

Effect of perennial dust mites allergy on symptom severity of autumn allergic rhinitis in adults

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ABSTRACT

Background: Multiple immunoglobulin E (IgE) mediated sensitizations and/or allergies often coexist in patients with allergic rhinitis (AR). Several simultaneous allergen exposures in multiple IgE-mediated sensitizations and/or allergies may increase the allergen load and be related to disease severity. No study has verified whether positive allergen serum IgE levels and allergen categories together are associated with AR severity in adults.

Objective: To investigate the effects of perennial dust mites (DMs) allergy and multiple serum sIgE-mediated autumn pollen allergy coexistence on symptom severity in adult patients with AR in autumn.

Methods: In total, 153 patients with AR and with autumn pollen allergy (*Artemisia argyi*, ragweed, and hop) with or without DMs allergy were recruited in the autumn pollen season. Symptom severity was assessed by using the Chinese version of the visual analog scale (VAS): four rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus, and nasal congestion) and two ocular symptoms (ocular itching and/or grittiness and/or redness, and ocular tearing) were scored at approximately the same period. We measured allergen serum sIgE levels for the inhaled allergens. The effects of DMs allergy and multiple autumn pollen allergy coexistence on symptom severity were analyzed.

Results: Neither the sum of the autumn pollen allergens categories (total number of positive autumn pollen allergens, i.e., *Artemisia argyi* or ragweed or hop positive: 1; *Artemisia argyi* and ragweed positive: 2; *Artemisia argyi*, ragweed, and hop positive: 3) nor serum sIgE levels (total sIgE levels of positive autumn pollen allergens) exerted any influence on the severity of nasal and ocular symptoms ($p > 0.05$). When the concomitant DMs allergy status was considered, the sum of the positive autumn pollen allergen categories and accumulated positive autumn pollen and DMs serum sIgE levels (total levels of serum sIgE of positive autumn pollen allergens plus the levels of serum sIgE of DMs) had no influence on patients' symptom severity ($p > 0.05$).

Conclusion: The coexistence of perennial DMs allergy and multiple autumn pollen allergy did not affect the severity of symptoms among adult patients with AR and with autumn pollen allergy in autumn.

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Allergic rhinitis (AR) is a hypersensitivity reaction caused when inhaled antigens contact the nasal mucosa and induce an immunoglobulin E (IgE) mediated inflammatory response.¹ AR is a global health

problem. The incidence of AR has been increasing in recent years, and the disease's prevalence, worldwide, is currently 10–40%.^{2,3} Developing allergic reactions to a particular allergen requires appropriate exposure and the subsequent development of a serum specific IgE (sIgE) response in a genetically susceptible host.⁴ Multiple IgE-mediated sensitizations often coexist in patients, and the combination of several exposures at a given time (the allergen load) has been proven to be related to disease severity.⁵ Thus, reductions in the allergen load (whether the level of multisensitizations or the level of one allergen) were considered key to successful treatment of the “allergic march” in children.⁵

Moreover, IgE-mediated sensitization is currently considered a nondichotomous variable. For example, the probability of wheeze was positively associated with reduced lung function and increased with an increasing sum of dust mites (DMs), cat, and dog serum sIgE levels in preschool children.⁶ It has also been found that the combination of the sum of serum sIgE antibody levels and the categories of allergens that elicited positive results (sIgE > 0.35 kU/L) was significantly associated with the likelihood of asthma in

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children.⁷ The categories of allergens to which an individual tests positive can be used as an indicator to identify allergic disease.^{8,9} However, so far, no study has verified whether the combination of the sum of sIgE levels and the categories of allergens is associated with AR severity in adults.

The existence of a considerable regional difference in the distribution of pollen species and counts is a result of geographic- and vegetation-related differences. *Artemisia argyi*, ragweed, and hop were reportedly three of the most commonly noted inhaled outdoor allergens in northern China in autumn, whereas DMs, especially *Dermatophagoides farinae* (Der f) and *Dermatophagoides pteronyssinus* (Der p) are predominant indoor aeroallergens in Chinese adult and pediatric perennial patients with AR.^{10,11} An estimation of the influence of DMs allergy, the sum serum sIgE levels of positive autumn pollen allergens, and the categories of positive pollen allergens on the severity of symptoms of patients with autumn pollen allergy may help in the determination of appropriate environmental interventions and treatment strategies aimed at reducing the frequency and intensity of AR attacks. Accordingly, we aimed to investigate the effects of the coexistence of perennial DMs allergy and multiple serum sIgE-mediated autumn pollen allergies on the severity of symptoms in adult patients with AR in autumn.

METHODS

Patients and Study Design

The pollen concentration data were obtained from the Beijing Meteorological Bureau. In Beijing, they reach their peak two times a year (March to May and August to September). Sampling was collected by a gravitational Durham sampler and counted under a microscope. The data were expressed as grains per 1000 mm² at 16 stationary monitoring stations distributed in the urban and suburban districts of Beijing. It showed that the highest pollen concentration was from August 18, 2018, to September 15, 2018 (range, 89–497 grains/1000 mm²).

Of the 512 outpatients with symptoms of AR in the autumn season who visited the Outpatient Department of Allergy in Beijing Tongren Hospital from August 25, 2018, to September 15, 2018, 430 agreed to participate in the study. Of them, 315 individuals fulfilled all the Allergic Rhinitis and its Impact on Asthma criteria for AR,¹² the inclusion criteria were the following: (1) a history of AR for at least 3 years and lived in Beijing for >10 years; (2) the presence of persistent or discontinuous symptoms of anterior rhinorrhea, continuous sneezing, nasal obstruction, and itching; (3) the demonstration of a pale and edematous nasal mucosa, nasal discharge, and swollen inferior turbinate by nasal endoscopy; (4) positive serum sIgE

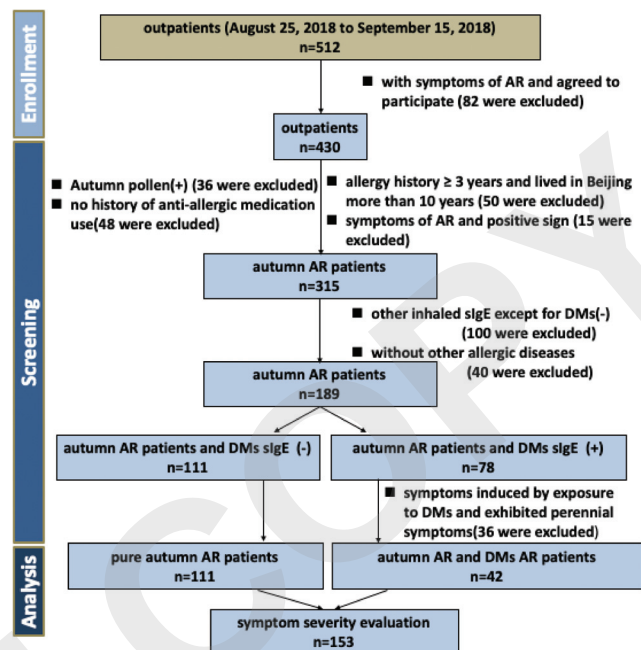


Figure 1. Flow diagram of the study. DMs = dust mites; AR = allergic rhinitis; sIgE = specific immunoglobulin E; ARIA = Allergic Rhinitis and its Impact on Asthma.

results to at least one of the autumn pollen (*A. argyi*, ragweed, hop); (5) no history of taking anti-allergic medications (such as antihistamines, corticosteroids, and immunotherapy) within 1 month of presenting to our hospital; and (6) absence of other allergic diseases (such as asthma, atopic dermatitis, and food allergies).

When individuals showed positive serum sIgE results to any other inhaled allergen (e.g., spring pollen, mold, pets), except for Der p and Der f sensitization, they were excluded from the present study. Overall, 189 cases fulfilled the criteria. Furthermore, the DMs AR diagnosis was further confirmed by the presence of symptoms induced by exposure to DMs, which meant that our diagnosis of DMs AR was based on medical history (to ensure patients with symptoms due to the exposure of DMs were identified) and a positive DMs serum sIgE response. Consequently, 153 individuals were included for further analysis. The study protocol is shown in Fig. 1. The study protocol was approved by the ethics committee of Beijing Tong Ren Hospital, and written informed consent was obtained from all the participants before study entry.

Evaluation of the Severity of Symptoms

The subjective assessment of AR symptoms is generally based on the scores of four nasal symptoms (sneezing, rhinorrhea, nasal itching, nasal obstruction) and two ocular symptoms (ocular itching and/or grittiness and/or redness, and ocular tearing).¹³ The validated Chinese version of the visual analog scale (VAS)

Table 1 Demographic and clinical characteristics of the study participants

Characteristic	DMs (–) (n = 111)	DMs (+) (n = 42)	p
Age, range (mean ± SD), y	18–52 (32.7 ± 6.35)	18–45 (31.6 ± 6.32)	0.34
Men/women, n (%)	51/60 (45.9/54.1)	20/22 (47.6/52.4)	0.86
Smoking status, yes/no, n (%)	9/102 (8.1/91.9)	5/37 (11.9/89.1)	0.53
Autumn pollen sensitization			
Category 1/2/3, n (%)	65/28/18 (58.6/25.2/16.2)	17/12/13 (40.5/28.5/31.0)	0.07
Level, mean ± SD	5.5 ± 2.78	6.0 ± 2.72	0.37
DMs level, mean ± SD	—	3.2 ± 1.68	—
VAS symptom scores, mean ± SD			
Sneezing	6.92 ± 2.133	6.68 ± 2.321	0.56
Rhinorrhea	6.28 ± 2.517	6.27 ± 2.785	0.98
Nasal itching	6.15 ± 2.465	6.33 ± 2.525	0.69
Nasal obstruction	6.03 ± 2.425	6.01 ± 2.628	0.97
Ocular itching and/or grittiness and/or redness	6.42 ± 2.532	6.29 ± 2.559	0.77
Ocular tearing	4.82 ± 3.102	4.65 ± 3.081	0.77

Level: the mean sIgE level of patients with positive autumn pollen allergy in the autumn pollen sensitization group. DMs level: the mean sIgE level of patients with positive dust mites allergy in the autumn pollen sensitization group.

(–) = Negative; (+) = positive; SD = standard deviation; DMs = dust mites; VAS = visual analog scale (range, 0–10).

was used to quantify the above-stated assessments.¹⁴ VAS shows the severity of symptoms in the past 1 week, has been fully validated in adult patients,¹⁵ and correlates well with the severity of AR.¹⁶ VAS provides a quantitative evaluation of disease severity, and it is a simple measure of severity. In this current study, patients graded their symptoms by drawing a vertical line across a 10-cm line. The distance (cm) from the starting point to the crossing point represents the severity score perceived by the patient at the moment, with scores ranging from 0 (“no symptoms”) to 10 (“highest level of symptoms”). The patients filled in the questionnaires at the same place (the consulting room of our outpatient facility) and at approximately the same time (from August 2018 to October 2018).

Measuring Serum sIgE Levels

Skin reaction is dependent on a number of variables that may alter performance of the skin tests. The quality of the allergen extract is importance. Drugs may also affect skin tests, so we chose an sIgE test. Peripheral blood samples were collected from all the participants at approximately the same time period (from August 2018 to October 2018), and their atopic status, evaluated by sIgE determination by using EUROline Allergy Diagnostics (Beijing Oumeng Biotechnology Co., Ltd., Beijing, China) with the same machine and the same technicians. To eliminate the influence of different batches of diagnostic reagents on the detection of allergens, we collected and stored all the samples and then did a unified examination by using the same batch of diagnostic reagents. The inhaled allergens included DMs (Der p and Der f), autumn pollen (*A. argyi*,

ragweed, and hop), spring pollen (multiple trees and weeds), animal hair (dog and cat), mold (indoor and outdoor mustiness or floriculture), and cockroaches.

The EUROline test system provides a semiquantitative *in vitro* assay for human sIgE against common inhalation and food allergens in serum or plasma for the diagnosis of allergic disease.^{17,18} This system is able to connect response magnitude (measured as band intensity) to an antibody concentration range (as exemplified by the EAST-class system). The range of intensity values that correspond to a certain EAST class are predefined in the EUROlineScan software. The basis for this definition existed in the use of precharacterized (with regard to sIgE measured by intensity to the respective EAST-class result, which covered the whole measurement range from class 1 to 6 [EUROIMMUN]). The quality of the test has also been tested by the manufacturer, and data on this analytical validation are summarized in the electronic repository. The intensity of the bands was measured and converted into EAST classes of 0–6 which will be divided into the following concentrations (all expressed in KU/L): class 0: <0.35KU/L; class 1: ≥0.35KU/L to <0.7KU/L; class 2: ≥0.7KU/L to <3.5KU/L; class 3: ≥3.5KU/L to <17.5KU/L; class 4: ≥17.5KU/L to <50.0KU/L; class 5: ≥50.0KU/L to <100.0KU/L; class 6: ≥100.0KU/L.

Statistical Analysis

To assess how the severity of symptoms was affected by participants' allergy status (the sum of serum sIgE levels and the categories of allergens that showed positive results) and by the presence of DMs allergy and autumn pollen allergy, we analyzed basic statistics of

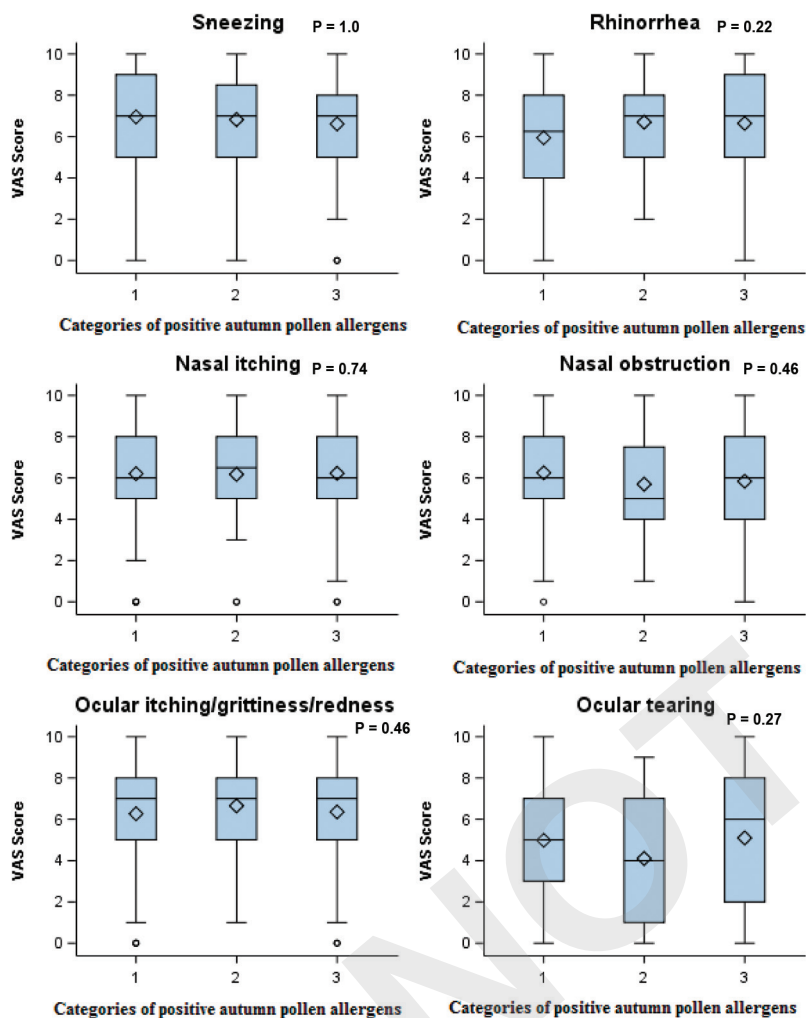


Figure 2. Estimated effects of the categories of autumn pollen allergens on the severity of nasal and ocular symptoms. 1: there was only one autumn pollen allergen; 2: there were two autumn pollen allergens; 3: there were three autumn pollen allergens. VAS = visual analog scale (range, 0–10).

the patient groups and graphs before moving to the estimation of the effects of allergy status on the severity of symptoms, which was the primary analysis. First, we compared the characteristics of those in the DMs (+) (DMs allergy positive) and DMs (–) (DMs allergy negative) groups. An unpaired *t*-test and the Fisher exact test were conducted to check for group differences in the numerical and categorical characteristics. Second, we evaluated the relationship between the sum of serum sIgE levels and the categories of positive autumn pollen allergen results, and the severity of symptoms. Analysis of variance (F-test) was used to assess group differences. To estimate the relationship between DMs allergy and the severity of symptoms, an unpaired *t*-test was used to assess group differences. Here, the sum of serum sIgE levels means the total level of serum sIgE of positive results for allergens and the categories of allergens means the total number of positive allergens (*i.e.*, one autumn pollen allergen, two autumn pollen allergens, three autumn pollen allergens).

Third, the primary analysis was conducted to estimate the effects of autumn pollen and DMs on the

severity of symptoms by using linear models, with the severity of each symptom as the dependent variable, and the autumn pollen allergy, DMs allergy, and their interaction as independent variables. If the *p* value of the interaction was <0.10 , then the interaction term would be retained in the model; otherwise, it would be removed from the linear model before the assessment of the main effects. If the *p* value of any main effect (VAS score of each symptom in autumn positive pollen allergy and DMs allergy) or their interaction (if retained) was lower than 0.05, then it was considered as having a statistically significant impact on the severity of symptoms. Unless otherwise specified, $p < 0.05$ was considered to indicate statistical significance. All the analyses were performed and all outputs were generated by using SAS 9.4 (SAS Co., Ltd, North Carolina).

RESULTS

Demographics

In total, the study population comprised 71 men and 82 women, ages 18 to 52 years; 14 were smokers. With

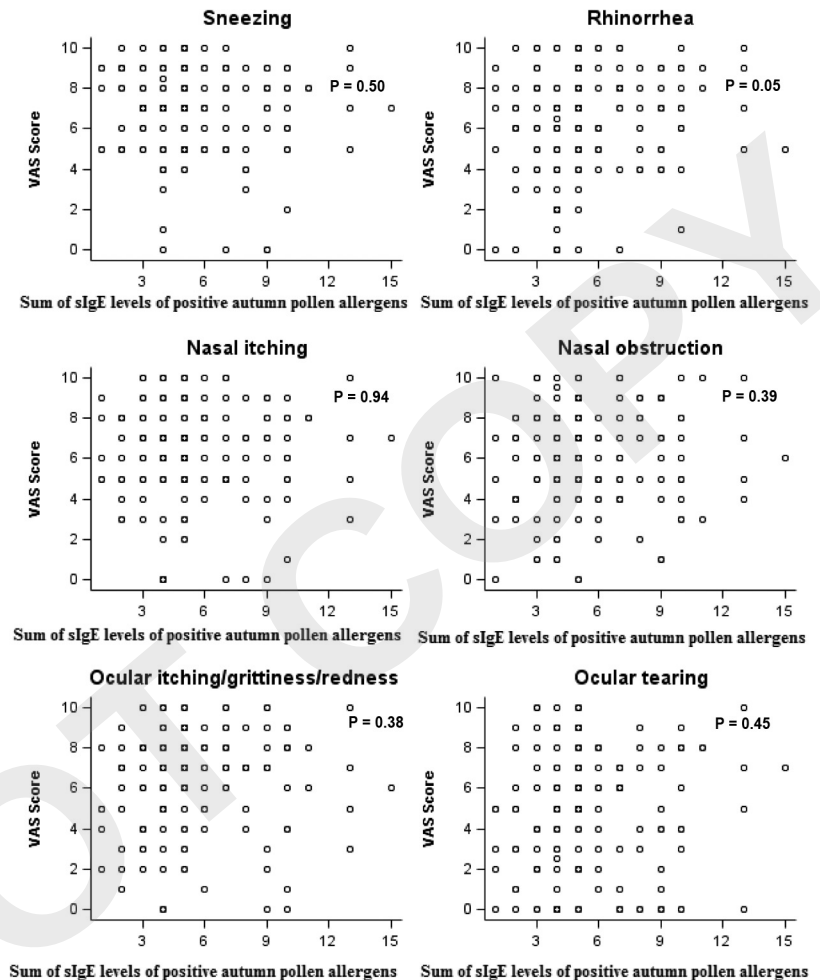


Figure 3. Estimated effects of the sum of the serum specific immunoglobulin E (sIgE) levels positive for autumn pollen allergens on the severity of nasal and ocular symptoms. VAS = Visual analog scale (range, 0–10).

respect to DMs allergy status, no significant differences were observed regarding age ($p=0.34$), sex ($p=0.86$), and smoking status ($p=0.53$) between the two groups ($p>0.05$). In addition, neither the categories distribution ($p=0.07$) nor sum sIgE level ($p=0.37$) of the autumn pollen allergens (*Artemisia argyi*, ragweed and hop) demonstrated any differences, regardless of DMs allergy. For those with DMs AR, the mean DMs sIgE level was 3.2. In addition, the subjective assessment of symptoms based on the VAS was performed, involving sneezing ($p=0.56$), rhinorrhea ($p=0.98$), nasal itching ($p=0.69$), nasal obstruction ($p=0.97$), ocular itching/grittiness/redness ($p=0.77$), and ocular tearing ($p=0.77$) (Table 1).

Effects of the Sum of Autumn Pollen Allergen Categories and Allergen Serum sIgE Levels on the Severity of Nasal and Ocular Symptoms

As shown in Fig. 2, the number of autumn pollen allergens had no effect on the severity of sneezing ($p=1.0$), rhinorrhea ($p=0.22$), nasal itching ($p=0.74$), nasal obstruction ($p=0.46$), ocular itching and/or grittiness and/or redness ($p=0.46$), and ocular tearing ($p=0.27$). Likewise, accumulated serum sIgE levels

had no effect on the severity of sneezing ($p=0.50$), rhinorrhea ($p=0.05$), nasal itching ($p=0.94$), nasal obstruction ($p=0.39$), ocular itching and/or grittiness and/or redness ($p=0.38$), and Fig. 3 ocular tearing ($p=0.44$).

Effects of the Coexistence of DMs Allergy on the Severity of Nasal and Ocular Symptoms in Patients with Autumn Hay Fever

When the concomitant DMs allergy presence was considered, we observed that the sum of positive autumn pollen allergens did not have any effect on the severity of sneezing ($p=0.67$), rhinorrhea ($p=0.35$), nasal itching ($p=0.60$), nasal obstruction ($p=0.89$), ocular itching and/or grittiness and/or redness ($p=0.93$), and ocular tearing ($p=0.73$), regardless of the presence of DMs allergy (Fig. 4). Similarly, no significant differences were observed in terms of the effect on the severity of sneezing ($p=0.56$), rhinorrhea ($p=0.98$), nasal itching ($p=0.69$), nasal obstruction ($p=0.97$), ocular itching and/or grittiness and/or redness ($p=0.77$), and ocular tearing ($p=0.77$) between the DMs allergy positive and negative results groups (Fig. 5). Moreover, we observed no effects on the severity of sneezing

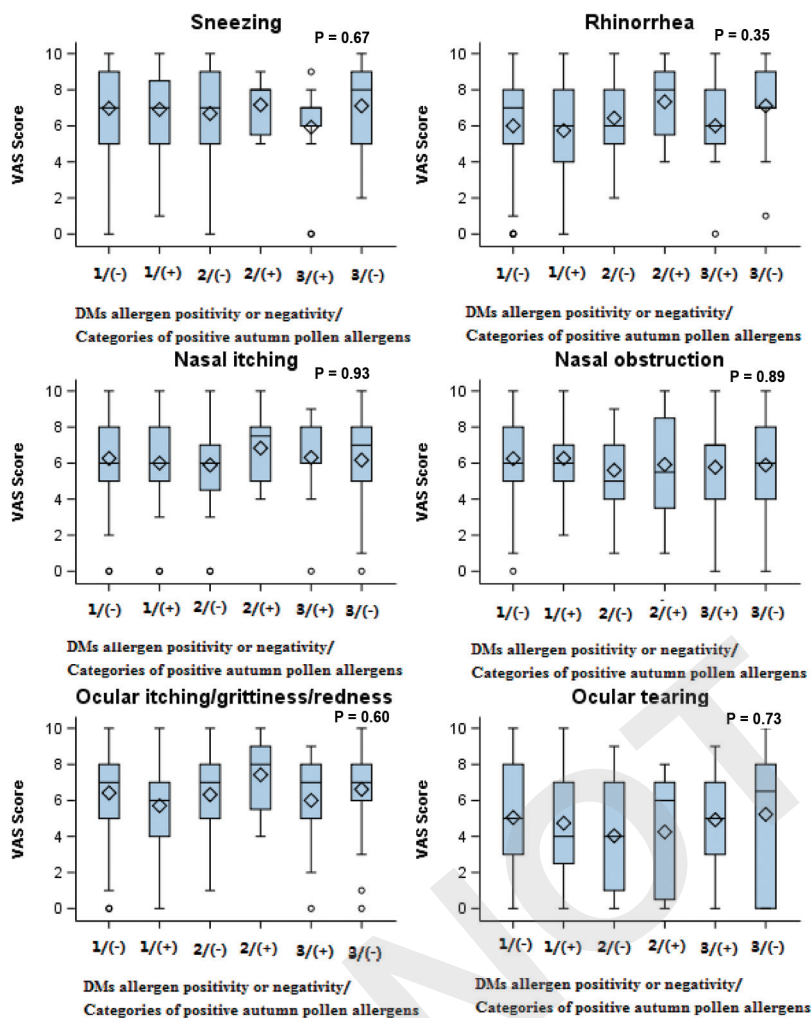


Figure 4. Effects of the categories of autumn pollen allergens on the severity of nasal and ocular symptoms when considering concomitant DMs allergy presence. 1: there was one autumn pollen allergen; 2: there were two autumn pollen allergens; 3: there were three autumn pollen allergens. (+) = Positive for DMs allergen; (-) = negative for DMs allergen; DMs = dust mites; VAS = visual analog scale (range, 0–10).

($p=0.78$), rhinorrhea ($p=0.45$), nasal itching ($p=0.86$), nasal obstruction ($p=0.46$), ocular itching and/or grittiness and/or redness ($p=0.93$), and ocular tearing ($p=0.19$) when the accumulated autumn pollen and DMs serum sIgE levels were considered (Fig. 6).

DISCUSSION

In the present study, we estimated the relationship between accumulated allergens sensitization and the severity of clinical symptoms among patients with hay fever in autumn and found that neither the coexistence of perennial DMs allergy nor accumulated multiple autumn pollen sensitization affected the severity of symptoms. To the best of our knowledge, our study was the first to examine the influence of perennial allergen on the severity of seasonal attacks in the pollen season in patients with AR.

Atopy is an important risk factor for allergic diseases such as asthma, AR, and eczema; the extent to which atopy accounts for these diseases and the exact relationships between early allergen exposure, sensitization, and the development of atopic disease remains

controversial.^{19,20} With regard to the dose relationship of allergy to the severity of allergic disease, it is well known that children with atopic diseases often exhibit sensitization.^{6,21,22} In adults, Bousquet *et al.*²³ demonstrated that the severity of nasal symptoms during the spring pollen season was not significantly different between patients allergic only to pollen and those allergic to grass pollen and other pollen species, including Cupressaceae, plane trees, olives, and *Parietaria*, which suggests that the intensity of symptoms is not related to sensitization or a serum sIgE immune response.

Furuhashi *et al.*²⁴ demonstrated that low doses of allergen were sufficient to prime T-helper type 2 cells (Th2 cells) and innate lymphoid cell type 2 (ILC2 cells) but insufficient to induce antibody responses. Repeated low-dose exposure produced the same features of T-helper type 2 cells and IgE/IgG1 antibodies to high-dose priming and so is closer to the way that patients with allergy are sensitized.²⁴ These findings are similar to that observed in our study, in which the sum of multiple autumn pollen serum sIgE levels and categories did not affect the severity of patients'

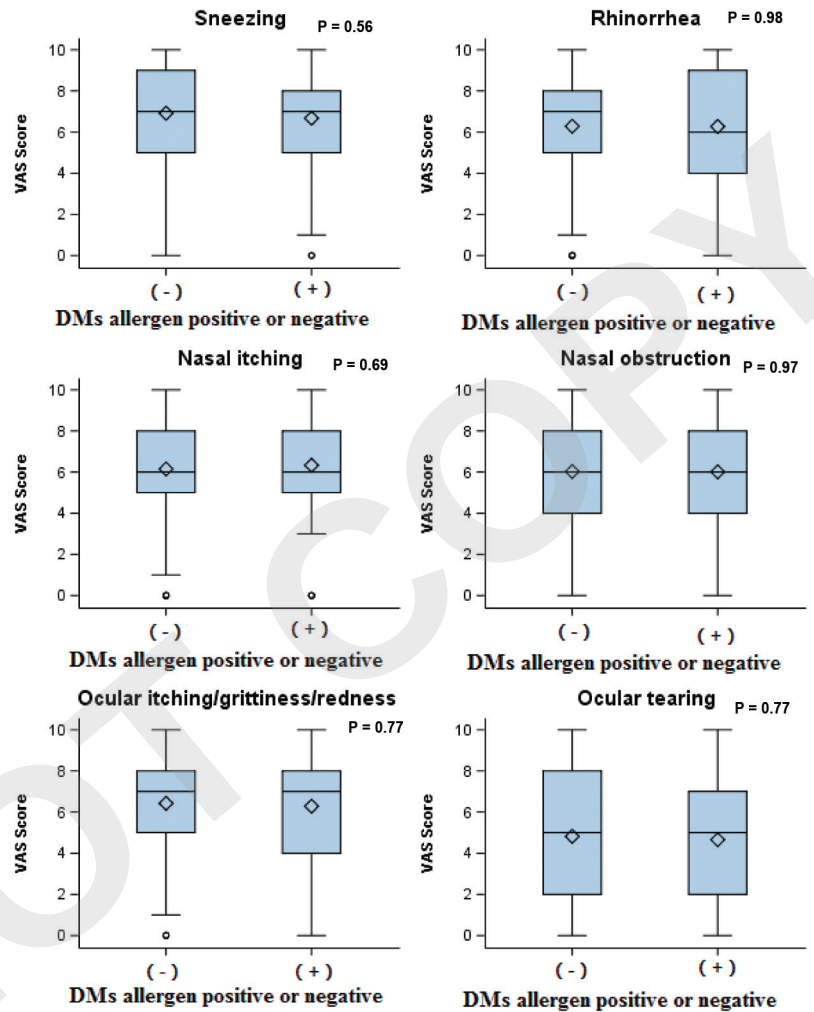


Figure 5. Difference in the severity of nasal and ocular symptoms between the DMs allergen positive group and DMs allergen negative group. (+) = Positive for DMs allergen; (-) = negative for DMs allergen. DMs = dust mites; VAS = visual analog scale (range, 0–10).

clinical symptoms. This phenomenon may be explained by the fact that children are still in an unstable process of the allergy march and the incidence of sensitization is far greater than that of allergic disease; in adults, the process of allergy is relatively stable.

Patients with asthma who are both sensitized and exposed to high levels of sensitizing allergens had a significantly higher disease severity than people with asthma and who were not exposed.²⁵ Similarly, a decrease in the cat allergen load was found to have a significant effect on the symptoms of nasal allergy when the environment was controlled.²⁶ Meanwhile, it has also been suggested that sensitization to one allergen may facilitate sensitization to another without the involvement of cross-reaction mechanisms, and the coexistence of specific allergens has been proven to be interactive in upper and lower respiratory diseases.²² An understanding of this concept may allow for the more effective management of patients' allergies. However, we unable to identify a positive correlation between the coexistence of perennial DMs allergy and the severity of symptoms. It is important to note that

patients may be sensitized to an allergen but remain asymptomatic, which suggests both the involvement of tolerance mechanisms and a threshold level for disease and/or symptoms.⁵ Therefore, our study possibly indicated that, once an adult has reached the symptoms threshold to one allergen, the load exerted by other kinds of concomitant allergens may have little impact on his or her disease severity.

This study had several limitations. First, individuals who had DMs allergy were roughly with a relatively average DMs exposure concentration, and, to more accurately evaluate the effect of DMs allergy on the clinical symptoms of patients with autumn pollen allergy, measurement of the indoor DMs concentration of each patient during the study period is necessary. Moreover, the fact that the EUROLIne test system only provides a semiquantitative *in vitro* assay for human sIgE against common inhalation allergens in serum may have somewhat affected our analysis. The use of the quantitative sIgE test system would have been more ideal. Also, the VAS score of symptoms is a subjective evaluation of the disease severity and does not reflect the extent to which

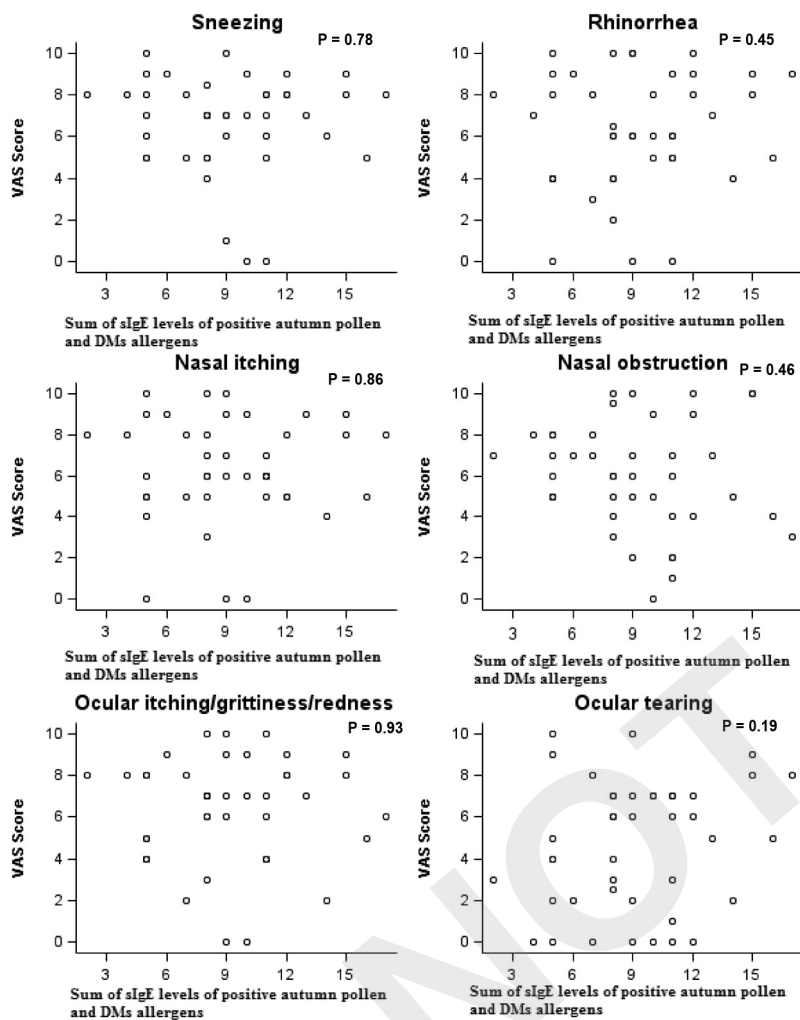


Figure 6. Estimated effects of the sum of positive autumn pollen results as well as DM serum specific immunoglobulin E (sIgE) levels on the severity of nasal and ocular symptoms. DMs = dust mites; VAS = visual analog scale (range, 0–10).

the patient's internal immune system changes due to different allergen burdens. In this sense, a further study that involves the changes of markers of the immune system should be addressed. Furthermore, the difference of symptoms between the individuals with or those without DMs allergy in nonautumn pollen season among the patients with autumn pollen allergy also should be recorded. We also can choose other objective scoring methods in the future.²⁷

Despite the limitations, and the reporting of negative results, this study, was the first to examine whether the coexistence of perennial DMs allergy as well as multiple autumn pollen allergy can affect the severity of symptoms among adult patients with AR in autumn. The rigorous manner in which samples were collected and stored enhanced the robustness of the study. Further, we used linear models to estimate the interaction effects of autumn pollen and DMs on the severity of symptoms. Our findings provided some insights into the pathogenesis of allergic diseases and will play a guiding role in future clinical diagnosis and basic research on this topic.

CONCLUSION

The coexistence of perennial DMs allergy as well as multiple autumn pollen allergies did not affect the severity of symptoms in autumn among adult patients with AR.

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