学位論文

小児アレルギー性鼻結膜炎の有症率と重症度に関連する因子の検討

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Factors associated with the prevalence and severity of childhood allergic rhinoconjunctivitis

第 1 編

Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren

Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren

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Short title: Impact of pollen exposure on allergic diseases in children

Abstract

Background: Patients allergic to pollen have been known to become more symptomatic during pollen season compared with the non-pollen season. However, there are few studies regarding whether higher exposure to pollen might increase the prevalence of allergic diseases.

Methods: An ecological analysis was conducted to evaluate whether pollen exposure is associated with the prevalence of allergic diseases in schoolchildren. Pollen count data of Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtusa*), which are the major pollen allergens in Japan, were obtained from each prefecture. The prevalence of allergic diseases in schoolchildren in each prefecture was based on a nationwide cross-sectional survey using the International Study of Asthma and Allergies in Childhood questionnaire.

Results: After omitting 3 prefectures where pollen data were not available, data of 44 prefectures were analysed. The prevalence of allergic rhinoconjunctivitis in children aged 6–7 years was positively associated with both cedar and cypress pollen counts (P = 0.01, both), whereas the prevalence of allergic rhinoconjunctivitis in children aged 13–14 years was positively associated with only cypress pollen counts (P = 0.003). Furthermore, the prevalence of asthma was positively associated with cedar pollen counts in 6- to 7-year-old children (P = 0.003) but not cypress pollen counts in either age group.

Conclusions: There are ecological associations between pollen counts and the prevalence of allergic diseases in Japanese schoolchildren. Further studies are needed to determine whether the difference between the effects of cedar and cypress pollens is attributable to pollen counts or allergenicity.

Introduction

Asthma and allergic rhinitis are the most common chronic diseases in childhood and impair the quality of life of the patients and their family [1,2]. The incidence of both disorders has increased dramatically worldwide in the last few decades [3]. However, the prevalence of allergic diseases varies widely throughout the world. The International Study of Asthma and Allergies in Childhood (ISAAC) showed that the prevalence of asthma and allergic rhinoconjunctivitis varies 20- to 40-fold in the world [4,5].

Pollens, along with climate and air pollutants, are among the environmental factors hypothesised to contribute to this variation [6]. In patients with allergic rhinitis, symptoms become more frequent and more severe when pollen counts increase [7,8]. Furthermore, patients with asthma require attendance at emergency departments and hospital admissions more frequently when the airborne pollen concentration is higher [9-12].

However, there are only a few studies evaluating the ecological associations between pollen counts and the prevalence of allergic diseases, and the results were inconsistent. Studies comparing the prevalence of allergic diseases between an area with higher pollen count and another with low pollen count showed that higher exposure to pollen was associated with a higher sensitisation rate in children [13] and prevalence of allergic rhinitis in adults [14,15]. By contrast, a large study performed in 28 centres within 11 countries showed that there was little relationship between pollen exposure and the prevalence of allergic symptoms in children [16]. This inconsistency may be attributable to geographical differences in the major pollen species and lifestyles of the study subjects. Ecological studies to evaluate this association for specific pollen exposure in a large homogeneous population are warranted.

Therefore, we performed an ecological analysis to evaluate whether there were associations between specific pollen counts (Japanese cedar and Japanese cypress) and the prevalence of allergic diseases in Japanese schoolchildren, using data on pollen counts and the prevalence of allergic diseases in each prefecture throughout Japan.

Methods

Study participants

The prevalence of allergic diseases in children aged 6–7 and 13–14 years in each prefecture was based on the data of a nationwide survey that was conducted throughout Japan in 2008; details of the methods and response rates have already been published [17]. In this survey, samples were randomly selected from all prefectures (n = 47) in Japan using public schools as the sampling units because more than 95% of schoolchildren attend public schools in Japan.

Questionnaire

The survey used the Japanese version of the written questionnaire of ISAAC, which was distributed by teachers at the participating schools [17]. The responses to the questions were reported by parents for children aged 6–7 years and were self-reported for children aged 13–14 years.

Allergic rhinoconjunctivitis was defined as positive answers to both of these questions: “In the past 12 months, have you (has your child) had a problem with sneezing, or a runny, or blocked nose when you (he/she) did not have a cold or the flu?” and “In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?” Asthma was defined as a positive answer to the question: “Have you (has your child) had wheezing or whistling in the chest in the last 12 months?”

Pollen and meteorological data

Japanese cedar (*Cryptomeria japonica*, family Taxodiaceae) and Japanese cypress (*Chamaecyparis obtusa*, family Cupressaceae) are the major causes of pollinosis in Japan. We used pollen data from the Association of Pollen Information in Japan. The cedar and cypress pollen counts were measured at observation facilities located in all prefectures except for Okinawa. Because a Durham’s sampler has been the most popular apparatus for measuring pollen counts in Japan, we omitted data from 2 prefectures in which the pollen counts were measured by different methods. The data from these 3 prefectures were excluded, and the data from the 44 remaining prefectures were included in the final analysis. The average values of the pollen counts per year over the past 4 years were used in this study because it may take time for children to become sensitised and develop allergic symptoms [8,18]. Meteorological data were obtained from the Japan Meteorological Agency (http://www.jma.go.jp/jma/indexe.html). The mean annual temperature and relative humidity measured at each prefectural capital in 2008 were used in this analysis.

Statistical analyses

Chi-square tests were used to assess whether the prevalence of allergic diseases differed between children included in this study and those who were excluded. The data for the 2 types of tree pollen and the 2 age groups were analysed separately. Associations between pollen counts and the prevalence of allergic rhinoconjunctivitis were determined using Pearson’s product-moment correlation coefficient. Multivariable regression analyses of the associations between pollen counts and the prevalence of allergic symptoms were adjusted for the gender ratio [17], mean annual temperature [19], and mean annual relative humidity [19]. The associations were analysed after adjustment for the pollen counts of other species as potential confounders, as cross-reactivity exists between cedar and cypress pollens [20]. The prevalence of allergic rhinoconjunctivitis was included as a confounder in the analyses of the associations between pollen counts and the prevalence of asthma because allergic rhinitis may affect asthma patients [21,22]. *P* values less than 0.05 were considered to indicate statistical significance. All analyses were performed using the statistical package SPSS for Windows version 19.

Ethics

The study protocol was approved by the independent review board of the National Center for Child Health and Development.

Results

Data were analysed in 44 prefectures, in which cedar and cypress pollen counts were measured separately, including 40,975 children aged 6–7 years and 45,787 children aged 13–14 years. The average values of cedar and cypress pollen counts in the 44 prefectures analysed were 2,967 counts/cm^2 (range, 34–7,912 counts/cm^2) and 1,245 counts/cm^2 (range, 1–6,048 counts/cm^2), respectively. Cedar pollen counts were higher in prefectures in eastern Japan (Fig. 1-A), and cypress pollen counts were higher in prefectures on the Pacific side than along the Sea of Japan (Fig. 1-B).

There was a wide range of the prevalence of allergic rhinoconjunctivitis (range, 8.1–29.2%) and asthma (range, 9.4–17.3%) between prefectures in the 6- to 7-year-old children. Similar to the 6- to 7-year-old children, the prevalence of allergic rhinoconjunctivitis ranged from 10.8% to 30.9% and that of asthma ranged from 6.1% to 13.2% in the 13- to 14-year-old children. The prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children was higher in prefectures in eastern Japan (Fig. 1-C), whereas the prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children was higher in prefectures on the Pacific side of eastern and central Japan (Fig. 1-D). Cedar pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children (R = 0.48, *P* = 0.001) (Fig. 2-A) but not in 13- to 14-year-old children (R = 0.18, *P* = 0.24) (Fig. 2-B). Cypress pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children (R = 0.43, *P* = 0.004) and 13- to 14-year-old children (R = 0.47, *P* = 0.001) (Fig. 2-C and D).

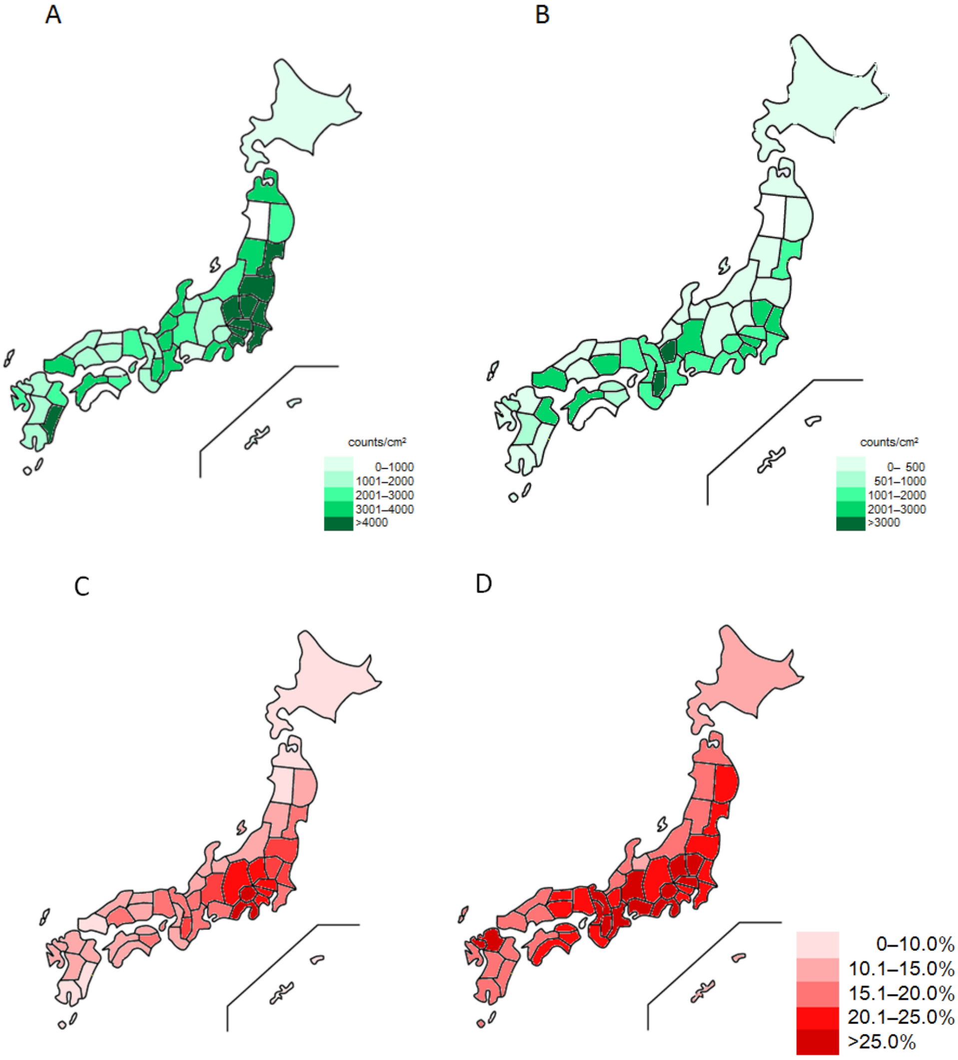
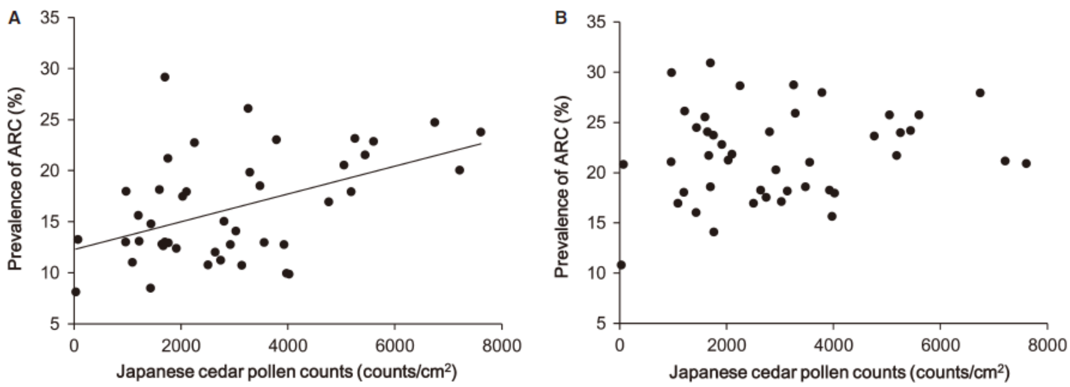


Figure 1 Maps of pollen counts and the prevalence of allergic rhinoconjunctivitis in Japan A: Japanese cedar pollen counts. B: Japanese cypress pollen counts. C: The prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children. D: The prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children



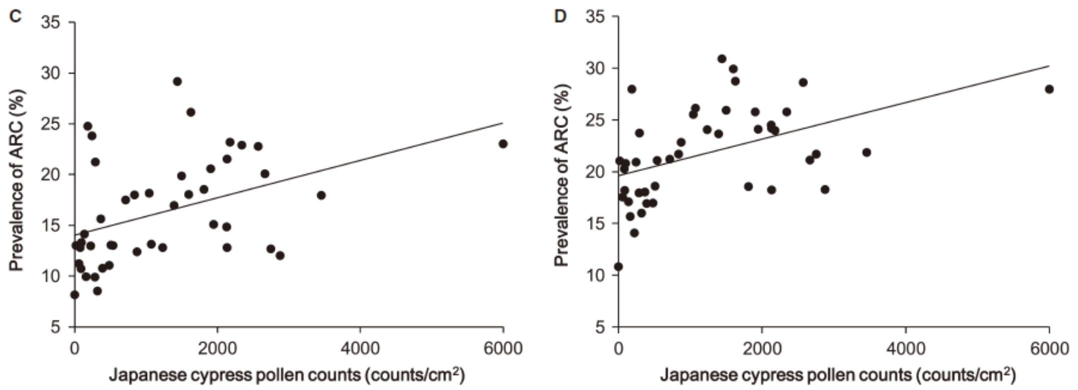


Figure 2 Pollen counts and the prevalence of allergic rhinoconjunctivitis (ARC).

A: Positive association between cedar pollen counts and the prevalence of ARC in 6- to 7-year-old children (R = 0.48, P = 0.001). B: No association between cedar pollen counts and the prevalence of ARC in 13- to 14-year-old children (R = 0.18, P = 0.24). C: Positive association between cypress pollen counts and the prevalence of ARC in 6- to 7-year-old children (R = 0.43, P = 0.004). D: Positive association between cypress pollen counts and the prevalence of ARC in 13- to 14-year-old children (R = 0.47, P = 0.001).

Even after adjustment for confounders, the prevalence of allergic rhinoconjunctivitis remained positively associated with cedar pollen counts for the 6- to 7-year-old children (P = 0.01) and cypress pollen counts for both the 6- to 7-year-old children and 13- to 14-year-old children (P = 0.01 and P = 0.003, respectively) (Table 1). Cedar pollen counts were not associated with the prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children after adjustment for confounders (P = 0.29).

Table 1 Associations between pollen counts and the prevalence of allergic diseases

	Japanese cedar		Japanese cypress	
	Coefficient (SE)	*P*-value	Coefficient (SE)	*P*-value
Allergic rhinoconjunctivitis				
6- to 7-year-old children	1.07 (0.39) *	0.01	1.49 (0.57) †	0.01
13- to 14-year-old children	0.34 (0.32) *	0.29	1.52 (0.49) †	0.003
Asthma				
6- to 7-year-old children	0.49 (0.16) ‡	0.003	-0.43 (0.23) §	0.07
13- to 14-year-old children	0.11 (0.15) ‡	0.46	0.04 (0.30) §	0.89

Coefficient is for each pollen count increment of 1000 counts/cm^2. SE = standard error.

*Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, and cypress pollen counts. †Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, and cedar pollen counts. ‡Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, cypress pollen counts, and prevalence of allergic rhinoconjunctivitis. §Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, cedar pollen counts, and prevalence of allergic rhinoconjunctivitis.

In general, the prevalence of allergic rhinoconjunctivitis was higher in 13- to 14-year-old children than in 6- to 7-year-old children. However, the difference between the 2 age groups was inversely associated with the prevalence of allergic rhinoconjunctivitis in the younger children (R = −0.52, $P < 0.001$) (Fig. 3-A). Therefore, we analysed the association between the pollen counts and the differences in the prevalence of allergic rhinoconjunctivitis between the 2 age groups. Differences in the prevalence of allergic rhinoconjunctivitis were inversely associated with cedar pollen counts (R = −0.50, $P = 0.001$) (Fig. 3-B) but not with cypress pollen counts (R = −0.28, $P = 0.86$) (Fig. 3-C).

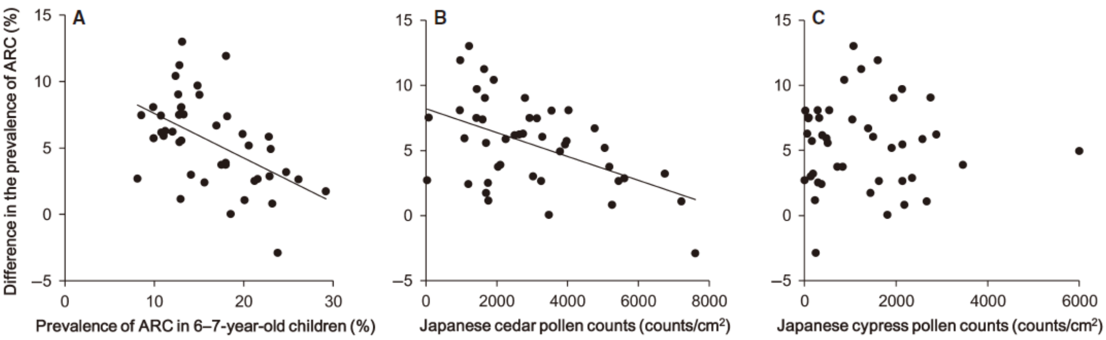


Figure 3 Differences in the prevalence of allergic rhinoconjunctivitis (ARC) between 6- to 7-year-old children and 13- to 14-year-old children.

A: Inverse association between the prevalence of ARC in 6- to 7-year-old children and the difference in the prevalence of ARC between the 2 age groups (R = −0.52, $P < 0.001$). B: Inverse association between cedar pollen counts and the difference in the prevalence of ARC between the 2 age groups (R = −0.50, $P = 0.001$). C: No association between cypress pollen counts and the difference in the prevalence of ARC between the 2 age groups (R = −0.03, $P = 0.86$)

We next analysed the associations between pollen counts and the prevalence of asthma (Table 1). After adjustment for confounders, cedar pollen counts were positively associated with the prevalence of asthma in 6- to 7-year-old children ($P = 0.003$) but not in 13- to 14-year-old children ($P = 0.46$). Cypress pollen counts were not associated with the prevalence of asthma in either age group ($P = 0.07$ for the 6- to 7-year-old children and $P = 0.89$ for the 13- to 14-year-old children).

Discussion

In this ecological study, we found a positive association between cedar and cypress pollen counts and the prevalence of allergic rhinoconjunctivitis and asthma in Japanese schoolchildren. Consistent with our finding, a study performed in Italian children aged 11–14 years revealed that children living in a high-pollen-count area showed a significantly higher percentage of sensitisation to pollens than those in another area with low pollen counts [13]. Similar results were shown in French adults [15] and the genetically homogeneous Inuit population [14], although their sample sizes were small. By contrast, an ecological study performed in 11 countries (9 European countries, Australia and Kuwait) revealed that there was little relationship between pollen exposure and the prevalence of allergic symptoms in children aged 13–14 years [16]. Inconsistency with our results might be explained by the geographical heterogeneity in the lifestyle of the study subjects [23,24] and the prevalence of plant species and their related allergens [25].

Cedar pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children but not in 13- to 14-year-old children. Although the prevalence of allergic rhinoconjunctivitis is generally higher in 13- to 14-year-old children than in 6- to 7-year-old children [5], the differences in the prevalence of allergic rhinoconjunctivitis between the 2 age groups were inversely associated with the cedar pollen counts. A retrospective analysis performed in the United States revealed that over 50% of children with allergic rhinitis were sensitised to at least one pollen by the age of 3 years and that the sensitisation rate increased with age and plateaued by the age of 8 years [18]. Together with our results, it is suggested that children in areas heavily exposed to cedar pollen might be sensitised to cedar pollen in early childhood, and the prevalence of allergic rhinoconjunctivitis might therefore plateau by the age of 6–7 years. By contrast, the prevalence of allergic rhinoconjunctivitis in less-exposed areas might not yet have plateaued by the age of 6–7 years and might thus continue to increase thereafter. Consequently, cedar pollen counts were not associated with the prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children.

Unlike cedar pollen counts, cypress pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children, and this positive association persisted in 13- to 14-year-old children. In Japan, cedar pollen counts are usually more than twice those of cypress. Therefore, the prevalence of allergic rhinoconjunctivitis due to cypress pollen might require additional time to reach a plateau than that caused by cedar pollen. The discrepancy between the results for cedar and cypress pollens may be attributable not only to differences in pollen counts but also to differences in antigenicity. T-cell reactivity differs between cedar and cypress pollens [26,27], although there is some cross-reactivity [20].

Cedar pollen counts were positively associated with the prevalence of asthma in 6- to 7-year-old children even after adjustment for confounders, including the prevalence of allergic rhinoconjunctivitis. Pollens may induce asthma symptoms independently of allergic rhinitis by 2 mechanisms. The first is inhalation of pollen allergens. Pollen grains are generally too large to penetrate the lower airway and, thus, do not provoke asthma symptoms. However, small particles of cedar pollen contain a major pollen allergen (Cry j 1) [28] and are likely to induce an asthma attack [29]. The second is that pollens may act as adjuvants to exacerbate asthmatic symptoms. Intranasal administration of ovalbumin with cedar pollen induced ovalbumin-specific IgE responses, although the administration of ovalbumin alone did not induce the production of ovalbumin-specific IgE [30]. Cedar pollen may thus enhance sensitisation to other allergens as well as pollen itself and thereby influence asthma in young children. The prevalence of asthma was not associated with cypress pollen counts. The reason for this discrepancy between cedar and cypress pollens remains unclear and warrants further investigation.

The strength of our study is that it addresses the associations between 2 types of tree pollen and the prevalence of allergic diseases in children in 2 different age groups. One limitation is that our study was a questionnaire-based survey without testing for sensitisation. Estimation of the prevalence of allergic rhinoconjunctivitis by a questionnaire only may be not very sensitive in young children [31]. However, sensitisation to any allergen is strongly associated with allergic rhinoconjunctivitis as assessed by the ISAAC questionnaire [32], and this questionnaire has previously been used for ecological analyses [6,16]. Another limitation is that we did not adjust our analysis for the levels of air pollutants, such as SPM, SO_2 and NO_X. Air pollutants can affect both allergic subjects [33] and the allergenicity of pollens [34]. The levels of these pollutants have been reported to be affected by the distance from major roads and the traffic count [35] and vary widely even within the same prefecture. Therefore, we did not include air pollutants as confounders in this analysis.

In conclusion, pollen counts of cedar and cypress are positively associated with the prevalence of allergic rhinoconjunctivitis and asthma in Japanese schoolchildren. Although both cedar and cypress pollens are tree pollens, they show different effects regarding the prevalence of allergic diseases. Further studies are required to elucidate the reason for this discrepancy.

Acknowledgments

We would like to thank all of the students and parents who participated in this survey. We are indebted to Mari Sasaki for critical reading of the manuscript.

Funding

This study was supported by a Health and Labour Sciences Research Grant for Research on Allergic Disease and Immunology from the Ministry of Health, Labour, and Welfare, Japan.

Author contributions

Koichi Yoshida analysed the data and wrote the paper. Yuichi Adachi and Akira Akasawa designed the study protocol and co-wrote the paper. Masayuki Akashi, Yukihiro Ohya and Hiroshi Odajima designed the study protocol. Toshiko Itazawa and Yoko Murakami analysed the data and discussed the results.

Conflict of interest

All authors declare that there are no conflicts of interest.

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第 2 編

Factors associated with the severity of childhood rhinoconjunctivitis

Factors associated with the severity of childhood rhinoconjunctivitis

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Abstract

Background: Allergic rhinitis is one of the most common chronic diseases in children. Although it has a large impact on the patient's quality of life, little is known about the factors associated with its severity. The aim of this study was to assess the factors associated with the severity of rhinoconjunctivitis among children in the general population.

Methods: A survey was conducted using an online research panel in 2012. Parents were asked to answer an International Study of Asthma and Allergies in Childhood-based questionnaire to identify children with current rhinoconjunctivitis and evaluate factors associated with the severity of its symptoms. Severity was rated according to the degree of impairment caused by the symptoms in the patient's daily life.

Results: Among 26,725 children aged 6 to 12 years old, rhinoconjunctivitis was defined in 5,175 (19.4%), and of these, 688 children (13.3% of children with current rhinoconjunctivitis) presented severe symptoms. Living in areas with a high cedar and cypress pollen count and having concurrent eczema were associated with severe rhinoconjunctivitis {adjusted OR (95% CI): 1.21 (1.00-1.46) and1.45 (1.20-1.75), respectively}. Further, a maternal history of asthma and allergic rhinitis was a significant risk factor for severe rhinoconjunctivitis {1.34 (1.04-1.74) and 1.30 (1.10-1.53), respectively}. However, living with fur-bearing animals (pets) before 1 year of age proved to be a protective factor against severe rhinoconjunctivitis {0.70 (0.52-0.94)}.

Conclusion: Environmental factors such as pets and pollen, together with comorbidities and a maternal history of allergic diseases, play an important role in determining the severity of rhinoconjunctivitis.

Introduction

Allergic rhinitis is characterized by rhinorrhea, sneezing, nasal obstruction, and nasal itching. It is frequently accompanied by ocular symptoms, collectively referred to as allergic conjunctivitis.[1] Most of the patients developed symptoms of allergic rhinitis before 20 years of age with 40% becoming symptomatic by the age of 6.[2] The International Study of Asthma and Allergies in Childhood (ISAAC) showed that the prevalence of current rhinoconjunctivitis in childhood has been on the rise in both developed and developing countries[3] with an average world-wide prevalence of 8.5% for 6-to-7-year old children and 14.6% for 13-to-14-year old children in Phase Three (1999-2004).[4]

Although allergic rhinitis and conjunctivitis have traditionally been considered nuisance diseases, recent studies have shown that they greatly affect quality of life, sleep quality, and cognitive function in adults and children[5-8] while also placing a considerable economic burden including direct and indirect costs.[8-10] Previously reported risk factors for childhood allergic rhinitis included the presence of asthma and food allergy, a familial history of allergic diseases, passive smoking, and living in an urban area.[11-13] However, in contrast to asthma, few studies have evaluated the factors affecting the severity of allergic rhinitis and conjunctivitis.[14, 15] Assessing the factors influencing the severity of childhood allergic rhinitis and conjunctivitis may lead to prevention or more effective treatment. We therefore analyzed these factors using a nation-wide, web-based survey.

Methods

Study design

A cross-sectional nation-wide survey was conducted using the Macromill online research system (MACROMILL, Inc. Tokyo, Japan), which maintains one of the largest research panels in Japan.[16] A total of 35,000 families with children aged 6 to 18 years were randomly selected from the research panel and asked to complete an online questionnaire from May to June, 2012. The questionnaire collected information about the general characteristics (such as age, sex, body weight, height, family history, and environmental factors) and the allergic symptoms of the respondents' children. The parents were asked to complete one questionnaire for each child in their family. In order to identify the factors influencing the severity of childhood rhinoconjunctivitis, children from 6 to 12 years of age were enrolled in this study.

The study protocol was approved by the independent review board of the Tokyo Metropolitan Children's Medical Center. All parents were provided with an online explanation of the purpose and the procedure of the study and gave informed consent before proceeding to the questionnaire.

Questionnaire and definitions

The questions used in the web-based survey were derived from the Japanese version of the ISAAC core questions for young children (6-7 years).[16, 17] According to the definition of the ISAAC,[4] the presence of current rhinoconjunctivitis can be established on the basis of positive answers to both of the following questions: 'In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' In children with current rhinoconjunctivitis, the severity of the condition was assessed on the basis of the response to the question: 'In the past 12 months, how much did this nose problem interfere with child's daily activities?' with 'a lot' indicating severe, and 'not at all,' 'a little,' and 'a moderate amount' indicating mild to moderate rhinoconjunctivitis. In children with current rhinoconjunctivitis, a 'perennial' symptom was defined as a symptom experienced by the patient for more than 9 months in a year.[2] History of pollinosis was established on the basis of the answer to the question: 'Has your child ever had pollinosis?'

Pollen data

The pollen counts for Japanese cedar and Japanese cypress, which are the major causes of pollinosis in Japan,[9, 18] were downloaded from a website of the Ministry of the Environment (http://www.env.go.jp/press/files/jp/18898.pdf). Exposure to these pollens was categorized into tertiles according to the average pollen count in each prefecture in 2012.

Statistical Analysis

For comparison, the chi-square test was used for categorical variables and the Mann-Whitney U test was used for continuous variables. Univariate and multivariate logistic regression analyses were used to assess the association between each variable and the severity of the disease. A p-value of <0.05 was considered statistically significant. All analyses were performed using the SPSS package version 19 (IBM Corp, Armonk, NY, USA).

Results

The prevalence of current and severe rhinoconjunctivitis

Among the 35,000 recruited families, 32,163 (49,096 children aged 6 to 18 years) responded to the survey (response rate, 91.9%) (Fig.1). After excluding incomplete data, 5,175 of the total of

26,725 children between 6 and 12 years of age had current rhinoconjunctivitis. A significant difference was detected between children with and without current rhinoconjunctivitis in terms of sex, age, birth weight, birth order, daycare attendance during infancy, pollen counts in the prefecture of residence, presence of current wheeze, presence of current eczema, and a familial history of allergic diseases (Table 1).

Table 1. Characteristics of children aged 6-12 years in a nation-wide survey

	Total (N=26725)		Children with CRC (N= 5175)		Children without CRC (N=21550)		p-value*
Sex (boys) (n, %)	13454	50.3	2744	53.0	10710	49.7	<0.01
Age (years) (mean +/- SD)		8.9+/-2.0		9.3+/-2.0		8.8+/-2.0	<0.01
Birth weight							
≥2500g (n, %)	23062	86.3	4513	87.2	18549	86.1	0.04
<2500g (n, %)	3663	13.7	662	12.8	3001	13.9	
Mode of birth delivery							
Vaginal delivery (n, %)	22402	83.8	4348	84.0	18054	83.8	0.69
Caesarean section (n, %)	4323	16.2	827	16.0	3496	16.2	
Birth order							
First child (n, %)	14951	55.9	3212	62.1	11739	54.5	<0.01
Subsequent child (n, %)	11774	44.1	1963	37.9	9811	45.5	
Breast-feeding							
Less than 6mo (n, %)	14560	54.5	2875	55.6	11685	54.2	0.09
More than 6mo (n, %)	12165	45.5	2300	44.4	9865	45.8	
Furry pet ownership							
No (n, %)	19724	73.8	3774	72.9	15950	74.0	0.23
From before age 1 (n, %)	2960	11.1	582	11.2	2378	11.0	
From after age 1 (n, %)	4041	15.1	819	15.8	3222	15.0	
Daycare during infancy (n, %)	2137	8.0	349	6.7	1877	8.3	<0.01
Paternal smoking (n, %)	7779	29.1	1489	28.8	6290	29.2	0.56
Maternal smoking (n, %)	2754	10.3	520	10.0	2234	10.4	0.51
Pollen counts in living area							
1st (≤1921 /mm^3) (n, %)	14704	55.0	2880	55.7	11824	54.9	<0.01
2nd (≥1928 ≤3128 /mm^3) (n, %)	5991	22.4	1011	19.5	4980	23.1	
3rd (≥3317 /mm^3) (n, %)	6030	22.6	1284	24.8	4746	22.0	
Current wheeze (n, %)	2902	10.9	947	18.3	1955	9.1	<0.01
Current eczema (n, %)	3573	13.4	1152	22.3	2421	11.2	<0.01

History of food allergy (n, %)	3076	11.5	1004	19.4	2072	9.6	<0.01
Obesity (≥ 95 percentile) (n, %)	2202	8.2	384	7.4	1818	8.4	0.02
Paternal history of allergy							
Asthma (n, %)	1886	7.1	451	8.7	1435	6.7	<0.01
Allergic rhinitis (n, %)	9489	35.5	2512	48.5	6977	32.4	<0.01
Atopic dermatitis (n, %)	1571	5.9	394	7.6	1177	5.5	<0.01
Maternal history of allergy							
Asthma (n, %)	1971	7.4	495	9.6	1476	6.8	<0.01
Allergic rhinitis (n, %)	9899	37.0	2859	55.2	7040	32.7	<0.01
Atopic dermatitis (n, %)	2347	8.8	591	11.4	1756	8.1	<0.01

CRC: current rhinoconjunctivitis. * Chi-square test was used to compare categorical variables and Mann-Whitney U test was used for continuous variables.

Among the 5,175 children with current rhinoconjunctivitis, 688 (13.3%), 439 (8.5%) and 3933 (76.0%) were assessed as having severe rhinoconjunctivitis, perennial symptoms, and a history of pollinosis, respectively. Sex was not significantly associated with severity (p=0.10). Perennial symptoms and a history of pollinosis were significantly associated with the severity of symptoms (p <0.01, both) (Table 2).

Table 2 Characteristics of children in this study

	Children with mild to moderate rhinoconjunctivitis (N=4487)		Children with severe rhinoconjunctivitis (N=688)		P-value*
Sex (boys) (n, %)	2359	52.6	385	56.0	0.10
Age (years) (mean +/- SD)		9.2+/-2.0		9.6+/-1.9	<0.01
Perennial symptoms (More than 9 mo. of the year) (n, %)	336	7.5	103	15.0	<0.01
History of pollinosis (n, %)	3320	74.0	613	89.1	<0.01

* Chi-square test was used comparing for categorical variables and Mann-Whitney U test was used for continuous variables.

Multivariate assessment of factors affecting severity

Low birth weight, mode of delivery, birth order, duration of breast feeding, passive smoking, and daycare attendance during infancy did not show any significant association with the severity of rhinoconjunctivitis (Table 3). Children who began living with fur-bearing animals (pets) before 1 year of age were significantly less likely to experience severe rhinoconjunctivitis than those who had not, demonstrating that fur-bearing pet ownership before 1 year of age was a significant protective factor according to the results of multivariate analysis (adjusted OR 0.70, 95%CI 0.52-0.94). On the other hand, univariate analysis showed that children who began living with furry pets after 1 year of age were significantly more likely to experience severe rhinoconjunctivitis than those who had never done so (p=0.04), but not after adjusting other study variables (adjusted OR 1.19, 95%CI 0.96-1.48). Children living in areas with a high cedar and cypress pollen count (≥ 3317 /mm^3) were significantly more likely to experience severe rhinoconjunctivitis than those living in areas with a low cedar and cypress pollen count (≤1921 /mm^3) (adjusted OR 1.21, 95%CI 1.00-1.46, p=0.048).

Multivariate analysis showed that severe rhinoconjunctivitis was significantly associated with the comorbidity of eczema (adjusted OR 1.45, 95%CI 1.20-1.75), but not with the comorbidity of wheeze. A maternal history of asthma and allergic rhinitis was an independent risk factor for severe rhinoconjunctivitis {adjusted OR (95% CI): 1.34 (1.04-1.74) and 1.30 (1.10-1.53), respectively}, although a paternal history of asthma and allergic rhinitis did not demonstrate a significant association with the severity of allergic rhinoconjunctivitis.

Table 3 Factors affecting the severity of rhinoconjunctivitis

	Children with severe RC							
	%	(n/N)	Crude OR	95% CI	p-value	aOR*	95% CI	p-value
Birth weight								
≥2500g	13.6	(612/4513)	1			1		
<2500g	11.5	(76/662)	0.83	0.64-1.07	0.14	0.85	0.65-1.10	0.21
Mode of birth delivery								
Vaginal delivery	13.5	(585/4348)	1			1		
Caesarean section	12.5	(103/827)	0.92	0.73-1.15	0.44	0.94	0.75-1.18	0.60
Birth order								
First child	13.0	(417/3212)	1			1		
Subsequent child	13.8	(271/1963)	1.07	0.91-1.27	0.40	1.04	0.88-1.23	0.64
Breast-feeding								
Less than 6mo	13.2	(379/2875)	1			1		
More than 6mo	13.4	(309/2300)	1.02	0.87-1.20	0.79	1.06	0.90-1.25	0.47
Furry pet ownership								
No	13.1	(496/3794)	1			1		
From before age 1	10.0	(56/562)	0.76	0.62-0.93	<0.01	0.70	0.52-0.94	0.02
From after age 1	16.6	(136/819)	1.36	1.02-1.81	0.04	1.19	0.96-1.48	0.11
Daycare during infancy								
No	13.2	(639/4826)	1			1		

Yes	14.0	(49/349)	1.07	0.78-1.46	0.67	1.05	0.76-1.44	0.78
Paternal smoking								
No	12.9	(475/3686)	1			1		
Yes	14.3	(213/1489)	1.13	0.95-1.34	0.17	1.09	0.90-1.31	0.39
Maternal smoking								
No	12.9	(602/4655)	1			1		
Yes	16.5	(86/520)	1.33	1.04-1.71	0.02	1.29	0.99-1.68	0.06
Pollen counts in living area								
1st (≤1921 /mm^3) (n, %)	12.8	(368/2880)	1			1		
2nd (1928–3128/mm^3) (n, %)	12.6	(127/1011)	0.98	0.79-1.22	0.86	0.95	0.77-1.19	0.66
3rd (≥3317 /mm^3) (n, %)	15.0	(193/1284)	1.21	1.00-1.46	0.049	1.21	1.00-1.46	0.048
Current wheeze								
No	13.1	(552/4228)	1			1		
Yes	14.4	(136/947)	1.12	0.91-1.37	0.29	1.04	0.84-1.28	0.76
Current eczema								
No	12.4	(498/4023)	1			1		
Yes	16.5	(190/1152)	1.40	1.17-1.68	<0.01	1.45	1.20-1.75	<0.01
Paternal asthma								
No	13.2	(622/4724)	1			1		
Yes	14.6	(66/451)	1.13	0.86-1.49	0.38	1.10	0.83-1.45	0.52
Paternal allergic rhinitis								
No	12.6	(336/2663)	1			1		
Yes	14.0	(352/2512)	1.13	0.96-1.33	0.14	1.13	0.96-1.34	0.13
Maternal asthma								
No	12.9	(604/4680)	1			1		
Yes	17.0	(84/495)	1.38	1.07-1.77	0.01	1.34	1.04-1.74	0.03
Maternal allergic rhinitis								
No	11.6	(268/2316)	1			1		
Yes	14.7	(420/2859)	1.32	1.12-1.55	<0.01	1.30	1.10-1.53	<0.01

RC: rhinoconjunctivitis   *Adjusted for sex, age, annual family income, obesity and all variables shown

Discussion

Our study demonstrated that several factors were associated with the severity of childhood rhinoconjunctivitis in the general population, a finding corroborated by other reports. A Spanish study demonstrated that children with severe rhinitis were more likely to suffer from conjunctivitis, asthma, and atopic dermatitis.[14] An Italian study of children recruited at a clinic showed that the severity of pollen-induced allergic rhinitis was associated with paternal smoking, having older siblings, asthma, and oral allergy syndrome, but not with a familial history of allergic diseases.[15] Our study discovered that environmental factors such as exposure to furry pets in infancy and the pollen count in the area of residence were associated with the severity of childhood rhinoconjunctivitis.

Pollen is one of the major environmental factors influencing allergic diseases. Japanese cedar and Japanese cypress are major causes of pollinosis in Japan, where more than 90% of pollinosis patients experience moderate to severe rhinitis according to ARIA.[19] We have reported that cedar and cypress pollen counts were positively associated with the prevalence of current rhinoconjunctivitis among Japanese school children.[18] In this study we showed that 89.1% children with severe rhinoconjunctivitis had a history of pollinosis. Although generally, not much data are available regarding the association of pollen exposure with the severity of rhinitis and/or conjunctivitis, the present study has shown that cedar and cypress pollen counts were associated with the severity of rhinoconjunctivitis among children in Japan. An Italian study of children with pollen-induced allergic rhinitis showed that children in Central and Southern Italy experienced a higher frequency of moderate to severe rhinitis and were more frequently sensitized to olive, cypress, and pellitory pollens than those in Northern Italy.[15] Pollens might affect the severity of rhinitis and/or conjunctivitis in many regions of the world.

By contrast, exposure to fur-bearing pets, which are also one of the major environmental factors influencing allergic diseases, was found to be a protective factor against severe rhinoconjunctivitis. However, our study showed no significant association between the presence of current rhinoconjunctivitis and the ownership of furry pets, a finding that accords with the result of a pooled analysis from 11 European birth cohorts.[20] A Dutch study showed that exposure to pets in the first two years of life was not associated with the development of current rhinitis or hay fever , but was inversely associated with sensitization to outdoor allergens in school-age children.[21] Pet ownership in infancy may not influence the development of rhinoconjunctivitis, but be a protective factor against sensitization to pollens leading to the reduced severity of rhinoconjunctivitis.

The severity of symptoms was significantly associated with a history of asthma and allergic rhinitis in the child’s mother, but not the father. A few studies have reported on the differences between the effect of maternal and paternal allergic diseases on children’s allergic rhinitis. The results of the Tucson children’s respiratory study showed that a maternal history of physician-diagnosed allergic diseases only affected children’s physician-diagnosed allergic rhinitis at 6 years of age.[22] In contrast, the Isle of Wight birth cohort study showed that paternal, but not maternal, rhinitis was significantly associated with childhood rhinitis at all ages.[23] An Italian study showed that the severity of pollen-induced allergic rhinitis among children was not associated with either a paternal or maternal history of allergic diseases.[15] The differences in these parental effects might be traceable to genetic or epigenetic factors associated with prenatal and postnatal environments. Further studies are needed to clarify the effect of parental allergic diseases on the severity of childhood allergic rhinoconjunctivitis.

This survey previously showed that the severity of rhinitis was associated with asthma control in patients with both current asthma and rhinitis.[16] However, the results of this analysis showed that the severity of rhinoconjunctivitis was not significantly associated with current wheeze. Whether the severity of rhinitis is associated with allergic comorbidities in patients with allergic rhinitis is still debated. An Italian survey[24] and a population-based study in six Western Europe countries[25] have showed no association between the severity of rhinitis and concomitant asthma similar to our results, whereas some studies have reported a significant association between the two conditions.[14 26 27] The differences in the results of these studies might be explained by the characteristics of the study subjects and the analytical methodology used, such as the definition of the severity of rhinitis and cofounders. On the other hand, the results of our analysis showed that the severity of rhinoconjunctivitis was significantly associated with current eczema, which was in line with a Spanish study.[14] This association in our study might be due to the high proportion of children with pollinosis among those with severe rhinoconjunctivitis, since Japanese cedar pollen is an exacerbation factor for allergic skin diseases in patients with Japanese cedar pollinosis.[28, 29]

Our study may have suffered from some limitations. The definition of allergic disease and the assessment of the severity of rhinoconjunctivitis were based on parental reports without sensitization testing or treatments for rhinitis and conjunctivitis. Although the definition of current rhinoconjunctivitis based on the ISAAC questionnaire was strongly associated with sensitization to allergens in general[30], the severity of rhinoconjunctivitis might have been influenced by sensitization to the allergens and the treatments. Furthermore, the differences between the factors associated with the severity of rhinoconjunctivitis in children with and without pollinosis were not analyzed, because almost all children with severe rhinoconjunctivitis had a history of pollinosis. The strengths of our study were the large sample size and the high response rate among the general population. The latter in particular was assisted by the use of the web-based ISAAC questionnaire, which enabled easy access to a broad cross-section of the population. Furthermore, previous studies comparing the web-based ISAAC questionnaire with its written version have reported that both approaches yielded equal results and reliability.[17, 31] These merits justified the use of the questionnaire in our study.

In conclusion, the severity of childhood rhinoconjunctivitis in the general population was affected by environmental factors along with a familial history of allergic diseases and comorbidities. Further understanding of these risks and protective factors may lead to the discovery of new interventions aimed at managing the disease and improving the quality of life of patients and their caregivers.

Acknowledgments

The authors thank the parents and children for their participation in this survey. We are indebted to James R. Valera for his critical reading of the manuscript. This study was supported by the Health and Labour Sciences Research Grant for Research on Allergic Disease and Immunology from the Ministry of Health, Labour and Welfare, Japan.

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