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To cite this article: Le Cui & Jia Yin (2019) Association of serum specific IgE levels with asthma in autumn pollen-induced allergic rhinitis: A retrospective analysis, Journal of Asthma, 56:5, 505-511, DOI: [10.1080/02770903.2018.1466316](https://doi.org/10.1080/02770903.2018.1466316)

To link to this article: <https://doi.org/10.1080/02770903.2018.1466316>



Accepted author version posted online: 18 Apr 2018.  
Published online: 09 Jul 2018.



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## Association of serum specific IgE levels with asthma in autumn pollen-induced allergic rhinitis: A retrospective analysis

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### ABSTRACT

**Background:** *Artemisia* and *Humulus* pollen are the two most important aeroallergens of autumn allergies in North China. Cross-sectional data in 2001 have shown that allergic rhinitis often preceded or occurred at the same time as asthma in patients with autumn pollinosis in North China. **Objective:** We used this cross-sectional data to investigate the association of serum specific IgE (sIgE) levels to *Humulus* and/or *Artemisia* pollen with the onset of asthma in patients with autumn pollen-induced allergic rhinitis. **Methods:** 1096 patients with autumn pollinosis were face-to-face interviewed and underwent sIgE tests to *Artemisia* and *Humulus*. The temporal sequence of allergic rhinitis and asthma was documented. 1013 patients were positive to *Artemisia* and/or *Humulus* by sIgE. Multinomial logistic regression and survival analysis were used to examine the potential implication of sIgE levels for the progression of asthma in autumn pollen-induced allergic rhinitis. **Results:** Of the 1013 participants with a positive sIgE test to *Artemisia* and/or *Humulus*, 563 (55.6%) had a history of allergic rhinitis which preceded or occurred at the same time as asthma. 450 (44.4%) had allergic rhinitis alone. After controlling of sex, age at onset of allergic rhinitis, and parental asthma, the risk of developing asthma increased with the levels of sIgE to both *Artemisia* and *Humulus* ( $p < 0.05$ ). In Kaplan–Meier analysis, IgE classes 5–6 to *Humulus* or *Artemisia* increased the risk of asthma development ( $p < 0.05$ ). **Conclusion:** Autumn pollen-induced allergic rhinitis often coexists with seasonal asthma. The incidence of asthma is more pronounced when the sIgE level was higher.

### ARTICLE HISTORY

Received 16 December 2017  
Revised 8 March 2018  
Accepted 15 April 2018

### KEYWORDS

Autumn pollinosis; allergic rhinitis; seasonal asthma; serum specific IgE

## Introduction

Allergic rhinitis (AR) is caused by an immunoglobulin E (IgE)-mediated reaction in allergen-sensitized subjects, and characterized by sneezing, rhinorrhea, nasal congestion and nasal pruritus, which are often accompanied by ocular pruritus, redness and/or lacrimation in 60–70% of patients (1). In fact, most of patients with allergic rhinitis have clinical asthma. A close relationship between asthma and allergic rhinitis in patients with autumnal pollinosis has been documented by epidemiological and clinical trials (2,3). Previously, the patients with autumn pollinosis underwent serum specific IgE (sIgE) test to *Artemisia* and *Humulus* (4). The coexistence of allergic rhinitis with asthma appeared in 585 (53.4%) patients. Based on Tasmanian Asthma Study, childhood allergic rhinitis was associated with the increased risk of asthma in preadolescence, adolescence, or adult life (5). Moreover, AR patients have a high incidence of asthma (6). The biomarker of asthma in allergic rhinitis patients would provide diagnostic and treatment approaches.

In North China, *Artemisia* pollen and *Humulus* pollen were the two most frequent and abundant pollen types and reach the largest peak concentration of the total autumn pollen according to daily airborne pollen monitoring (7). *Artemisia* and *Humulus* pollen revealed the highest positive sIgE rate, up to 78.6% and 57.9%, respectively, in patients with autumn pollinosis in North China (8). Moreover, a significant correlation between *Artemisia* or *Humulus* pollen count in the air and the severity of asthma symptoms in patients with autumn pollinosis was established (9). However, the association of sIgE levels with asthma onset in patients with autumn pollen-induced allergic rhinitis has not been reported.

Cross-sectional data in 2001 have revealed that allergic rhinitis often preceded or occurred at the same time as asthma in patients with autumn allergies (4). In this study, we used the sIgE data to investigate the potential implications of sIgE levels for asthma onset in patients with autumn pollen-induced allergic rhinitis.

## Methods

### Ethics

The study was approved by the institutional Review Board of Peking Union Medical College Hospital. Verbal informed consent was obtained from each patient and the parents of all participating children. All the parameters assessed were routinely obtained in this department at the time of the study. Researchers adhered to the principle of voluntary and autonomy of the participants, and paid attention to protect the privacy of participants.

### Population

A cross-sectional study of 1096 patients with autumn allergies was conducted (Figure 1). The participants comprised of children and adults (5–75 years old) from North China and had nasal allergies from July to October with/without asthma. A thorough medical history taken by senior allergists detailed their history of asthma, cough, allergic rhinitis and their parental history of allergies. The temporal sequence of allergic rhinitis and asthma and the use of asthma medications were reviewed. All participants underwent intradermal skin tests (IDT) to inhaled allergens (mite, mold, cat dander, spring pollen, autumn pollen, etc.), and sIgE tests to *Artemisia* and *Humulus*.

### Case selection

In order to control the possible synergistic effect of the other allergens, individuals with a positive IDT to other allergens such as mite, mold or cat dander were excluded. Individuals with a serum sIgE test negative to both *Artemisia* and *Humulus* were also excluded. Individuals who were included in the analysis also met the following criteria: repeated episodes of nasal itching, sneezing, rhinorrhea, congestion; the nasal symptoms almost occurred during the period from July to October; allergic to *Artemisia* and/or *Humulus* by serum sIgE tests;

without any other allergen identified for the episode of nasal symptoms by IDT.

### Definitions

*Artemisia* and/or *Humulus* were the common types of the autumn pollen. Participants were considered to have allergic rhinitis with *Artemisia* and/or *Humulus* exposure if they reported a history of nasal allergies with symptoms from July to October and had a negative IDT to perennial allergens such as mite, mold or cat dander, etc.

Asthma was defined by allergist in the 2001 cross-sectional survey when the participants had a history of recurrent dyspnoea, wheezing or cough episodes, positive airway reversibility testing (FEV1 increasing  $\geq 12\%$  and 200 mL after inhalation of 400 mg of salbutamol or treatment with inhaled glucocorticoid or anti-leukotriene drugs for 4–8 weeks) (10).

### Measurement of serum specific IgE

sIgE was measured using ImmunoCAP (Phadia AB, Uppsala, Sweden) as previously described (11). sIgE with a value of 0.35 kU/L or more (0.35–100 kU/L) were considered sIgE-positive. sIgE were divided into six degrees: Class 1: values  $\geq 0.35$ –0.7 kU/L, Class 2: values  $\geq 0.7$ –3.5 kU/L, Class 3: values  $\geq 3.5$ –17.5 kU/L, Class 4: values  $\geq 17.5$ –50 kU/L, Class 5: values  $\geq 50$ –100 kU/L, and Class 6: values  $\geq 100$  kU/L.

### Intradermal skin test (IDT)

IDT was performed with commercial allergen extracts (Xinhualian®, Beijing) according to a standard protocol. The experienced nurses performed the IDT and allergists read the IDT results. Intracutaneous tests were carried out with a battery of common aeroallergens (house dust, summer-autumn pollens I, polyvalent molds I, *Artemisia sieversiana*, spring pollen II, Dermatophagoides farina, polyvalent molds II, polyvalent molds III, *Sabina chinensis*, Cockroach, Cladosporium cladosporioides, cat hair, Fraxinus Americana, Kochia scoparia, Ailanthus altissima, Platanus acerifolia, *Humulus scandens*, *Alternaria alternata*). For positive and negative controls, we used histamine chlorhydrate at 10 mg/mL and 0.9% saline solution. Skin reactions were interpreted at 15 minutes after skin testing and found to be positive when the diameter of the wheal was  $> 5$  mm with local erythema. The following grading system was used according to Ye ST10: (1) wheal  $< 5$  mm and no or small erythema = negative; (2) wheal 5–10 mm and small erythema = 1+; (3) wheal 10–15 mm and erythema  $> 10$  mm = 2+ (4) wheal  $> 15$  mm and erythema  $> 10$  mm or with pseudopod formation = 3+; (5)

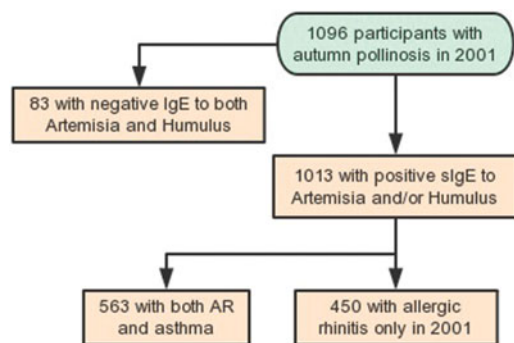


**Figure 1.** A schematic illustrates the enrollment and follow-up of participants in the study.

local response as grade 3+, accompanying with systemic allergic reaction = 4+.

### Statistical analysis

Categorical data were compared by using the  $\chi^2$  test. Logistic regression analysis was used to examine the effect of sIgE levels on the onset of asthma in patients with autumn pollen-induced allergic rhinitis. Models were adjusted for sex, age at onset of rhinitis, parental history of asthma. Odds ratios (OR) were estimated using the regression models and 95% confidence intervals (95% CI) were generated using a  $p$ -value of 0.05 as significant. Cumulative incidence was estimated using Kaplan–Meier survival probabilities. The timescale was number of years from age at the first allergic rhinitis to age at the first asthma attack, and for those without incident asthma, between the age at the first allergic rhinitis and age at presentation. All possible interactions between the explanatory variables were tested and were not significant. Proportional odds assumption was checked using the parallel lines test. The analysis was performed with SPSS version 13 (SPSS Inc., Chicago, IL, USA).

### Results

Based upon the asthma status of the 1013 participants with autumn pollinosis included in the statistics, 450 (44.4%) had allergic rhinitis alone, while 563 (55.6%) had both allergic rhinitis and asthma. Of the asthmatics, allergic rhinitis preceded asthma in 377 participants, allergic rhinitis occurred at the same time as asthma in 186 participants.

The participants with both allergic rhinitis and asthma were majorly found in autumn pollen season from July to October. Moreover, the frequencies showed remarkable

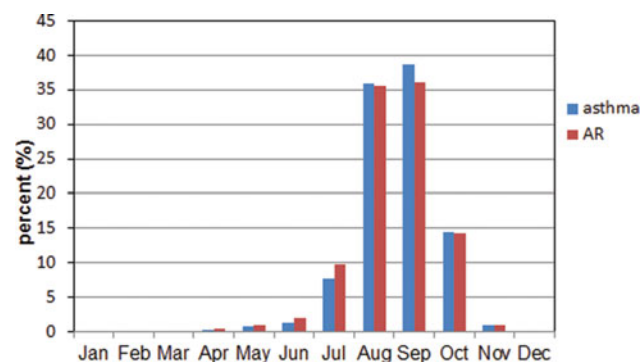


**Figure 2.** Involved months in patients who are allergic to autumn pollen.

consistency in the involved months in patients who are allergic to autumn pollen (Figure 2).

The mean age for the first allergic rhinitis was 27.79 (12.035) years and the mean age for the first asthma attack was 32.48 (12.525) years. A comparison of baseline characteristics between asthmatics and non-asthmatics was shown in Table 1. The age at the first allergic rhinitis and sex ratio were not significantly different between the two groups. Patients with AR alone were younger at the initial visiting our clinic than those with asthma (median, 36.7 vs 39.7 years;  $p < 0.001$ ). This allowed for the potential that those with AR alone might not have had time to develop asthma.

There is no significant difference between the two groups regarding periods with nasal symptoms in the fall. Smoking and the history of allergies (eczema or food allergy) were comparable between the two groups. Additionally, there was a strong cross-sectional association of parental asthma with asthma development ( $p < 0.05$ ).

*Humulus* sensitization frequency in asthmatic group was 68.7%, compared with 50.0% in nonasthmatic group ( $p < 0.05$ ). The prevalence of *Artemisia* sensitization was

**Table 1.** Baseline characteristics of participants with and without asthma. Abbreviations: AR, allergic rhinitis; OR, odds ratio; SD, standard deviation.

|                                          | AR with asthma (n = 563) | AR alone (n = 450) | crude OR estimates (95% confidence interval) |
|------------------------------------------|--------------------------|--------------------|----------------------------------------------|
| Age at onset of AR, year, mean (SD)      | 28.2(11.9)               | 27.3(12.2)         | 1.006(.996–1.017)                            |
| Age at visiting clinics, year, mean (SD) | 39.7(13.2)               | 36.7(13.7)         | 1.017(1.007–1.026)                           |
| Female, n (%)                            | 313(55.6%)               | 255(56.7%)         | .957(.746–1.229)                             |
| Smoking, n (%)                           | 50(8.9%)                 | 37(8.2%)           | 1.273(.802–2.021)                            |
| Eczema or food allergy, n (%)            | 115(20.4%)               | 74(16.4%)          | 1.304(.945–1.801)                            |
| Parental asthma, n (%)                   | 41(7.3%)                 | 17(3.8%)           | 2.001(1.121–3.572)                           |
| AR duration, day, mean (SD)              | 60.1(25.5)               | 59.7(41.1)         | 1.000(.997–1.004)                            |
| IgE to <i>Humulus</i> , n (%)            |                          |                    |                                              |
| 0                                        | 176 (31.3%)              | 225 (50.0%)        | 1.644 (1.445–1.870)                          |
| 1–2                                      | 119 (21.2%)              | 99 (22.0%)         |                                              |
| 3–4                                      | 189 (33.6%)              | 114 (25.3%)        |                                              |
| 5–6                                      | 79 (14.0%)               | 12 (2.7%)          |                                              |
| IgE to <i>Artemisia</i> , n (%)          |                          |                    |                                              |
| 0                                        | 107 (19.0%)              | 58 (12.9%)         | 1.032 (.907–1.174)                           |
| 1–2                                      | 79 (14.0%)               | 82 (18.2%)         |                                              |
| 3–4                                      | 239 (42.5%)              | 249 (55.3%)        |                                              |
| 5–6                                      | 138 (24.5%)              | 61 (13.6%)         |                                              |

81.0% in asthmatic group and 87.1% in nonasthmatic group but without significant difference.

Logistic regression showed that after controlling of sex, age at onset of allergic rhinitis, age at visiting clinics, duration of allergic rhinitis, smoking, eczema or food allergy, parental history of asthma, IgE sensitizations to *Humulus* and/or *Artemisia* were significantly associated with the onset of asthma in patients with autumn pollen-induced allergic rhinitis ( $p < 0.05$ ) (Table 2). The history of allergies and family history of asthma were also risk factors for asthma attacks ( $p < 0.05$ ).

The Kaplan–Meier model was then applied to analyze the relationship between the progression from allergic rhinitis to asthma and sIgE levels (Figures 3 and 4). In order to balance the interaction between *Humulus* and *Artemisia* pollen, the other pollen was stratified when one type of pollen was evaluated. Taking into account the sample size and avoiding excessive stratification, sIgE levels were represented as three degrees. For both *Humulus* and *Artemisia* pollen, a low level of sIgE represented

**Table 2.** Logistic regression of the effect of sIgE levels on the onset of asthma. Abbreviations: AR, allergic rhinitis; OR, odds ratio.

|                         | adjusted OR estimates (95% confidence interval) |
|-------------------------|-------------------------------------------------|
| Age at onset of AR      | .971 (.950–.993)                                |
| Age at visiting clinics | 1.048 (1.027–1.069)                             |
| Female                  | .969 (.742–1.265)                               |
| Smoking                 | 1.190 (.727–1.947)                              |
| Eczema or food allergy  | 1.430 (1.011–2.022)                             |
| Parental asthma         | 2.112 (1.149–3.883)                             |
| AR duration             | 1.000 (.996–1.003)                              |
| IgE to <i>Humulus</i>   | 1.872 (1.617–2.168)                             |
| IgE to <i>Artemisia</i> | 1.374 (1.176–1.604)                             |

a low probability of the coexistence of allergic rhinitis and asthma ( $p < 0.05$ ). A high sIgE level represented a high probability of the coexistence of allergic rhinitis and asthma ( $p < 0.05$ ).

Because of the influence of high IgE levels to *Artemisia* pollen, in participants with *Artemisia* pollen sIgE level 5–6, the different IgE levels to *Humulus* pollen did not show a significantly different association with the development from allergic rhinitis to asthma (Figure 3D).

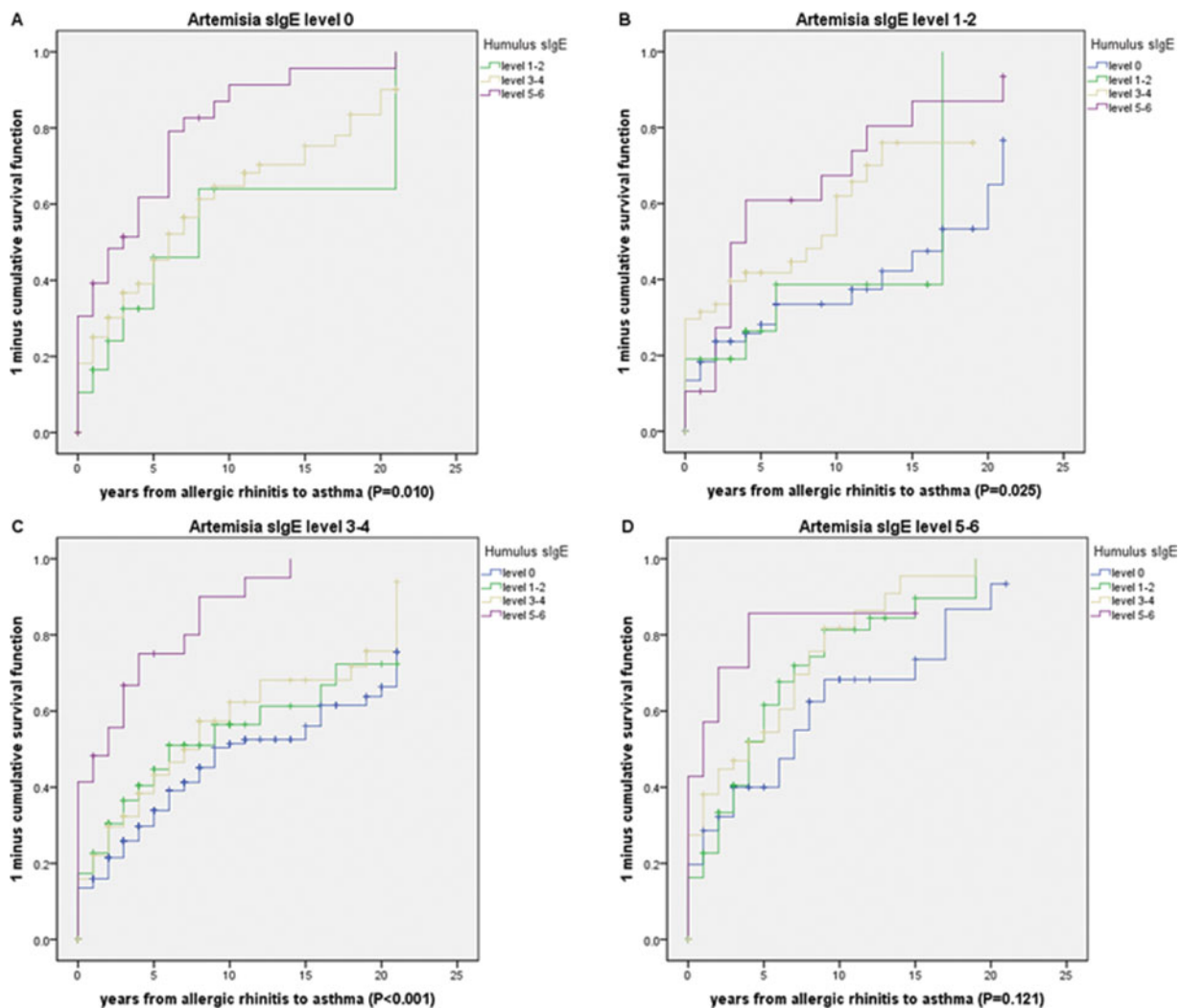


**Figure 3.** *Humulus* sIgE levels and probability from allergic rhinitis to asthma at a given *Artemisia* sIgE level of 0, 1–2, 3–4, 5–6 (A–D).

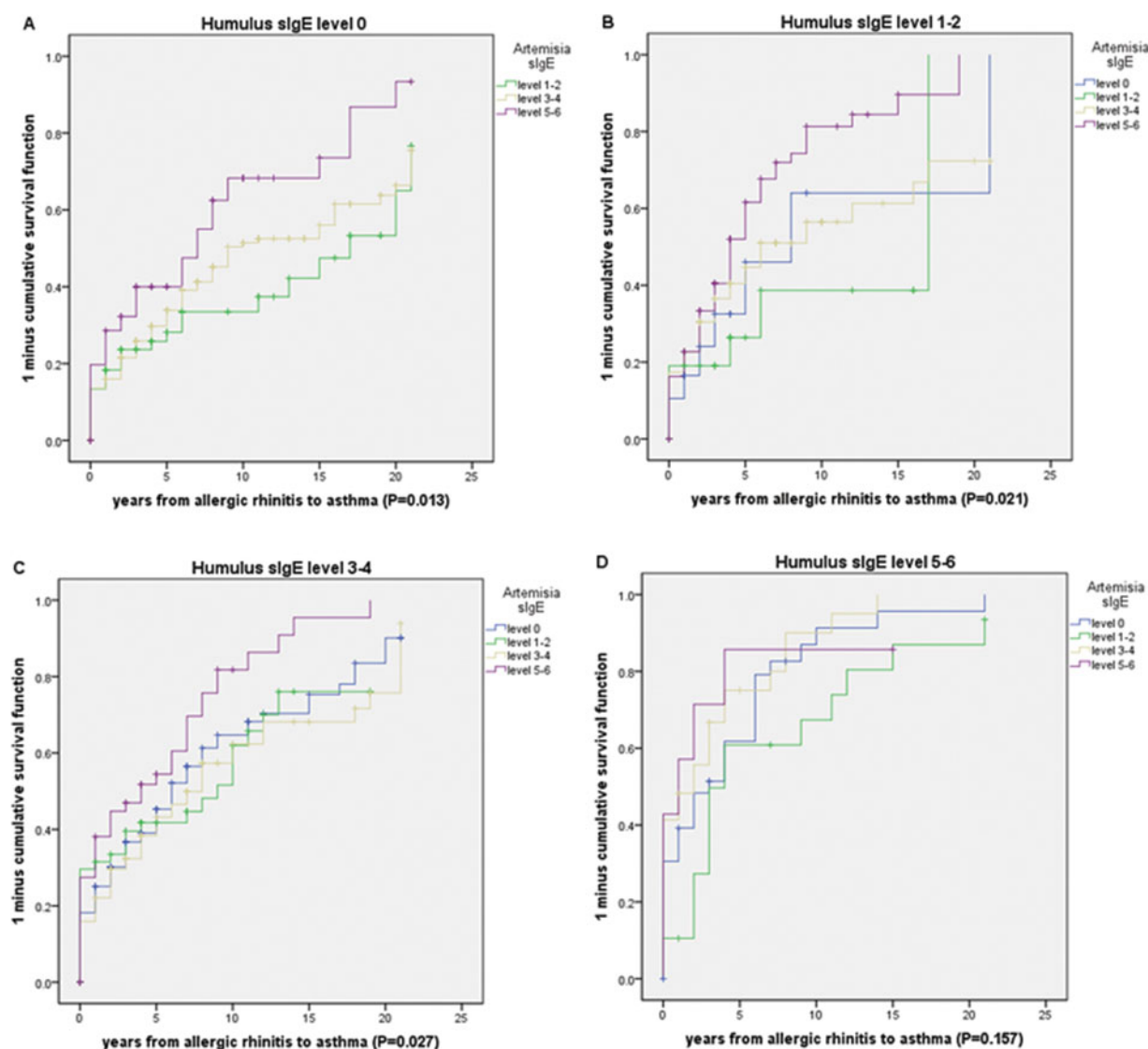


**Figure 4.** *Artemisia* sIgE levels and probability from allergic rhinitis to asthma at a given *Humulus* sIgE level of 0, 1–2, 3–4, 5–6 (A–D).

After stratification analysis of *Humulus* pollen, similar conclusions can also be drawn from *Artemisia* pollen (Figure 4D).

## Discussion

Asthma and rhinitis are often coexisting and share common risk factors, including atopy (12–14). In a previous study, we found that allergic rhinitis often preceded or occurred at the same time as asthma in patients with autumn allergies (4). Here, we further proposed that the incidence of asthma is more pronounced in autumn pollen-induced allergic rhinitis when the sIgE level was higher.

In North China, *Artemisia* pollen and *Humulus* pollen were the two most frequent and abundant pollen types of the total autumn pollen. In addition to *Artemisia* and *Humulus* found mostly in autumn, cypress pollen

(*Cupressaceae*) was also important sensitized pollens in spring (15). However, due to the short propagation time of cedar pollen in spring, the number of patients was relatively small. Therefore, we selected the patients with allergy to *Artemisia* and *Humulus*. In addition to pollen, the mite, mold and cat dander were also the potential allergic factors. Considering the crossing and complicated conditions caused by a variety of allergens, we excluded other allergens in allergic patients through the skin test in this study.

The respondents in this study were from the specialty practice in Peking Union Medical College Hospital. Therefore, the respondents were patients, who were different from those in general practice clinics. These patients had received treatment before they came to our hospital. Some of the patients came to our hospital because they were not satisfied with the treatments in the outside hospital. Therefore, it is understandable that the

numbers of patients with asthma were higher than those with simple rhinitis. Previous studies have shown that the level of serum sIgE was related to the severity of asthma (16,17), and we need to be alert because the severity of asthma was more severe in the asthmatic patients, which would influence the association between serum sIgE level and asthma attack. Of the 563 patients with asthma in this study, 152 (27%) had an acute exacerbation of asthma and needed emergency treatment. This ratio was lower than a previous survey in the Asia Pacific Region.

Quantitative detection of sIgE not only provides implication for the allergen type that the patient is sensitized to, but also assesses the risk of onset of a special allergic disease in the future (18,19). Within the context of a population-based birth cohort, Marinho et al showed that the probability of rhinitis/rhinoconjunctivitis increased with increasing levels of sIgE level (20). Also, the probability of wheeze and reduced lung function increases with increasing specific IgE antibody levels (21). Especially, sIgE level to house-dust mite might be a reliable biomarker for symptom severity in patients with AR (22).

In this study, patients with autumn pollen-induced allergic rhinitis were more likely to present with seasonal asthma when they had higher sIgE levels to *Humulus* and/or *Artemisia*. This association was also present after adjusting for sex, age at onset of allergic rhinitis, and parental history of asthma. Our study found that serum sIgE levels to autumn pollen sensitization were not only consistent with the current asthma status but also might be implicated in the progression from autumn pollen-induced allergic rhinitis to asthma. Inflammatory changes can be detected in both the upper and lower airways without indication of clinical symptoms (23). Allergic diseases are traditionally referred to as immediate or type 1 hypersensitivity reactions, with IgE antibodies as a critical factor (24,25).

Since IgE is involved in allergic inflammation (26), the systemic propagation of inflammation from the nasal to the bronchial mucosa is a possible explanation for the association of sIgE with asthma development in autumn pollen-induced allergic rhinitis. However, further studies are still needed to identify the possible mechanisms. Although we proposed a possibility that sIgE could be a biomarker for diagnosis of asthma in autumn pollen-induced allergic rhinitis. The exact level of sIgE was not standardized. Therefore, large population-based studies are required to further confirm this possibility.

*Humulus* pollen extract can successfully establish a type of mouse model of allergic pulmonary inflammation (27). Therefore, other environmental factors are not critical for *Humulus* pollen-induced allergy. However, other environmental factors might promote serum sIgE levels. For example, Paramesh revealed that the global and

climate change worsened the pollen allergies (28). As the limited sample size, it is difficult to obtain environmental data in all regions, and therefore we cannot investigate the influence of other environmental factors.

In conclusion, our study provides an indication for a role of sIgE in the progression from autumn pollen-induced allergic rhinitis to asthma. The retrospective finding of an association of sIgE levels to *Artemisia* and *Humulus* pollen with the coexistence of asthma and autumn pollen-induced allergic rhinitis raises the possibility that the link between allergic rhinitis and asthma might be a systemic propagation of inflammation.

## Author contributions

JY conceived and designed the study. LC analyzed the data and wrote the paper. JY and LC reviewed and edited the manuscript. All authors read and approved the manuscript.

## Acknowledgments

This work was supported by grants from National Epidemiology Study of Asthma and Allergies in China (200802001), CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-1-003). The sponsor or funding organization had no role in the design or conduct of this research. All authors contribute to this manuscript.

## Funding

This work was supported by grants from National Epidemiology Study of Asthma and Allergies in China (200802001), CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-1-003). The sponsor or funding organization had no role in the design or conduct of this research.

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