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Trends of Sensitization to Inhalant Allergens in Korean Children Over the Last 10 Years

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Purpose: Climate and lifestyle changes increase an individual's susceptibility to various allergens and also the incidence of allergic diseases. We aimed to examine the changes in sensitization rate for aeroallergens over a 10-year period in Korean children.
Materials and Methods: We retrospectively reviewed the medical records of 4493 children who visited the allergy clinic at a tertiary hospital in Korea for allergic rhinitis or asthma from January 2009 to December 2018. The serum specific immunoglobulin E (IgE) levels were measured to confirm the sensitization against *Dermatophagoides farinae* (*D. farinae*), *Alternaria*, weed and tree pollen mixtures, as well as cat and dog dander through ImmunoCAP test.
Results: *D. farinae* was the most common sensitizing aeroallergen (45.9%) during the 10-year span. The sensitization rate for tree pollen mixture (p for trend <0.001), weed pollen mixtures (p for trend <0.001), dog dander (p for trend=0.025), and cat dander (p for trend=0.003) showed ascending trends during the 10-year study period. Furthermore, the sensitization rate for multiple allergens (≥2) in 2018 increased significantly compared to that in 2009 (p for trend=0.013). Compared with children without sensitization to *D. farinae*, those with sensitization to *D. farinae* showed higher sensitization rates to other aeroallergens (p for interaction <0.001).
Conclusion: Children's sensitization rate to cat and dog dander and weed and tree pollen mixtures significantly increased during the 10-year period in Korea. Children with sensitization to *D. farinae* are likely to be sensitized to other aeroallergens as well.

Key Words: Allergy, aeroallergen, sensitization, children, specific IgE

INTRODUCTION

The global prevalence of allergic diseases has increased,[1,2] and the involvement of heredity and industrialization, westernized lifestyle, air pollution, and global warming factors are crucial to the prevalence of allergic diseases.[3-5] Due to the rapid socioeconomic development and industrial growth in Asia, excessive air pollution has become an emerging problem.[6,7] The concentrations of carbon dioxide, nitrous dioxide, and ozone have drastically increased over time, thereby affecting the climate, and leading to global warming and eventually to increased pollen count.[8] Climate change accelerates the onset of pollen release and lengthens the exposure period.[7] These changes can negatively influence lung development in children and affect the distribution and diversity of inhalant allergens.[5,6]

The number of pet-raising households has been growing rapidly in Korea. According to a public opinion survey on animal protection in 2015, one-fifth of all households were raising pets.[9] As the number of pet owners increased, direct or indirect exposure to pets may also increase the rate of sensitization to pet allergens.[10] Exposure to house dust mites (HDM), pollens, molds, and animal dander is a significant risk factor in the development of allergic diseases in children.[6]

The changes in sensitization to inhalant allergens and the factors associated with it have been evaluated. HDM is the most

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commonly inhaled allergen in Korea, and skin reactivity to molds and animal hair has not changed over the last 30 years, as reported by a single-center study on Korean adult patients.[11] Conversely, pollens and animal dander are the most prevalent allergens in Europe, and the incidence of sensitization to these allergens have been reported to increase with age.[12] Skin reactivity to tree pollen significantly increased, while that to grass and weed pollen decreased in Korean adult patients.[11] Conversely, the sensitization rate for weed pollen increased in Korean children from 1997 to 2009.[13]

In this study, we aimed to investigate the trend of sensitization to aeroallergens and the proportion of children with positive sensitization over a 10-year period. We also aimed to assess the interaction of HDM with other allergens in children who were admitted in a single tertiary hospital in Seoul, Korea.

MATERIALS AND METHODS

Participants

This study retrospectively reviewed the medical records of 4493 children (boys: 54.4%) aged ≤18 years [mean±standard deviation (SD), 5.9±3.2 years; interquartile range, 3.3–7.7 years] who visited the allergy clinic at a tertiary hospital for allergic rhinitis (n=2502, 55.7%), asthma (n=2248, 50.0%), or atopic dermatitis (n=1608, 35.8%) from January 2009 to December 2018 in Seoul, Korea. Among them, 771 underwent an allergy test more than twice (mean number of test, 2.4) with a mean interval of 1.8 years. A total of 5560 allergy tests were performed. Demographic data, including age, sex, and the result of serum specific immunoglobulin E (IgE) test to confirm the sensitization to six common aeroallergens, were obtained. In the inclusive years, the allergy specialist and diagnostic methods for serum specific IgE tests did not change. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (no. 2020-04-019).

ImmunoCAP measurement

The ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) was used to measure the serum total and specific IgE levels of *Dermatophagoides farinae (D. farinae), Alternaria*, cat dander, dog dander, weed pollen mixture (a combination of short ragweed, mugwort, ox-eye daisy, dandelion, and goldenrod), and tree pollen mixture (a combination of gray alder, hazel, elm, willow, and cottonwood). The results were expressed as kUA/L. A specific IgE level of >0.35 kUA/L indicated a positive detection.

Statistical analysis

All statistical analyses were performed using STATA software (ver. 16.0 for Windows; StataCorp LLC., College Station, TX, USA). Data were expressed as mean and SD for continuous variables, and as number (%) for categorical variables. Categorical variables were analyzed using a chi-square test, while continuous variables were analyzed using either one-way analysis of variance or t-test. Multivariate logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of the sensitization rates in each year compared with those in 2009, after adjusting for age, sex, and the season. Multinomial logistic regression analysis was performed to explore the relationship between the number of positive aeroallergens and year, after adjusting for age, sex, and season. In sensitivity analysis, the generalized estimating equations (GEE) method was used to adjust for the bias of repeated measurement data within the same patients. All of the tests were two-tailed, and p values <0.05 were considered significant.

RESULTS

Demographic data

The participants' demographic data are summarized in Table 1. A total of 4493 children (2442 boys and 2051 girls) who visited the allergy clinic for allergy-related diseases and underwent allergen-specific IgE test were enrolled in this study. The mean age of the children was 5.9±3.2 years.

Of the 4493 children, 2311 (51.4%) were not sensitized to any of the aeroallergens, while 2182 (48.6%) had positive serum-specific IgE results to one or more aeroallergens. Moreover, 1392 (31.0%) children were monosensitized, while 790 (17.6%) were multisensitized (sensitized to multiple allergens).

Prevalence of aeroallergen sensitization and patterns of sensitization in the follow-up setting

The overall sensitization rates of six common aeroallergens from 2009 to 2018 are shown in Fig. 1. The most frequent aeroallergen was *D. farinae* (45.9%), followed by dog dander (11.1%), tree pollen mixture (9.9%), cat dander (9.5%), weed pollen mixture (7.2%), and *Alternaria* (6.2%). No significant differences were observed in the sensitization rate of each allergen according to the specific allergic disease (data not shown).

We analyzed the trend of sensitization among the 771 children who underwent allergic test multiple times (Table 2). We divided the patients into four groups according to the results of initial and follow-up tests: all negative, negative→negative; positive conversion, negative→positive; negative conversion, positive→negative; and all positive, positive→positive. The mean age for initial test showed no difference among the four groups: 9.4±3.1 years in all negative group, 10.1±3.2 years in the positive conversion group, 11.5±3.4 years in the negative conversion group, and 10.7±3.8 years in all positive group (p value=0.43). Approximately 37.4% of children showed no sensitization to any allergen on all tests, whereas 48.5% showed sensitization on all tests. A total of 99 (12.8%) children showed conversion from no sensitization to sensitization, whereas only 10 (1.3%) showed remission. Among the allergens with posi-

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Table 1. Patients' Demographic Data from 2009 to 2018 (n=4493)

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Whole group	*p* value
Number of subjects	259	162	362	337	525	599	597	619	499	534	4493	<0.001
Male	136 (52.5)	84 (51.9)	191 (52.8)	198 (58.8)	273 (52.0)	347 (57.9)	310 (51.9)	341 (55.1)	265 (53.1)	297 (55.6)	2442 (54.4)	0.332
Age (yr)	4.7±1.8	5.0±2.0	5.6±2.1	6.0±2.4	5.8±2.8	5.5±3.1	6.2±3.3	6.0±3.5	6.1±3.9	6.5±4.2	5.9±3.2	<0.001
Positive rate of aeroallergens												<0.001
Non-sensitized	148 (57.1)	94 (58.0)	161 (44.5)	142 (42.1)	269 (51.2)	319 (53.3)	308 (51.6)	319 (51.5)	266 (53.3)	285 (53.4)	2311 (51.4)	
Monosensitized*	90 (34.8)	50 (30.9)	139 (38.4)	129 (38.3)	175 (33.3)	179 (29.9)	184 (30.8)	180 (29.1)	137 (27.5)	129 (24.2)	1392 (31.0)	
Multisensitized†	21 (8.1)	18 (11.1)	62 (17.1)	66 (19.6)	81 (15.4)	101 (16.9)	105 (17.6)	120 (19.4)	96 (19.2)	120 (22.5)	790 (17.6)	

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.
*Monosensitized represents sensitization to only one allergen, †Multisensitized represents sensitization to more than two allergens.

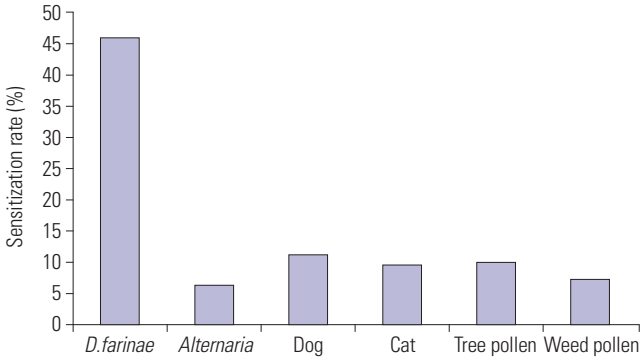

Fig. 1. Prevalence of common aeroallergen sensitization at a tertiary care hospital in Seoul, Korea.

tive conversion, the incidence of *D. farinae* (11.2%) was the highest, followed by cat dander (6.0%), tree pollen mixture (5.6%), dog dander (5.3%), weed pollen mixture (4.4%), and *Alternaria* (3.0%).

Trend of monosensitization and multisensitization during the 10-year period

A multinomial logistic regression analysis was performed to assess the changes in monosensitization and multisensitization rates from 2009 to 2018, using the data from 2009 as a reference. The OR of multisensitization from 2009 to 2018 was significantly increased compared to that in 2009 (p for trend= 0.013), whereas the OR for monosensitization was significantly decreased (p for trend <0.001) (Fig. 2).

Trend of sensitization to each aeroallergen during the 10-year period

Logistic regression analysis of the annual sensitization rate of each allergen from 2009 to 2018 was conducted after adjusting for age, sex, and season (2009 as a reference year); the results showed increasing trends in the sensitization rate for tree pollen mixture (p for trend <0.001), weed pollen mixture (p for trend < 0.001), dog dander (p for trend=0.025), and cat dander (p for trend=0.003). No significant trend was observed in the rate of sensitization to *Alternaria*, while the rate of sensitization to *D. farinae* showed a tendency to decrease (p for trend <0.001) (Fig. 3). The GEE method was used to determine the association between the rate of sensitization to each aeroallergen and the year; the results were similar to those of the original analyses (data not shown).

Trends of sensitization to aeroallergen in terms of co-sensitization to *D. farinae*

Logistic regression analysis was conducted to investigate the trends of sensitization to other allergens according to the rate of co-sensitization to *D. farinae* from 2009 to 2018, using the data from 2009 as a reference (Fig. 4). The prevalence of sensitization to allergen was higher in children who were co-sensitized to *D. farinae* than in those who were not co-sensitized. Com-

Table 2. Longitudinal Patterns of Sensitization at Individual Level with Follow-Up Tests (n=771)

Initial	Follow-up	Aeroallergen						
		Any allergen	*D.farinae*	*Alternaria*	Dog	Cat	Tree pollen	Weed pollen
Negative*	→ Negative	288 (37.4)	357 (46.3)	706 (91.6)	654 (84.8)	671 (87.0)	660 (85.6)	692 (89.8)
Negative†	→ Positive	99 (12.8)	86 (11.2)	23 (3.0)	41 (5.3)	46 (6.0)	43 (5.6)	34 (4.4)
Positive‡	→ Negative	10 (1.3)	5 (0.7)	3 (0.4)	8 (1.0)	5 (0.7)	10 (1.3)	9 (1.2)
Positive§	→ Positive	374 (48.5)	323 (41.9)	39 (5.1)	68 (8.8)	49 (6.4)	58 (7.5)	36 (4.7)
	All	771 (100.0)	771 (100.0)	771 (100.0)	771 (100.0)	771 (100.0)	771 (100.0)	771 (100.0)

Data are presented as n (%).
*The mean age for initial test in all negative group was 9.4±3.1 years, †The mean age for initial test in positive conversion group was 10.1±3.2 years, ‡The mean age for initial test in negative conversion group was 11.5±3.4 years, §The mean age for initial test in all positive group was 10.7±3.8 years.

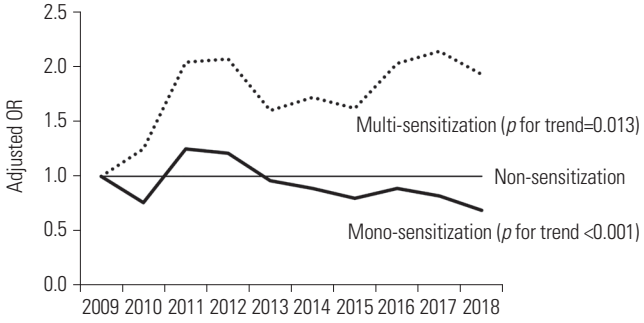

Fig. 2. Patterns of monosensitization and multisensitization over the last 10 years. The OR of multisensitization from 2009 to 2018 significantly increased compared to that in 2009 (*p* for trend=0.013). Meanwhile, the OR of monosensitization significantly decreased (*p* for trend <0.001). OR, odds ratio.

pared to children without co-sensitization to *D. farinae*, those with co-sensitization showed an increasing trend of annual allergen sensitization (*p* for interaction <0.001). The results showed almost the same tendency when analyzed by the GEE method (data not shown).

DISCUSSION

The present study retrospectively reviewed the trend of aeroallergen sensitization in Korean children over a 10-year period. The sensitization rate for tree pollen mixture, weed pollen mixture, and cat and dog dander increased significantly from 2009 to 2018. These changes in sensitization rates may be attributed to the adoption of a westernized lifestyle, such as raising pets at home, as well as the increase in pollen count due to air pollution and global warming.[1,2,13] However, the sensitization rate for *Alternaria* did not show a significant change, and the trend of *D. farinae* sensitization even decreased over the past decade. HDM are the most common aeroallergen in Korea, and 40–60% of the Korean population is sensitized to HDM.[6,14] Conversely, the prevalence of sensitization to HDM in European children aged 7–8 years was <2% in the general population, whereas the prevalence of sensitization to tree pollen and cat and dog dander was higher than the prevalence of sensitization to HDM.[12]

In Korea, HDM are not only the most common allergen but also the allergen to which children are more likely to develop early sensitization. As shown in the present study, children with HDM sensitization had a higher sensitization rate for other allergens compared those without HDM sensitization. Sensitization to *D. farinae* may increase the probability of co-sensitization with other allergens in Korean children. To the best of our knowledge, this is the first study to compare the prevalence of allergen sensitization depending on the rate of *D. farinae* sensitization by year.

We analyzed the longitudinal pattern of sensitization in children who underwent serial allergen tests more than two times and demonstrated high persistence of sensitization. In the follow-up setting, 12.8% of the children showed a conversion to sensitization from non-sensitization at initial test, while 48.5% still remained sensitized to allergen from initial sensitization. On the contrary, sensitization change from positive to negative was only found in 1.3% of the children. Therefore, once sensitized, there is an extremely low risk of remission. In line with this study, several longitudinal studies showed low remission of sensitization throughout childhood and adolescence.[15,16] Therefore, patients should be checked regularly for sensitization to other aeroallergens, especially when they are sensitized to *D. farinae*.

In this study, the prevalence of monosensitization tended to decrease over the years, while that of multisensitization tended to increase significantly each year. A longitudinal population-based study including school-aged children to adolescents showed an increasing prevalence of multisensitization by age, and stated that the early onset of sensitization was an important factor for multisensitization.[12] In agreement with the results of the present study, several investigations found an increasing trend of multisensitization to aeroallergens.[17,18] Monosensitization and multisensitization can be immunologically different. Multisensitized patients may have more severe symptoms, and are less responsive to immunotherapies.[19] Therefore, it is important to evaluate whether a patient is sensitized to one or more than two allergens to control the disease severity and implement an appropriate treatment plan.

Among mold allergens, we conducted a serum specific IgE test to *Alternaria*, which showed a higher rate of sensitization

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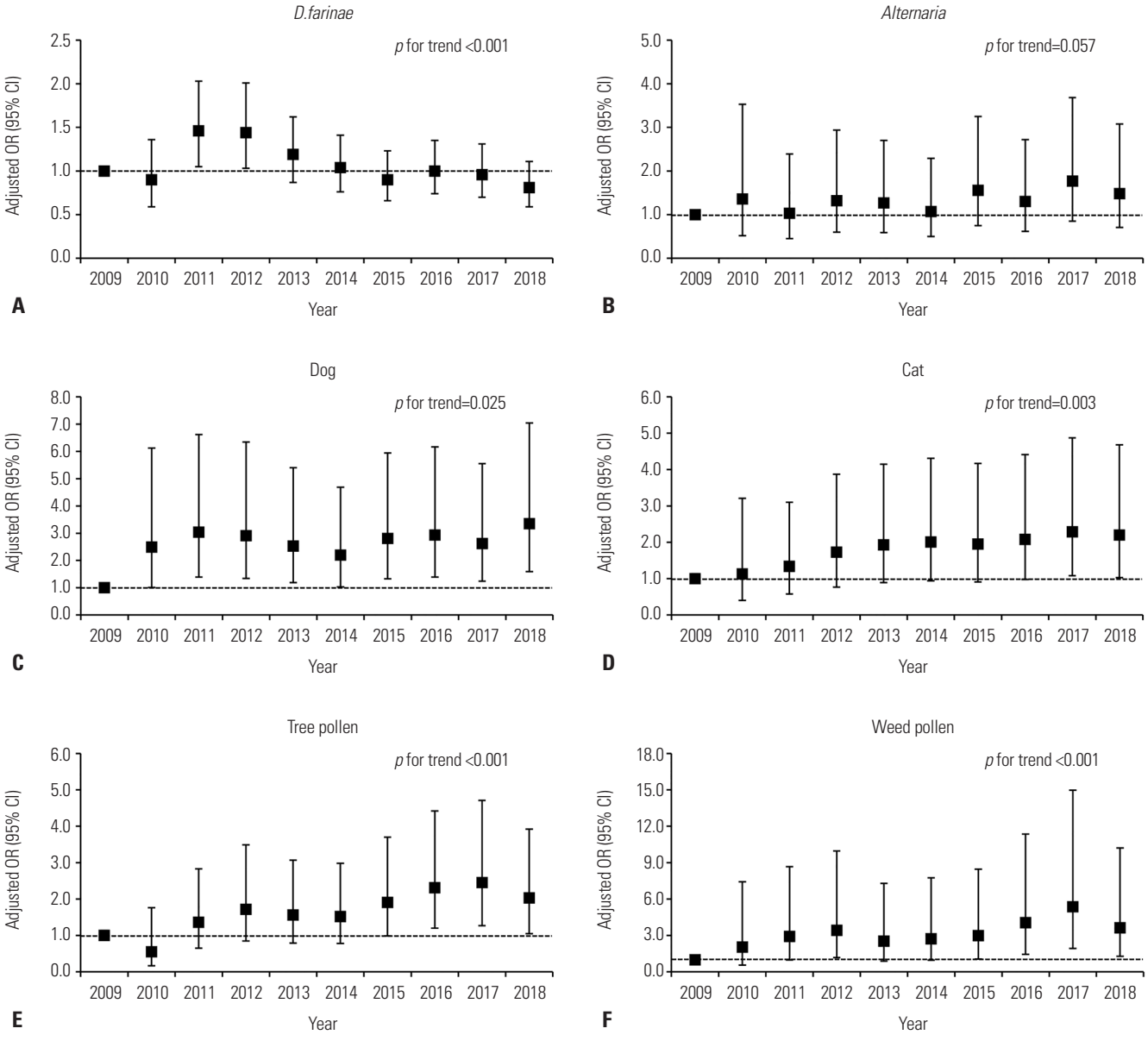

Fig. 3. Patterns of adjusted OR (95% CI) of sensitization rate to (A) *D. farinae*, (B) *Alternaria*, (C) dog dander, (D) cat dander, (E) tree pollen, and (F) weed pollen from 2009 to 2018. Increasing trends of sensitization rate were observed in tree pollen mixture, weed pollen mixture, dog dander, and cat dander (*p* for trend <0.001, <0.001, 0.025, and 0.003, respectively). No significant difference was observed in the trend of sensitization to *Alternaria*, while the rate of sensitization to *D. farinae* showed a tendency to decrease (*p* for trend <0.001). OR, odds ratio; CI, confidence interval.

compared to other molds.[20] The sensitization rate of molds did not change over the years.[11,20] In the present study, patients with sensitization to *Alternaria* showed an ascending trend in 2018 compared with that in 2009, but no statistical significance was observed.

Unlike HDM and *Alternaria*, the sensitization rate for pollen increased over time.[21] The increase prevalence of sensitization to pollen was associated with the increase in atmospheric pollen concentration. Air pollution and global warming are crucial factors that affect pollen concentration.[13,21,22] Economic development and high levels of vehicle emission caused air pollution; as a consequence, large amounts of air pollutants, such as carbon dioxide (CO_2) and ozone (O_3), result in climate change.[7,23] The increase in atmospheric pollen concentration has exposed children to more allergens, making them vulnerable to airway inflammation.[24] Moreover, increased CO_2 concentrations stimulate pollen production and floral initiation via photosynthesis and vegetative growth, which increases the rate of sensitization to pollen.[7,8,25] Therefore, climate change and increased pollen concentration affect the rate of sensitization to pollen.[4,23] Similarly, the annual weed pollen concentration and the proportion of patients with sensitization to weed pollens increased throughout the years.[13] In addition, an increase in the rate of sensitization to tree, grass, and

weed pollen was observed in the 10-year period, although a difference was observed in the degree of sensitization.[26] Our results also showed that the rate of sensitization to tree and weed pollen mixture had increased from 2009 to 2018, supporting the finding of previous studies.[13,26]

Compared to those in Asia, atopic patients in Europe and the United States tend to have a higher sensitivity to cat and dog dander.[6] As people's lifestyle in Korea became more westernized, the number of animal companions increased. According to a survey conducted by the Seoul Institute in 2014–2018, the

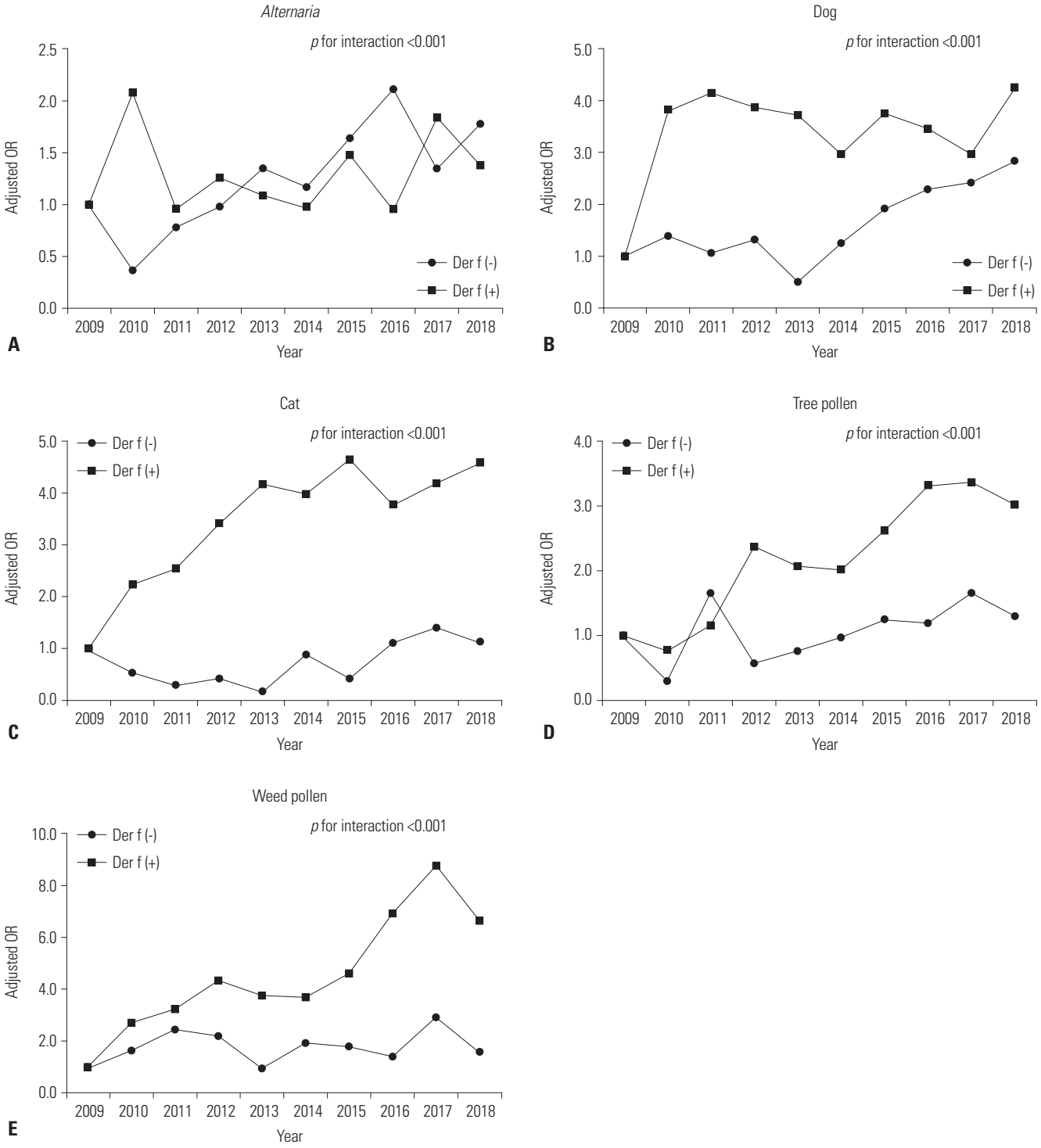

Fig. 4. Trends of adjusted OR of sensitization to (A) *Alternaria*, (B) dog dander, (C) cat dander, (D) tree pollen, and (E) weed pollen in terms of co-sensitization to *D. farinae*. The prevalence of sensitization to all allergens was higher in children with *D. farinae* sensitization than in those without *D. farinae* sensitization over the last 10 years (*p* for interaction <0.001, respectively). OR, odds ratio; CI, confidence interval.

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proportion of animal companions increased from 18.8% in 2014 to 20.0% in 2018.[27] The rate of cat ownership is lower than that of dog ownership, but the incidence of having cats as pets is increasing, and many stray cats in Seoul seem to attribute to the high prevalence of sensitization to cat dander.[28] Furthermore, an increase in the rate of furry pet ownership may indirectly influence the prevalence of sensitization in individuals who do not raise dogs and cats by close contact.[29,30] In the present study, the sensitization rate of cat and dog dander showed ascending trends over the years, especially in those who had co-sensitization to *D. farinae*. These findings suggest that, as the level of exposure to pets increased, the rates of sensitization to animal antigens increased; and these sensitizations were aggravated in children with sensitization to *D. farinae*. Therefore, children with sensitization to *D. farinae* should be careful when it comes to raising furry animals.

Our study had some limitations. First, our findings cannot be generalized, as this study only analyzed the results of allergy tests conducted in children who visited the hospital with allergic symptoms, rather than data of the general population. Second, since this was a retrospective study that focused on the positive rates of serum specific IgE, a family history of allergic diseases, possession of companion animals, household income, and other factors were not considered, making it difficult to determine the exact association between these factors and the sensitization rate. Third, as the tree and weed pollen allergens were bound to a mixed antigen, the sensitization rates to each pollen allergen could not be estimated. Moreover, tree pollen mixture did not include oak and beech, which are among the prevalent allergens in Korean individuals. The actual sensitization rate of tree pollen might be higher than that observed in this study.[31,32] However, there could be a considerable cross-reactivity in tree pollens with the same clades.[33] Finally, the characteristics of inhaled allergens vary from region to region. The present study was also limited in that it only included patients from a single tertiary hospital in Seoul; therefore, it would be difficult to generalize our results to the entire Korean population. However, unlike skin prick tests, which depend on the skill of the personnel and the batch of allergens, the measurement of specific IgE to six aeroallergens using the same immunoCAP in the same hospital during the study period supported the validity of this study.

Our study could demonstrate the trend of aeroallergen sensitization in children with allergic diseases over the course of 10 years. The prevalence of aeroallergen sensitization showed a significant annual increase during the 10-year period, especially for dog and cat dander as well as tree and weed pollen mixture. The multisensitization rate also significantly increased. The high incidence of multisensitization may become a major concern, as it makes prevention and control of symptoms more difficult in children. A novel finding was that the incidence of sensitization in Korean children significantly increased over the last decade when they were co-sensitized to *D. farinae*. Identifying the changes in allergen sensitization may help allergy practitioners in planning for disease prevention and management.

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AUTHOR CONTRIBUTIONS

Conceptualization: Yea Ji Kim and Jung Yeon Shim. Data curation: Yea Ji Kim, Jung Yeon Shim, Hye Lim Jung, Jae Won Shim, Deok Soo Kim, Ji Hee Kwak, A Ram Yang, and In Suk Sol. Formal analysis: Yea Ji Kim and Jung Yeon Shim. Investigation: Yea Ji Kim, Jung Yeon Shim, Hye Lim Jung, Jae Won Shim, Deok Soo Kim, Ji Hee Kwak, A Ram Yang, and In Suk Sol. Methodology: Yea Ji Kim and Jung Yeon Shim. Project administration: Jung Yeon Shim. Resources: Jung Yeon Shim. Software: Yea Ji Kim, Jung Yeon Shim, and Mi Yeon Lee. Supervision: Jung Yeon Shim. Validation: Yea Ji Kim, Jung Yeon Shim, and In Suk Sol. Visualization: Yea Ji Kim, Jung Yeon Shim, and Mi Yeon Lee. Writing—original draft: Yea Ji Kim and Jung Yeon Shim. Writing—review & editing: Yea Ji Kim and Jung Yeon Shim. Approval of final manuscript: all authors.

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