Allergology International 65 (2016) 166–171

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original article

Factors associated with the severity of childhood rhinoconjunctivitis

Koichi Yoshida [a, *], Mari Sasaki [a], Yuichi Adachi [b], Toshiko Itazawa [b], Hiroshi Odajima [c], Hirohisa Saito [d], Akira Akasawa [a]

[a] Division of Allergy, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan
[b] Department of Pediatrics, University of Toyama, Toyama, Japan
[c] Department of Pediatrics, Fukuoka National Hospital, Fukuoka, Japan
[d] Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan

ARTICLE INFO

Article history:
Received 9 July 2015
Received in revised form
18 October 2015
Accepted 19 October 2015
Available online 29 November 2015

Keywords:
Allergic conjunctivitis
Allergic rhinitis
Pets
Pollen
School-aged children

Abbreviations:
ISAAC International Study of Asthma and Allergies in Childhood

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 6–12 years old, rhinoconjunctivitis was defined in 5175 (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) and 1.45 (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)].

Conclusions: 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 nationwide, web-based survey.

* Corresponding author. Tokyo Metropolitan Children's Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8561, Japan.
E-mail address: kouichi_yoshida@tmhp.jp (K. Yoshida).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.10.006

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 6–18 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 6–18 years) responded to the survey (response rate, 91.9%) (Fig. 1).

After excluding incomplete data, 5175 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). Among the 5175 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).

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 ($\geq$3317/mm^3) were significantly more likely to experience severe rhinoconjunctivitis than those living in areas with a low cedar and cypress pollen count ($\leq$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

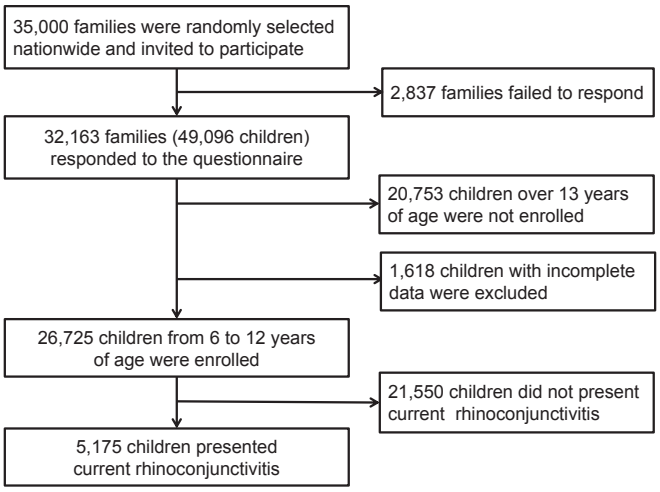

Fig. 1. Flow chart of the study subject.

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

	Total (N = 26,725)		Children with CRC (N = 5175)		Children without CRC (N = 21,550)		*p*-value*
Sex (boys) (n, %)	13,454	50.3	2744	53.0	10,710	49.7	<0.01
Age (years) (mean ± SD)	8.9 ± 2.0		9.3 ± 2.0		8.8 ± 2.0		<0.01
Birth weight							
≥2500 g (n, %)	23,062	86.3	4513	87.2	18,549	86.1	0.04
<2500 g (n, %)	3663	13.7	662	12.8	3001	13.9	
Mode of birth delivery							
Vaginal delivery (n, %)	22,402	83.8	4348	84.0	3496	16.2	0.69
Caesarean section (n, %)	4323	16.2	827	16.0	18,054	83.8	
Birth order							
First child (n, %)	14,951	55.9	3212	62.1	11,739	54.5	<0.01
Subsequent child (n, %)	11,774	44.1	1963	37.9	9811	45.5	
Breast-feeding							
Less than 6mo (n, %)	14,560	54.5	2875	55.6	11,685	54.2	0.09
More than 6mo (n, %)	12,165	45.5	2300	44.4	9865	45.8	
Furry pet ownership							
No (n, %)	19,724	73.8	3774	72.9	15,950	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, %)	14,704	55.0	2880	55.7	11,824	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.

(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.

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 Allergic Rhinitis and its Impact on Asthma.[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, there was 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

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.

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

Table 3
Factors affecting the severity of rhinoconjunctivitis.

	Children with severe RC % (n/N)	Crude OR	95% CI	p-value	Adjusted OR†	95% CI	*p*-value
Birth weight							
≥2500 g	13.6 (612/4513)	1			1		0.21
<2500 g	11.5 (76/662)	0.83	0.64–1.07	0.14	0.85	0.65–1.10	
Mode of birth delivery							
Vaginal delivery	13.5 (585/4348)	1			1		0.60
Caesarean section	12.5 (103/827)	0.92	0.73–1.15	0.44	0.94	0.75–1.18	
Birth order							
First child	13.0 (417/3212)	1			1		0.64
Subsequent child	13.8 (271/1963)	1.07	0.91–1.27	0.40	1.04	0.88–1.23	
Breast-feeding							
Less than 6mo	13.2 (379/2875)	1			1		0.47
More than 6mo	13.4 (309/2300)	1.02	0.87–1.20	0.79	1.06	0.90–1.25	
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		0.78
Yes	14.0 (49/349)	1.07	0.78–1.46	0.67	1.05	0.76–1.44	
Paternal smoking							
No	12.9 (475/3686)	1			1		0.39
Yes	14.3 (213/1489)	1.13	0.95–1.34	0.17	1.09	0.90–1.31	
Maternal smoking							
No	12.9 (602/4655)	1			1		0.06
Yes	16.5 (86/520)	1.33	1.04–1.71	0.02	1.29	0.99–1.68	
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		0.76
Yes	14.4 (136/947)	1.12	0.91–1.37	0.29	1.04	0.84–1.28	
Current eczema							
No	12.4 (498/4023)	1			1		<0.01
Yes	16.5 (190/1152)	1.40	1.17–1.68	<0.01	1.45	1.20–1.75	
Paternal asthma							
No	13.2 (622/4724)	1			1		0.52
Yes	14.6 (66/451)	1.13	0.86–1.49	0.38	1.10	0.83–1.45	
Paternal allergic rhinitis							
No	12.6 (336/2663)	1			1		0.13
Yes	14.0 (352/2512)	1.13	0.96–1.33	0.14	1.13	0.96–1.34	
Maternal asthma							
No	12.9 (604/4680)	1			1		0.03
Yes	17.0 (84/495)	1.38	1.07–1.77	0.01	1.34	1.04–1.74	
Maternal allergic rhinitis							
No	11.6 (268/2316)	1			1		<0.01
Yes	14.7 (420/2859)	1.32	1.12–1.55	<0.01	1.30	1.10–1.53	

RC, rhinoconjunctivitis.
† Adjusted for sex, age, annual family income, obesity and all variables shown.

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 (H22-Men'eki-Ippan-006), Japan.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

KY and YA contributed to the design, data analyses, and drafted the manuscript. MS analyzed data and drafted the manuscript. TI, HO, HS, and AA were involved in study conception and data interpretation. All authors approved the manuscript.

References

1. Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol* 2011;**11**:471–6.
2. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;**108**:S2–8.
3. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–43.
4. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;**64**:123–48.
5. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, Sheth KK, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 2009;**124**:S43–70.
6. Meltzer EO, Nathan R, Derebery J, Stang PE, Campbell UB, Yeh WS, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 2009;**30**:244–54.
7. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007;**62**(Suppl 85):17–25.
8. Pitt AD, Smith AF, Lindsell L, Voon LW, Rose PW, Bron AJ. Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. *Ophthalmic Epidemiol* 2004;**11**:17–33.
9. Yamada T, Saito H, Fujieda S. Present state of Japanese cedar pollinosis: the national affliction. *J Allergy Clin Immunol* 2014;**133**:632–9. e5.
10. Blaiss MS. Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc* 2010;**31**:375–80.
11. Zhang YM, Zhang J, Liu SL, Zhang X, Yang SN, Gao J, et al. Prevalence and associated risk factors of allergic rhinitis in preschool children in Beijing. *Laryngoscope* 2013;**123**:28–35.
12. Saulyte J, Regueira C, Montes-Martinez A, Khudyakov P, Takkouche B. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. *PLoS Med* 2014;**11**:e1001611.
13. Morais-Almeida M, Santos N, Pereira AM, Branco-Ferreira M, Nunes C, Bousquet J, et al. Prevalence and classification of rhinitis in preschool children in Portugal: a nationwide study. *Allergy* 2013;**68**:1278–88.
14. Ibanez MD, Valero AL, Montoro J, Jauregui I, Ferrer M, Davila I, et al. Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain. *Pediatr Allergy Immunol* 2013;**24**:678–84.
15. Dondi A, Tripodi S, Panetta V, Asero R, Businco AD, Bianchi A, et al. Pollen-induced allergic rhinitis in 1360 Italian children: comorbidities and determinants of severity. *Pediatr Allergy Immunol* 2013;**24**:742–51.
16. Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H, et al. Factors associated with asthma control in children: findings from a national Web-based survey. *Pediatr Allergy Immunol* 2014;**25**:804–9.
17. Yoshida K, Adachi Y, Sasaki M, Furukawa M, Itazawa T, Hashimoto K, et al. Test-retest reliability of the International Study of Asthma and Allergies in Childhood questionnaire for a web-based survey. *Ann Allergy Asthma Immunol* 2014;**112**:181–2.
18. Yoshida K, Adachi Y, Akashi M, Itazawa T, Murakami Y, Odajima H, et al. Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren. *Allergy* 2013;**68**:757–63.
19. Gotoh M, Yuta A, Okano M, Ohta N, Matsubara A, Okubo K. Severity assessment of Japanese cedar pollinosis using the practical guideline for the management of allergic rhinitis in Japan and the allergic rhinitis and its impact on asthma guideline. *Allergol Int* 2013;**62**:181–9.
20. Lodrup Carlsen KC, Roll S, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One* 2012;**7**:e43214.
21. Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen NA, van Vliet P. Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy* 2002;**32**:361–6.
22. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;**94**:895–901.
23. Arshad SH, Karmaus W, Raza A, Kurukulaaratchy RJ, Matthews SM, Holloway JW, et al. The effect of parental allergy on childhood allergic diseases depends on the sex of the child. *J Allergy Clin Immunol* 2012;**130**:427–34. e6.

24. Antonicelli L, Micucci C, Voltolini S, Feliziani V, Senna GE, Di Blasi P, et al. Allergic rhinitis and asthma comorbidity: ARIA classification of rhinitis does not correlate with the prevalence of asthma. *Clin Exp Allergy* 2007;**37**:954–60.
25. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;**60**:350–3.
26. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 2005;**35**:728–32.
27. Higuchi O, Adachi Y, Itazawa T, Ito Y, Yoshida K, Ohya Y, et al. Rhinitis has an association with asthma in school children. *Am J Rhinol Allergy* 2013;**27**:e22–5.
28. Yokozeki H, Satoh T, Katayama I, Nishioka K. Airborne contact dermatitis due to Japanese cedar pollen. *Contact Dermatitis* 2007;**56**:224–8.
29. Murakami Y, Matsui S, Kijima A, Kitaba S, Murota H, Katayama I. Cedar pollen aggravates atopic dermatitis in childhood monozygotic twin patients with allergic rhino conjunctivitis. *Allergol Int* 2011;**60**:397–400.
30. Braun-Fahrlander C, Wuthrich B, Gassner M, Grize L, Sennhauser FH, Varonier HS, et al. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. *Pediatr Allergy Immunol* 1997;**8**:75–82.
31. Raat H, Mangunkusumo RT, Mohangoo AD, Juniper EF, Van Der Lei J. Internet and written respiratory questionnaires yield equivalent results for adolescents. *Pediatr Pulmonol* 2007;**42**:357–61.