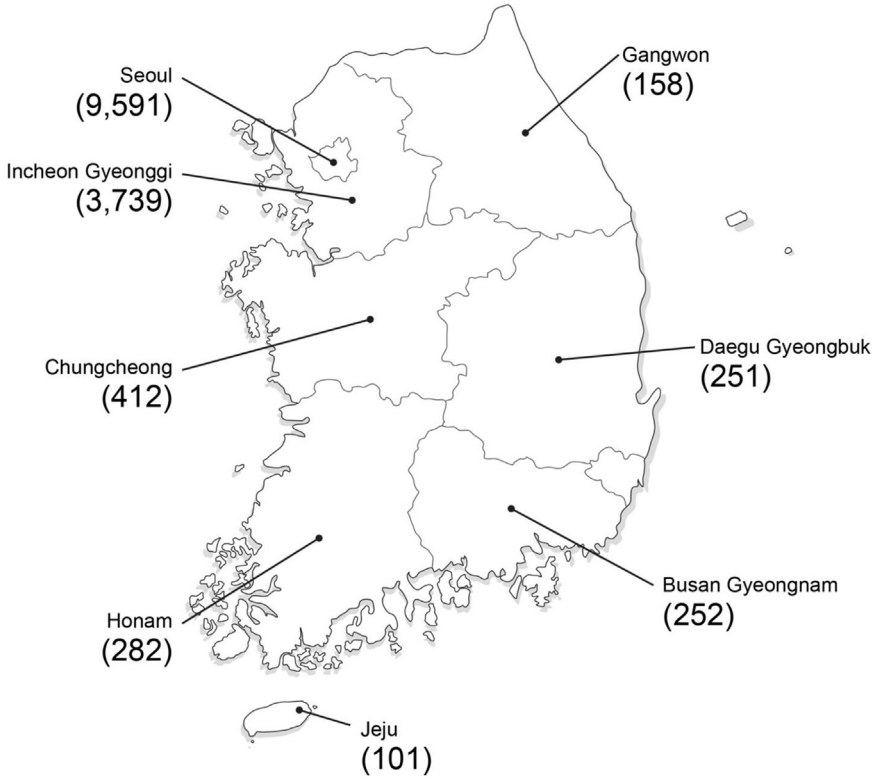

Fig. 1. A map of eight administrative areas in Korea. The numbers inside the parentheses indicate the sample size for each area.

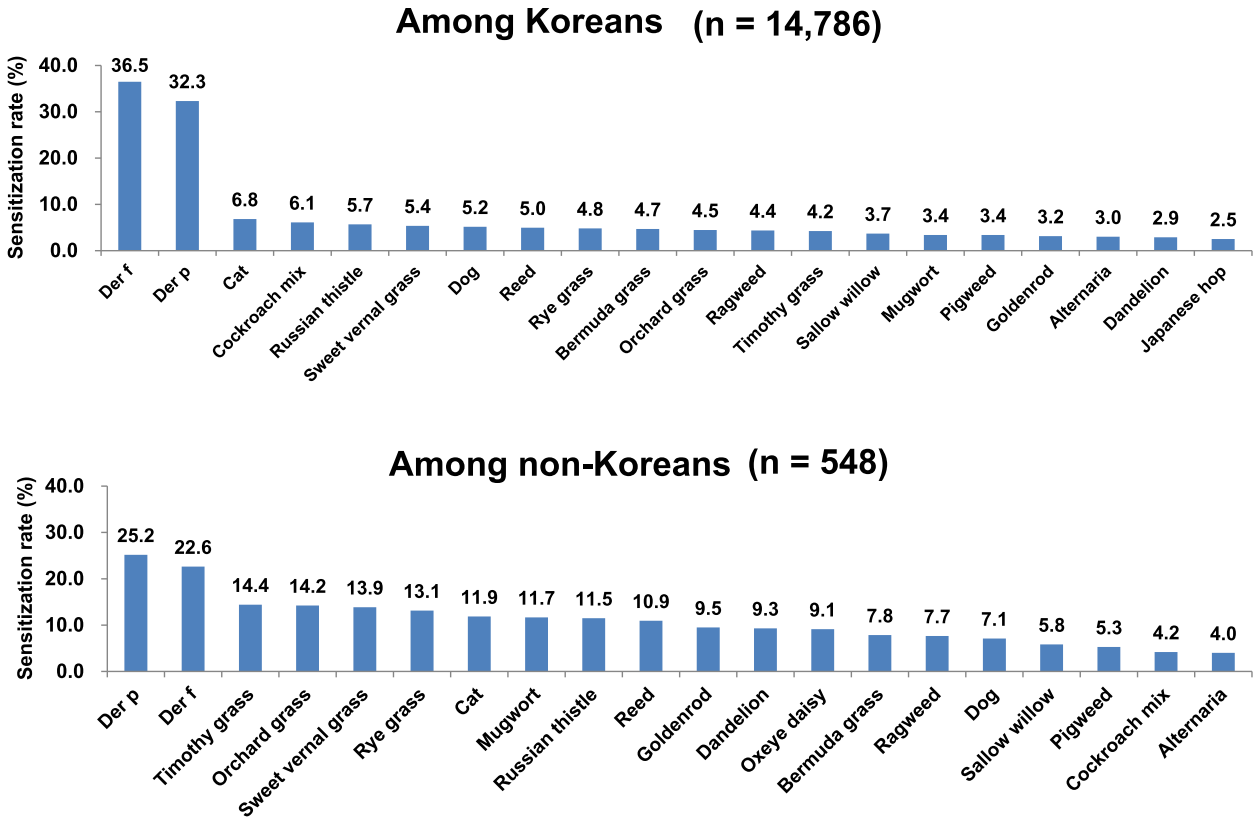

Fig. 2. Comparing the sensitization rates for major inhalant allergens among Koreans and non-Koreans. *Der f, Dermatophagoides farinae; Der p, Dermatophagoides pteronyssinus.*

grass (14.2%), sweet vernal grass (13.9%), and cat dander (11.9%). Among Koreans, the third most common allergen was cat dander (6.8%), whereas non-Koreans had 16 allergens with rates of >6.8% (Fig. 2). The full results for all 33 allergens are shown in Supplementary Figure 1. The proportion of HDM sensitization was significantly higher among sensitized Koreans than among sensitized non-Koreans (5803 Korean individuals [77.3%] vs. 151 non-Korean individuals [54.3%], $p < 0.001$) (Fig. 3).

Comparing allergen sensitization among Koreans according to residential region

The 14,786 Koreans were categorized according to their residential regions. The proportion of individuals with allergen sensitization was similar for all regions except Gangwon and Jeju. In Gangwon, the HDM-positive rate was <30%, which was noticeably lower than the average rate among all Koreans. However, the sensitization rates for pollen allergens (e.g., Russian thistle, reed, Bermuda grass) were >10%, which were noticeably higher than those in the other Korean regions. In Jeju, the HDM-positive rate was also <30%; furthermore, the high rate for Japanese cedar (17.8%) was unique to this region, as it was rarely observed in the other areas ($p < 0.001$) (Fig. 4). The complete results are shown in Supplementary Figure 2.

The total allergen sensitization rate was higher in urban areas than in rural areas ($p = 0.074$); the sensitization rate to HDM was also relatively high in urban areas. Non-HDM allergens accounted for <7% of cases in urban areas, whereas 10 pollen allergens accounted for >7% of cases in rural areas (Supplementary Fig. 3).

Comparing allergen sensitization among non-Koreans according to country

The allergen sensitization rates were calculated for non-Koreans according to their nine residential regions. The results for individuals from East Asia and South Asia were similar to those for individuals from Korea, with HDM being the dominant allergen and other allergens being relatively uncommon. However, large differences were observed for the Americas and Central Asia compared with the other regions.

Of the 172 individuals from the Americas, 134 individuals were from the United States and 22 individuals were from Canada. Timothy grass (24.4%) was the most common allergen in this region, followed by *Der f* (23.8%), *Der p* (23.3%), and orchard grass (22.7%). Pollen and animal dander allergens were relatively common in this region (vs. other regions), with relatively high proportions observed for non-HDM allergens.

There were many differences observed in Central Asia, with HDM being relatively rare. The 10 most common allergens (rates of >20%) in this region were all pollen types, including mugwort (35.6%) and oxeye daisy (31.7%). However, *Der p* (15.8%) and *Der f* (13.9%) were only the 11th and 13th most common allergens, respectively.

The most common allergen in Russia was HDM (25.4% for *Der p* and 22.0% for *Der f*). The Russian rates were relatively high for animal dander (13.6% for cat dander and 10.2% for dog dander) but relatively low for pollen allergens compared with all non-Koreans. The most common allergen in Europe was HDM, which was followed by several grass pollens and cat dander. The most common allergens in the Middle East were HDM, grass pollen, and cockroach (Fig. 5). The complete results are shown in Supplementary Figure 4. Individuals from the four African countries were excluded from the analysis because they all had negative MAST results.

Demographic characteristics of allergen sensitization among Koreans and non-Koreans

Among both Koreans and non-Koreans, the total allergen sensitization rate and the sensitization rate to HDM were significantly higher among males than females ($p < 0.001$) (Supplementary Fig. 5).

Among Koreans, the total allergen sensitization rate peaked among adolescents and young adults, then subsequently decreased with age. The sensitization rates for HDM and animal dander also exhibited similar patterns, with higher rates among individuals who were <30 years old compared with older individuals ($p < 0.001$) (Fig. 6A). The sensitization rates for tree, grass, and weed pollen did not decrease with age, with relatively similar rates being observed for the various age groups. Interestingly, the five most common allergens for the three groups of individuals who were <30 years old were identical: *Der f*, *Der p*, cat dander, dog dander, and *Alternaria* (Supplementary Fig. 6).

Among non-Koreans, the total allergen sensitization rate generally peaked among adolescents and young adults, then subsequently decreased with age. The sensitization rate for animal dander was also high among individuals who were <30 years old, then decreased with age ($p < 0.001$) (Fig. 6B). The complete results according to age are shown in Supplementary Figure 7.

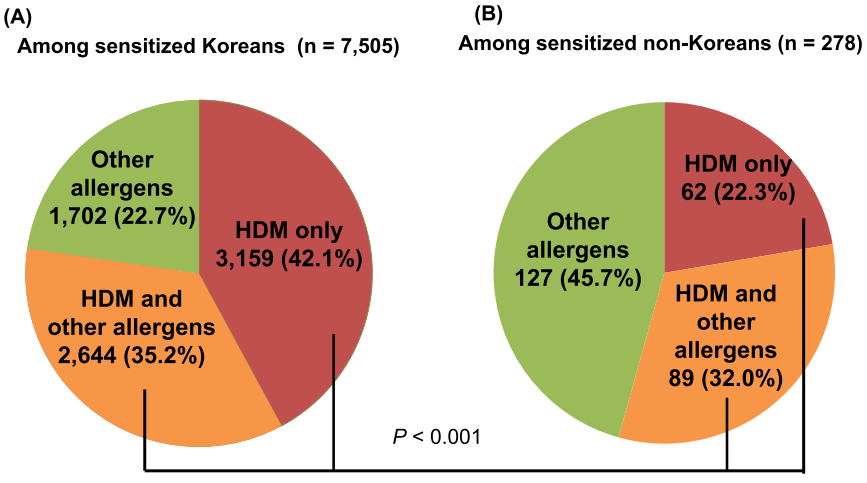

Fig. 3. Comparing the sensitization rates for house dust mite among sensitized Koreans and non-Koreans. HDM, house dust mite.

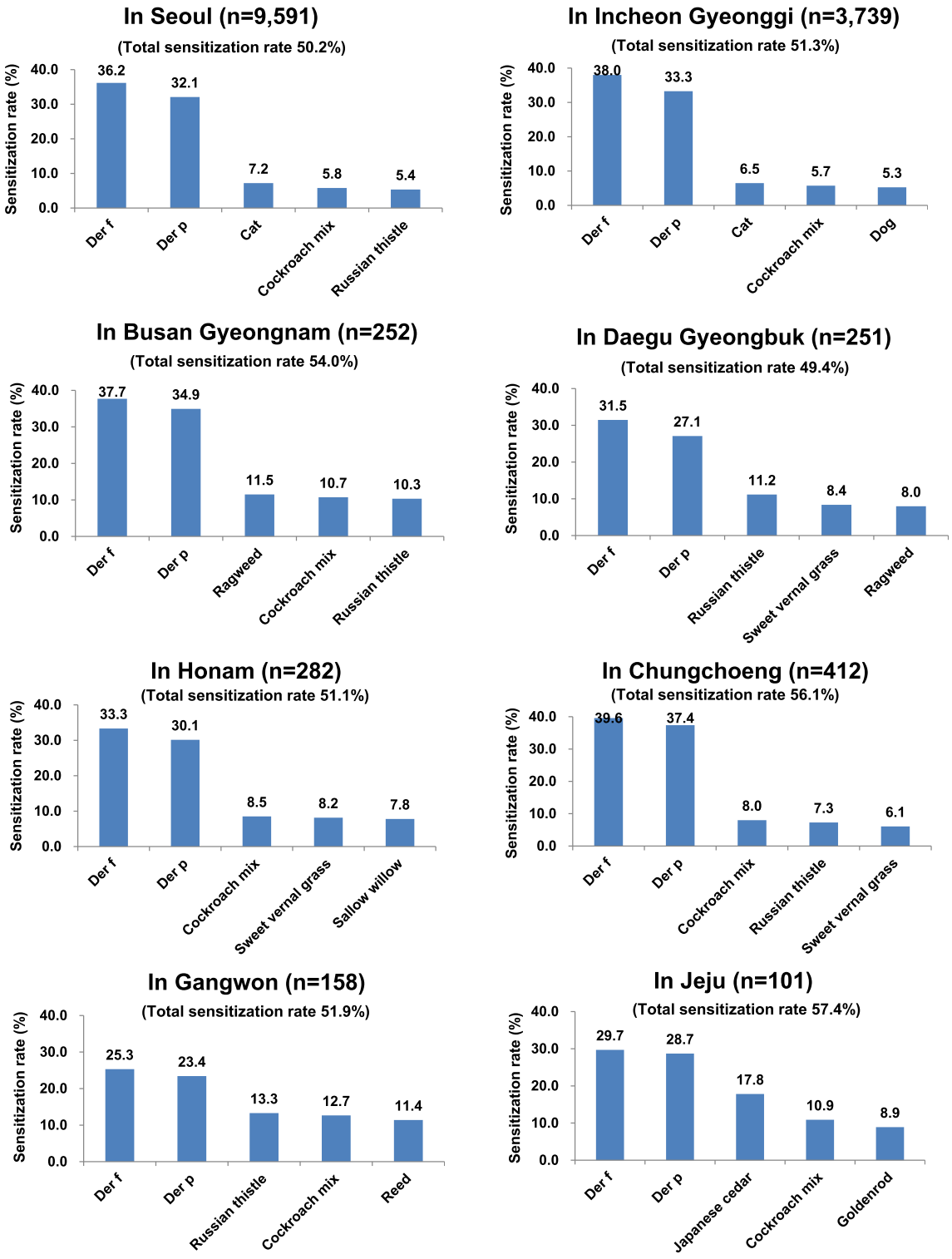

Fig. 4. The common inhalant allergens according to residential region in Koreans. *Der f, Dermatophagoides farinae; Der p, Dermatophagoides pteronyssinus.*

The most noticeable difference between Koreans and non-Koreans was that non-Koreans had high sensitization rates for pollen and animal dander, without a predominance of HDM cases. The adolescent age group had the highest allergen sensitization rate among Koreans. Their HDM sensitization rate was 56.1%, whereas the rate for grass pollen was only 8.7% (Fig. 6A). Among non-Koreans, the young adult age group had the highest allergen sensitization rate. However, their sensitization rate for HDM was 35.5%, whereas their rate for grass pollen was 30.8% (Fig. 6B).

Discussion

HDM is the most important and common allergen in Korea, being detected in 85% of households in Seoul.[11,14–17] *Der p* and *Der f*

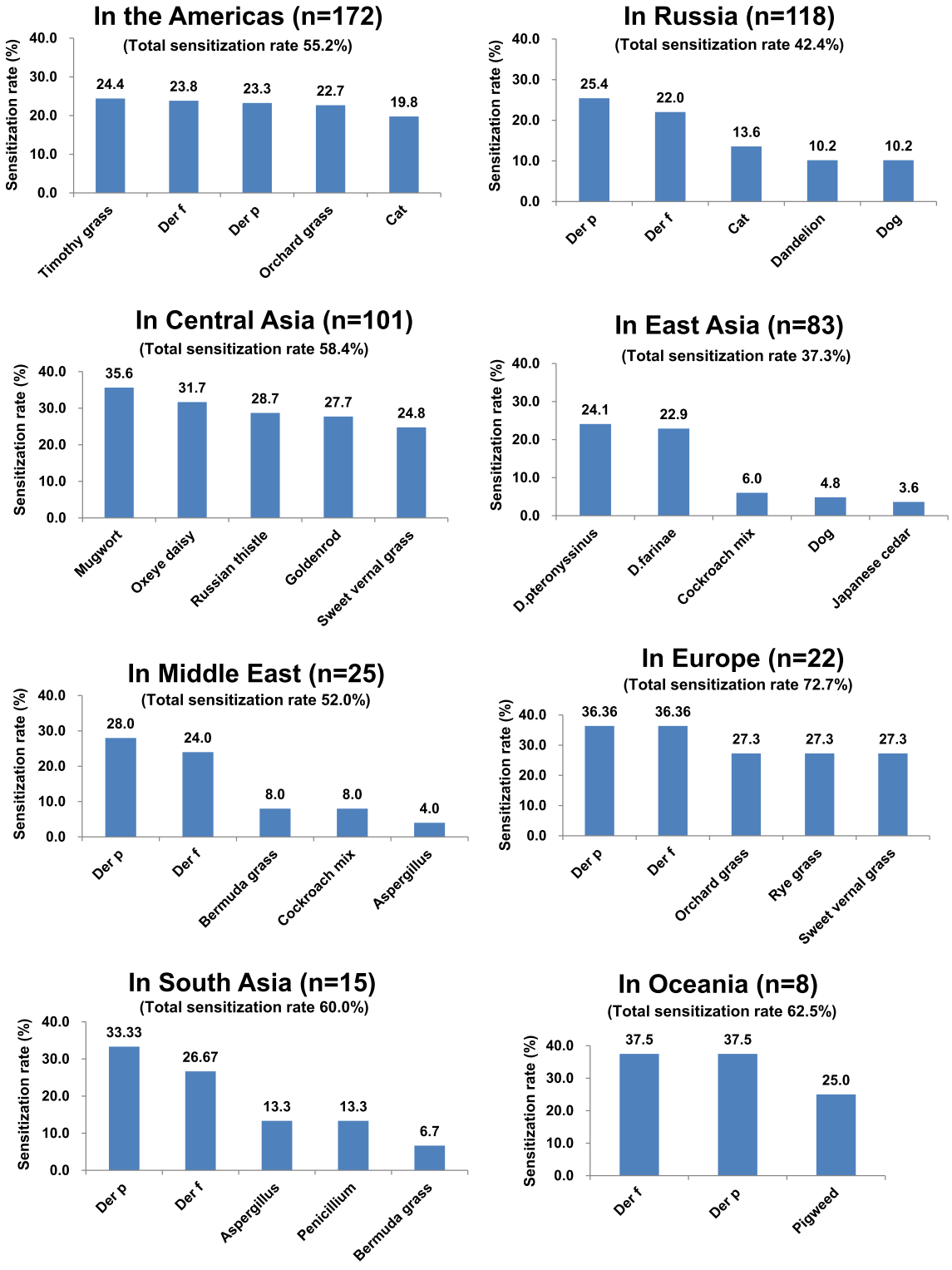

Fig. 5. The common inhalant allergens according to country of residence in non-Koreans. *Der f, Dermatophagoides farinae; Der p, Dermatophagoides pteronyssinus.*

coexist in most global areas, although *Der f* is the dominant species in Korea.[11,14–16] Previous studies have confirmed that the residential environment can affect sensitization to prevalent inhalant allergens.[14,17,18] The Gangwon region is the most alpine area in Korea (82% of its area is mountainous),[17] which is associated with higher sensitization rates to weed, grass, and tree pollen than other regions in the present study. Interestingly, Japanese cedar pollen (JCP), a major allergen contributing to seasonal allergic rhinitis in Japan,[19] was common in Jeju. Japanese cedar trees were systemically planted to provide windbreaks for tangerine orchards in Jeju, which explains why JCP is the major outdoor allergen for early spring pollinosis (late January to mid-April) in Jeju.[18,20]

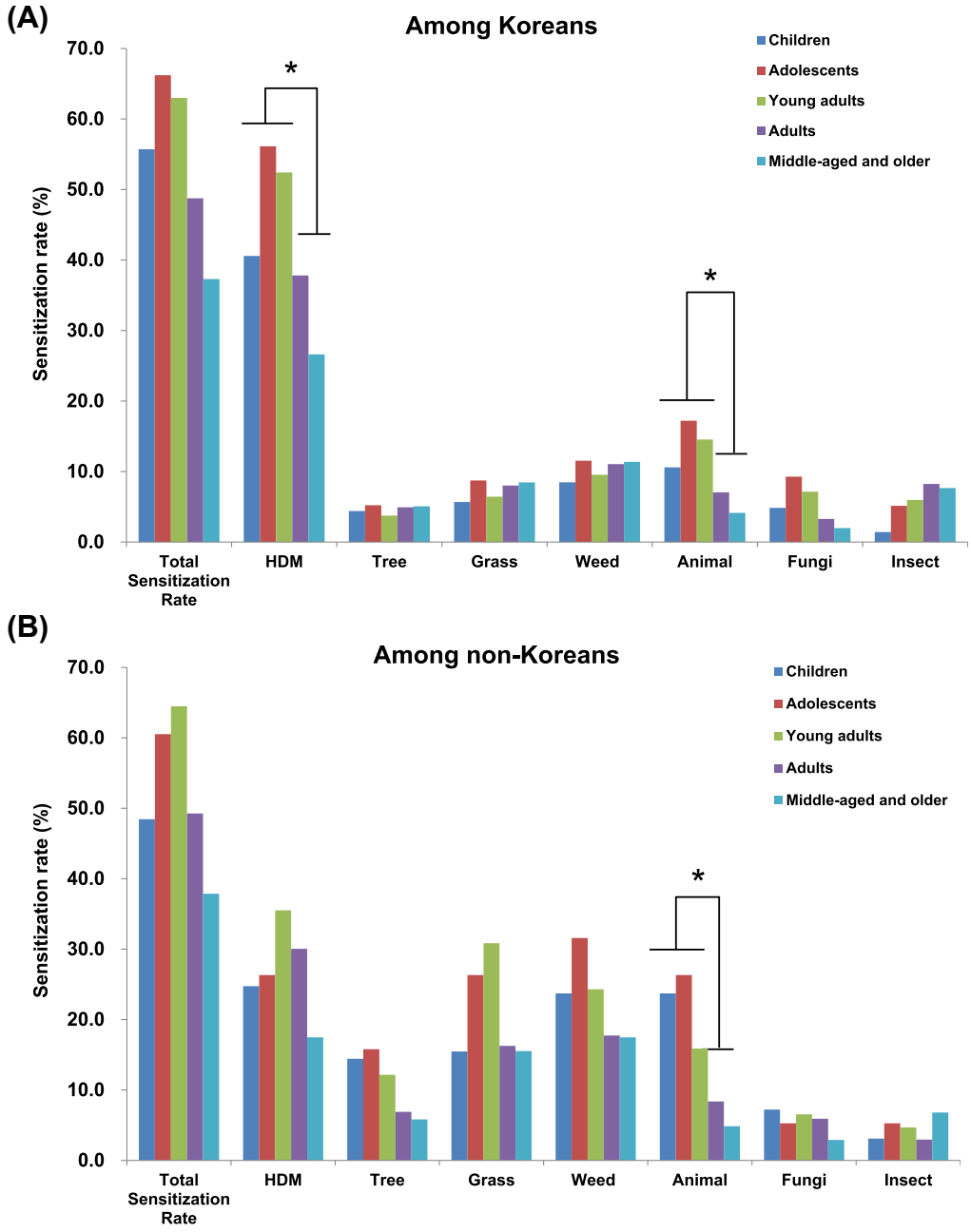

Fig. 6. Comparison of the total sensitization rate and sensitization rate of each allergen group by age among **(A)** Koreans and **(B)** non-Koreans. *$P < 0.05$ for <30-year-old individuals vs. ≥30-year-old individuals. HDM, house dust mite.

The prevalence of allergen sensitization is also affected by urbanization. We observed a higher allergen sensitization rate in urban areas compared with rural areas, in agreement with previous studies.[8,9,12,21,22] The relatively traditional lifestyle in rural villages may protect individuals from allergic sensitization, even though it is not a farming-based lifestyle.[16,23]

In our study, the most common pollen types in Korea were Russian thistle and several grass pollens; this differs from previous reports in which weed pollen was the most common pollen type.[11,15] Russian thistle (also known as tumbleweed) is native to Russia and Siberia and is common in dry climates.[24,25] It was recently classified as being part of the *Amaranthaceae* family.[26] Because there is strong cross-reactivity between Russian thistle, *Amaranthaceae,* and *Chenopodium*,[27] our results suggest that Russian thistle, *Amaranthaceae,* and *Chenopodium* are distributed throughout Korea. Furthermore, grass pollen should be included in routine allergen testing, based on the introduction of a large number of reed fields in Korea.[28]

Unlike the overwhelming predominance of HDM among Koreans, non-Koreans had high rates of sensitization to other allergens. Our results for individuals from the Americas suggest that pollen and animal dander are relatively common throughout the Americas, which agrees with the findings of previous American[8] and Canadian studies.[13]

The ranking of common allergens for individuals from Central Asia was noticeably different than that for individuals from other

countries in our study. Weed and grass pollen accounted for the 10 most common allergens in this region. Furthermore, the sensitization rate for HDM was relatively low, which is consistent with previous studies.[12,29] These results can be explained by the many grasslands and dry climates in Central Asia: the "steppe" grasslands are associated with frequent exposure to grass and weed pollen. Furthermore, it is difficult for HDM to survive in the arid cold climate of this region, where the average annual temperature is less than −2.9 °C in Mongolia with 250 mm of annual precipitation in Kazakhstan.[30,31]

In Russia, low sensitization rates for outdoor allergens were found in the present study and in previous reports.[32,33] These findings are related to the long winter, prevalence of household pets, and dry climate in Siberia, with relatively low exposure to pollen and fungi.

Although the allergen sensitization rates in our study were relatively high among individuals from Europe, South Asia, and Oceania compared with other non-Koreans, the small sample size limits any analysis of this difference. Further studies are needed to evaluate a larger sample of individuals.

One previous study did not detect any sex-based differences in the sensitization rates,[7] whereas the present study and another survey revealed relatively high allergen sensitization among male individuals.[8] Although asthma predominantly affects males before puberty and females after puberty,[34,35] the MAST results do not necessary reflect the occurrence of allergic disease. Therefore, further research is needed to address this issue.

The allergen sensitization rate decreased with age among both Koreans and non-Koreans in our study. Previous reports have also confirmed that the prevalence of allergen sensitization and elevated IgE levels decrease with age.[7,11,36] In addition, the Korean sensitization rate for HDM decreased with age, which may be related to older Koreans having relatively limited exposure to Western-style residential environments, such as sofas and mattresses that could harbor HDM.[17,23] Among both Koreans and non-Koreans, and especially among <30-year-old individuals, animal dander allergens were relatively common; this may be related to the residential environment when many pets are allowed to be kept in the house. It is also possible that younger individuals are more likely than older individuals to have pets.

The present study was based on MAST results. Our study screened for various allergens during the first visit of all patients with suspected respiratory allergic diseases. Skin prick test was not included in this study because it was difficult to perform in infants or patients with current medication use. ImmunoCAP was also not included because it was costly and required the addition of all suspected allergens into the panel; thus, various allergens could not be screened realistically. In addition, the AdvanSure™ assay and ImmunoCAP have shown similar diagnostic performance,[2] which adds further weight to our study design using MAST.

Our study has some limitations that warrant consideration. First, the number of non-Koreans was relatively small, and these patients might not be representative of all people from international categories. Further studies are needed to generalize our results to the groups of non-Koreans. Second, we did not consider the length of time that non-Koreans spent in Korea before the MAST test was performed. Because environmental effects are important for allergen sensitization, additional studies should examine this duration. Third, the present study evaluated the samples using a MAST assay designed in Korea. This assay can detect the most common allergens in Koreans, but it may miss allergens that are common in non-Koreans. For example, the grass pollens tested in the present study were generally temperate grasses. However, subtropical grasses (e.g., *Chloridoideae* [Bermuda grass], *Panicoideae* [Bahia grass, Johnson grass]) are abundant in India, Thailand, Australia, and the southern United States. Thus, physicians should consider including subtropical grass pollen in the allergen testing of non-Koreans from subtropical regions.[8,37–40] The Middle Eastern individuals in our study had negative results for most pollen, which suggests that non-tested pollen (e.g., *Salsola imbricate, Chenopodium murale, Prosopis juliflora*) are responsible for the high pollen sensitization rates in the Middle East (rather than a low sensitization rate).[41] Finally, although allergen sensitization is a significant risk factor for the development of allergic disease, the sensitization rate is not the same as the disease's prevalence because there can be asymptomatic sensitized people. Moreover, the allergen sensitization pattern may be different depending on clinical diseases (e.g., allergic rhinitis, asthma). This study focused on the sensitization rates of patients with suspected respiratory allergic diseases according to geographic and demographic factors. We are planning further research on the relationship between inhalant allergen sensitization and clinical diseases.

Despite these limitations, ours is the first study to compare allergen sensitization rates between Koreans and non-Koreans using the same equipment at a single institution. Furthermore, we evaluated a relatively large sample of patients and large number of allergens, and performed our analysis according to region, age, and sex. Thus, our findings of regional and age-related differences in allergen sensitization rates provide practical information regarding the selection of allergens for testing. Moreover, we hope that this information can be used to help patients avoid causative allergens and help physicians select specific allergens for immunotherapy.

In conclusion, allergen sensitization rates vary according to residential country, region, and age. The most common allergen in both Koreans and non-Koreans was HDM, but Koreans had a greater proportion of sensitization. We also observed high sensitization rates for various pollen types in Gangwon and JCP in Jeju. Among non-Koreans, grass pollen and animal dander were relatively common for individuals from the Americas, whereas weed and grass pollen were relatively common for individuals from Central Asia. The total allergen sensitization rate, as well as the sensitization rates to HDM and animal dander, peaked among adolescents and young adults, then subsequently decreased with age. We hope that this information will help improve the understanding of allergen sensitization among Koreans and non-Koreans who are evaluated in Korea, as well as guide policymaking regarding allergic diseases.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.alit.2018.07.005.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

SCP, CSH, H-JC, and C-HK conceived and designed the study. SCP, CSH, HJC, MP, SSAS, H-JC, and C-HK collected the data. SCP, CSH, HJC, MP, SSAS, J-HY, and C-HK analyzed and interpreted the data. SCP, MP, SSAS, H-JC, J-HY, and C-HK drafted the manuscript for important intellectual content. All authors had full access to the study data and approved the final manuscript.

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