surveys for allergic diseases. A national Web-based survey administered in the United States in 2007 assessed 1812 adult patients with moderate-to-severe asthma and reported that 55% had uncontrolled disease in a real-world setting (5).

The aim of this study was to evaluate the factors associated with uncontrolled paediatric asthma in the general population using a Web-based survey.

Methods

Study population and participation

This study was conducted using the Macromill online research system (MACROMILL, Inc. Tokyo, Japan), which maintains one of the largest research panels in Japan.

In June 2012, we conducted the primary survey among parents with at least one child aged 6–18 yr to evaluate the prevalence of allergic diseases. Parents filled in an online questionnaire regarding the child's general characteristics (such as age, sex, body weight, height, family history and other environmental factors) and whether the child had symptoms of allergic diseases. This survey consisted of the ISAAC (International Study of Asthma and Allergies in Childhood) core questionnaire module for wheeze, eczema and rhinitis (13). If a parent had two or more children satisfying this condition, they completed the questionnaire for each child.

We sampled children defined as asthma by the questionnaire of the primary survey and conducted the secondary survey among them using a questionnaire regarding the child's medication and symptoms. Because this was completed by a parent, we used the official Japanese version of the Childhood Asthma Control Test (C-ACT), which consists of four questions for the child and three questions for the caregiver, and scores range from 0 (poorest asthma control) to 27 (optimal asthma control). C-ACT has been developed and validated for children and their caregivers to answer to assess the level of asthma control for those aged 4–11 yr (14). Thus, 6- to 11-yr-old children were included in the current analysis.

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 by proceeding to the questionnaire.

Definitions and classifications

The definitions used in this study are presented in Table 1. Current asthma was defined based on the ISAAC questionnaire and the use of medication for wheezing symptoms. A C-ACT score of 19 or less was classified as uncontrolled asthma (14). Current eczema, history of eczema, current rhinitis and the severity of rhinitis were defined according to the ISAAC questionnaire. History of food allergy was assessed by whether the child ever had a doctor diagnosis or was suspected of having this disease.

The child's body mass index (BMI) was categorized according to the reference BMI values for Japanese children (15). Children who were at the 95th percentile or more were defined as obese. Birthweight of <2500 g was defined as low birthweight (LBW).

Statistical analysis

All analyses were performed using the SPSS package version 21 (IBM Corp, Armonk, NY, USA). For comparison, unpaired t-tests were used for continuous variables; chi-square tests were used for categorical valuables. Univariable logistic regression analysis was used to assess the association between each variable and asthma control. Variables were further analysed by multiple logistic regressions. All study variables were forced into the model. We used the Jonckheere–Terpstra test to assess

Table 1 Definitions of the variables included in the study

Variable	Definition
Current asthma	Positive response to the question 'Has your child ever had wheezing in the chest in the past 12 months'? or 'Has your child been prescribed daily medication for wheezing symptoms in the past 4 wk'?
Uncontrolled asthma	Current asthma with C-ACT score of 19 or less
Current eczema	Positive response to these two questions 'Has your child had this itchy rash at any time in the past 12 months'? and 'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes'?
History of eczema	Positive response to the question 'Has your child ever had atopic dermatitis'?
Current rhinitis	Positive answer to the question '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'?
Mild to moderate rhinitis	Current rhinitis with answering 'not at all', 'a little', 'a moderate amount' to the question 'In the past 12 months, how much did this nose problem interfere with your child's daily activity'?
Severe rhinitis	Current rhinitis with answering 'a lot' to the question 'In the past 12 months, how much did this nose problem interfere with your child's daily activity'?
History of food allergy	Positive answer to the question 'Has a doctor ever said the child had food allergy or the suspect of food allergy'?
Obese	Body mass index (BMI) at the 95th percentile or more
Low birthweight (LBW)	Birthweight of <2500 g

trends for continuous variables. A p-value of <0.05 was considered statistically significant.

Results

Among the 35,000 parents, 32,163 (91.9%) responded to the primary survey for 49,096 children. The primary survey showed that the prevalence of current asthma among 6 to 18 yr old Japanese children was 9.8%, and 3231 children were aged 6 to 11. Responses to the secondary survey were collected for 3066 children, constituting a 94.9% response rate (Fig. 1).

Uncontrolled asthma was found in 14.6% children with current asthma. Patients with well-controlled asthma and uncontrolled asthma were not significantly different with regard to sex and age. The proportion of children using inhaled corticosteroids was 16.6% and 46.1% in the well-controlled asthma and the uncontrolled asthma groups, respectively (Table 2).

Table 3 shows the relationship of each study variable and asthma control. Children with low birthweight were significantly more likely to have uncontrolled asthma and were at risk even after adjusting for other study variables (adjusted OR 1.65, 95% CI 1.25–2.18). Day care attendance during infancy and breastfeeding for at least 6 months did not show significant differences in the two groups. Annual income and paternal education were not significantly different, although maternal education level showed statistical significance in relationship with asthma control in the multivariable analysis (adjusted OR 1.33, 95% CI 1.02–1.73). Maternal smoking (adjusted OR 1.42, 95% CI 1.02–1.97), though not paternal smoking, was an independent risk factor for uncontrolled disease.

Pet ownership had a significant relationship with asthma control depending on when it started. Pet ownership from before birth (adjusted OR 1.68, 95% CI 1.24–2.29) and before 12 months of age (adjusted OR 5.50, 95% CI 2.16–14.05) were both indicated as significant risk factors for uncontrolled asthma. Obesity was also a risk factor for uncontrolled disease (adjusted OR 1.44, 95% CI 1.05–1.99).

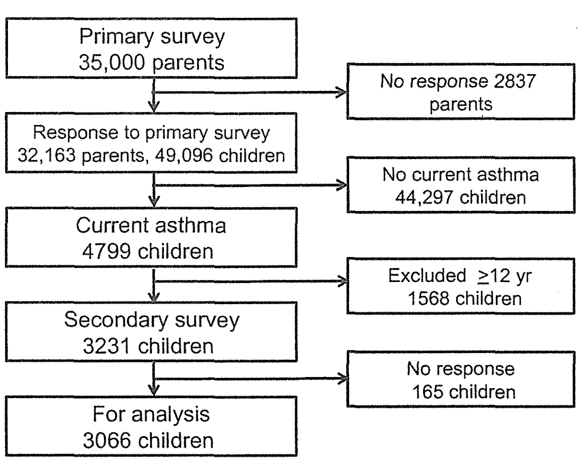

Figure 1 Flow chart of the study subjects.

Table 2 Characteristics of the respondents of the secondary survey

	Total (n = 3066)	Controlled asthma (n = 2619)	Uncontrolled asthma (n = 447)	p value
Age (Y)				
Mean ± s.d.	8.00 ± 1.69	8.00 ± 1.69	8.00 ± 1.68	0.97
Sex				
Male	1818	1554 (59.3%)	264 (59.1%)	0.91
Female	1248	1065 (40.7%)	183 (40.9%)	
Controller medication				
ICS use	641	435 (16.6%)	206 (46.1%)	<0.01
LTRA use	554	425 (16.2%)	129 (28.9%)	
β-stimulant only	221	176 (6.1%)	45 (10.1%)	
None	1650	1583 (60.4%)	67 (15.0%)	

ICS use: inhaled corticosteroid alone or in combination with other medication. LTRA use: leukotriene modifiers only or in combination with medication other than ICS. None: no medication or use of medication other than LTRA, ICS, β-stimulant.

Comorbidities, such as current rhinitis, history of eczema and history of food allergy, were each individually associated with uncontrolled asthma ($p < 0.01$, $p < 0.01$, $p = 0.02$, respectively). The risk of having uncontrolled disease was higher when the rhinitis symptoms were severe (adjusted OR 3.88, 95% CI 2.05–6.00) than mild–moderate (adjusted OR 1.62, 95% CI 1.22–2.17).

The severity of rhinitis symptoms was inversely correlated with the C-ACT score ($p < 0.001$; Fig. 2).

Discussion

In this study, we were able to identify several factors associated with uncontrolled asthma in the general paediatric population. Our findings are mostly consistent with what is reported in the literature, but also add new insight for identifying children at increased risk for uncontrolled asthma.

LBW had a significant relationship with uncontrolled asthma in our analyses. Previous studies have shown that LBW is related to subsequent wheeze or asthma in childhood, which is possibly associated with reduced airway growth (16). Although controversy remains surrounding the role of LBW in asthma, a recent meta-analysis of 147,252 children in 31 birth cohort studies has reported that younger gestational age at birth was associated with school-age asthma and that the association of LBW with asthma is largely explained by gestational age at birth (17). Meanwhile, the association of LBW or prematurity with the control of asthma is less studied. The current analyses suggest that foetal development may be relevant not only for the development of asthma, but also for the control of disease.

Pet ownership starting before birth and during infancy was significantly associated with uncontrolled asthma in our analyses. The results of previous reports regarding the association of pet ownership with the development of asthma or

Table 3 Association between uncontrolled asthma and environmental factors, demographics and comorbid allergic diseases

Variable	(N)	Uncontrolled asthma % (n)	Crude OR (95% CI)	p value	Adjusted OR* (95% CI)	p value
Birthweight						
≥2500 g	(2574)	13.6 (349)	1	<0.01	1	<0.01
<2500 g	(472)	20.3 (96)	1.63(1.27–2.09)		1.65 (1.25–2.18)	
Daycare during infancy						
No	(2810)	14.8 (417)	1	0.22	1	0.06
Yes	(250)	12.0 (30)	0.78 (0.53–1.16)		0.64 (0.41–1.10)	
Breastfeeding						
<6 months	(1574)	15.7 (247)	1	0.11	1	0.29
More than 6 months	(1408)	13.6 (192)	0.85 (0.69–1.04)		0.89 (0.71–1.11)	
Annual income (yen)						
<5 million	(1151)	16.1 (185)	1		1	
≥5 < 7.5 million	(994)	13.9 (138)	0.84 (0.66–1.07)	0.16	0.81 (0.62–1.05)	0.11
≥7.5 million	(670)	14.9 (100)	0.92 (0.70–1.19)	0.52	0.89 (0.66–1.20)	0.44
Paternal education level						
Less than college	(1484)	15.3 (227)	1	0.34	1	0.87
Completed college	(1473)	14.1 (207)	0.91 (0.74–1.11)		0.98 (0.76–1.26)	
Maternal education level						
Less than college	(2255)	14.1 (318)	1	0.17	1	0.04
Completed college	(781)	16.1 (126)	1.17 (0.94–1.47)		1.33 (1.02–1.73)	
Paternal smoking						
No	(2052)	13.0 (267)	1	<0.01	1	0.14
Yes	(1014)	17.8 (180)	1.44 (1.17–1.77)		1.20 (0.94–1.54)	
Maternal smoking						
No	(2677)	13.6 (363)	1	<0.01	1	0.04
Yes	(389)	21.6 (84)	1.76 (1.35–2.29)		1.42 (1.02–1.97)	
Paternal asthma						
No	(2603)	14.1 (367)	1	0.08	1	0.43
Yes	(463)	17.3 (80)	1.27 (0.97–1.66)		1.13 (0.84–1.50)	
Maternal asthma						
No	(2542)	14.0 (355)	1	0.03	1	0.14
Yes	(524)	17.6 (92)	1.31 (1.02–1.69)		1.23 (0.93–1.63)	
Pet ownership						
No	(2238)	13.0 (291)	1		1	
From before birth	(381)	22.0 (84)	1.89 (1.44–2.48)	<0.01	1.69 (1.24–2.29)	0.01
From infancy	(26)	42.3 (11)	4.91 (2.23–10.79)	<0.01	5.50 (2.16–14.05)	<0.01
From after age 1	(404)	14.4 (58)	1.12 (0.83–1.52)	0.46	0.98 (0.70–1.38)	0.91
Body mass index						
<95 percentile	(2704)	14.0 (379)	1	0.02	1	0.03
≥95 percentile	(362)	18.8 (68)	1.42 (1.07–1.89)		1.44 (1.05–1.99)	
Current rhinitis						
No	(791)	9.2 (73)	1		1	
Mild–moderate	(2090)	15.3 (320)	1.78 (1.36–2.33)	<0.01	1.62 (1.22–2.17)	0.01
Severe	(185)	29.2 (54)	4.05 (2.72–6.04)	<0.01	3.88 (2.50–6.00)	<0.01
History of eczema						
No	(2063)	12.1 (249)	1	<0.01	1	<0.01
Yes	(1003)	19.7 (198)	1.79 (1.46–2.20)		1.58 (1.25–2.00)	
History of food allergy						
No	(2010)	12.8 (257)	1	<0.01	1	0.02
Yes	(1056)	18.0 (190)	1.50 (1.22–1.84)		1.31 (1.04–1.65)	

OR, odds ratio; CI, confidence interval.
*Adjusted for sex, age and all variables shown.

sensitization are controversial (18). However, for patients who have developed asthma, pet allergen exposure has been reported to be associated with worsening symptoms similar to our results (19, 20). A study among school-aged asthmatic children showed that the severity of wheezing symptoms was significantly associated with the exposure to low levels of

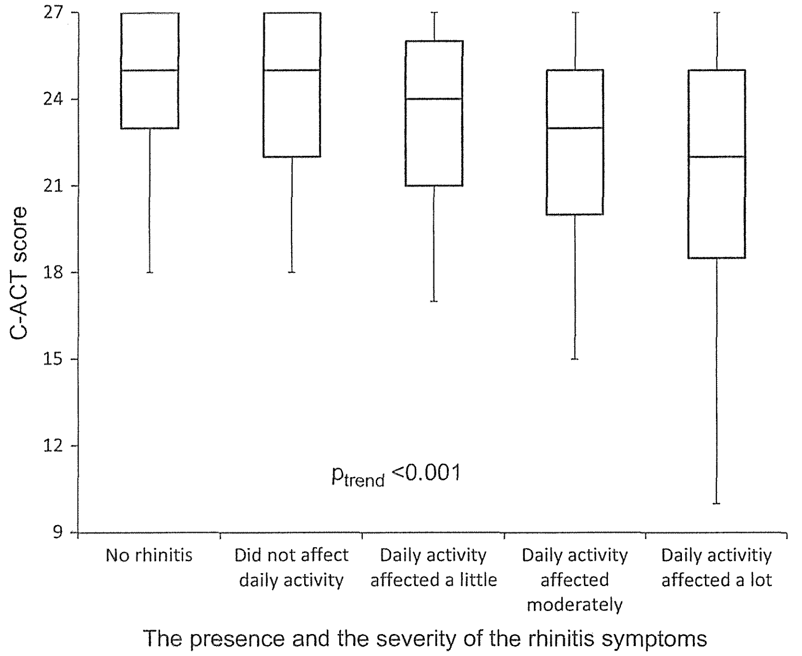

Figure 2 Distribution of the C-ACT score based on the presence and the severity of the rhinitis symptoms. No rhinitis was defined as a negative answer to the question 'In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu'? Rhinitis was defined as a positive answer to this question, and then, the severity was assessed by the answer to the question 'In the past 12 months, how much did this nose problem interfere with your child's daily activity'? where possible answers were 'not at all', 'a little', 'a moderate amount' or 'a lot'. Box and whisker plots represent median, 25% to 75% range and 5% to 95% range.

household cat and dog allergens for those who are sensitized (19). Several studies have indicated that the negative effect of pet allergen exposure may be significant for non-sensitized asthma patients as well (21, 22). The association of pet ownership with asthma control in our analyses differed depending on when it started. This fact might be due to the difference in the amount of the cumulative allergen exposure. Further exploration is probably difficult without the measurement of exposure and sensitization and is expected in future studies. The possibility that children with uncontrolled asthma avoid owning pets after developing symptoms also exists and would mask the negative effect of pet ownership starting after the first year.

Allergic rhinitis is widely accepted to have similar pathogenesis to asthma and has been recognized as a cause of uncontrolled asthma in adults (7, 23). A nationwide survey among Japanese adult asthma patients showed that 68.5% had self-reported rhinitis, and significantly more of these patients had uncontrolled asthma than those without rhinitis (25.4% vs. 18.0%) (23). The impact of rhinitis on the level of asthma control among children is less well studied, but we have recently conducted a large population-based nationwide study among more than 100,000 Japanese children and have reported that rhinitis symptoms is a risk factor of current asthma and severe asthma (24). Our current analyses have confirmed these results and have also shown that the severity of rhinitis correlates with the degree of asthma control.

The major limitation of this study is that all data were self-reported and retrospectively obtained, lacking objective data such as IgE and lung function tests. Defining asthma and other allergic diseases mainly based on the ISAAC questionnaire may have resulted in over-diagnosis in some children, as previously reported (25). As the information about asthma treatment was limited to the name of the medications prescribed, the exact treatment step could not be included in the assessment. The treatments of rhinitis symptoms were also not evaluated. However, the strength of this study is that it has collected thorough data among a large number of children with asthma in the general population and measured their symptom control by a widely used tool. This has enabled the assessment of children without having regular follow-up by physicians and cannot been assessed by hospital-based studies.

It should also be noted that discrepancies of the assessment of asthma control has been reported between C-ACT and GINA criteria showing that the generally used cut-off points may overestimate the proportion of children with controlled asthma as defined with GINA (26, 27). Nevertheless, these tools have shown good correlation in these studies, and the cut-off score of 19 by C-ACT in our study has surely detected the children with uncontrolled asthma defined with GINA criteria.

Finally, the generalizability of this study is another concern because of the use of a Web-based questionnaire. However, the Japanese Ministry of Internal Affairs and Communications has shown that the Internet diffusion rate among people aged 20–49 yr exceeds 90%, which means that most parents of schoolchildren currently use the computer and the Internet in Japan (28). Furthermore, the Web-based ISAAC questionnaire, ACT/C-ACT has been shown to be reproducible and comparable with the paper-based versions, even preferred by respondents (29, 30). Therefore, our current Web-based survey is likely to contain comprehensive and reliable information about the general paediatric population.

In conclusion, we found several factors associated with asthma control in a population-based study. Further understanding of these risk factors may lead to possible interventions to improve disease control.

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Conflict of interest

The authors declare no conflict of interest.

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Time-dependent variation in the responses to the web-based ISAAC questionnaire

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A R T I C L E I N F O

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A B S T R A C T

Background: Epidemiologic studies have shown seasonal variations in responses to the written questionnaire for rhinitis symptoms.
Objective: To evaluate whether the timing of data collection affected responses to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire in a Web-based study.
Methods: The Web-based ISAAC questionnaires were completed by parents with children 6 to 12 years old using an online research system. The authors conducted surveys of asthma symptoms every month for 1 year and surveys of rhinitis and eczema symptoms every season throughout 1 entire year.
Results: There was a significant fluctuation in the positive responses to questions about wheezing in the past 12 months ($P < .001$) but not in the positive responses to questions about exercise-induced wheezing in the past 12 months and asthma ever ($P = .75$ and $P = .15$, respectively). The positive responses to questions about rhinitis and allergic rhinoconjunctivitis in the past 12 months and pollinosis ever exhibited significant seasonal variations ($P = .002$, $P < .001$, and $P < .001$, respectively). In contrast, there were no significant variations in positive responses regarding eczema in the past 12 months and eczema ever ($P = .33$ and $P = .55$, respectively).
Conclusion: There were time-dependent fluctuations in responses to the Web-based questionnaire regarding allergic symptoms. Timing of data collection should be taken into account when evaluating prevalence of asthma and rhinitis in children.

Introduction

Epidemiologic surveys remain essential for providing fundamental insight into asthma and allergic diseases. Most allergic disease questionnaires focus on lifetime or 1-year prevalences in cross-sectional studies. However, responses to questions that focus on symptoms throughout the lifetime or over the previous year may vary owing to the timing of data collection because allergic symptoms vary over the year, and recall of lifetime or 1-year symptoms might be influenced by recent symptoms. Therefore, traditional epidemiologic studies comparing the prevalences of allergic diseases have been standardized for the season of data collection.[1,2]

Seasonal variations in responses to the International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire were investigated in New Zealand from 1992 to 1993.[3] No season-of-response effect was present in 6- to 7-year-olds regarding the asthma questions, but a single question (regarding sleep disturbances owing to wheezing in the past 12 months) of the 8 total questions exhibited a significant variation across seasons in 13- to 14-year-olds. The season did not affect the responses regarding eczema in either age group. In contrast, significant seasonal variations in the responses to the rhinitis questions were observed in the 2 age groups. Based on these results, the ISAAC protocol recommends that at least half of any study population should be investigated before the major pollen season of the study area.[4]

Recently, Web-based questionnaires have been applied in lieu of traditional paper- or interview-based questionnaires in epidemiologic studies.[5] Web-based questionnaires have been used in Europe[6] and the United States[7] in studies of allergic diseases. However, few studies have investigated time-dependent variations in responses to asthma and allergy questions by the Internet. This study aimed to

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evaluate whether the timing of data collection would affect responses to the ISAAC questionnaire in a Web-based survey.

Methods

Study Population and Participants

This study was conducted using the Macromill online research system (Macromill, Inc, Tokyo, Japan), which maintains one of the largest research panels in Japan. From parents with at least 1 child 6 to 12 years old, the authors randomly invited 1,800 parents to participate each month from February 2011 through January 2012. If a parent had at least 2 children 6 to 12 years old, they were asked to complete the questionnaire for each child. Twelve surveys throughout the entire year were conducted to investigate the responses to the asthma questions because the numbers of primary care visits and hospital admissions owing to childhood asthma attacks are known to vary from month to month.[8,9] In addition, the authors conducted surveys investigating responses to the rhinitis and eczema questions in February, May, August, and November that were taken as examples of each season. The study protocol was approved by the independent review board of the Tokyo Metropolitan Children's Medical Center (Tokyo, Japan).

Questionnaire

The Web-based ISAAC questionnaire is based on the Japanese version of the written questionnaire.[10,11] The Web-based questionnaire has a multiple-page design, and questions that are irrelevant to the respondent are automatically skipped.[12] Wheezing in the past 12 months was defined by a positive response to the question, "Has your child had wheezing or whistling in the chest in the past 12 months?" Exercise-induced wheezing in the past 12 months was defined by a positive response to the question, "In the past 12 months, has your child's chest sounded wheezy during or after exercise?" Asthma ever was defined by a positive response to the question, "Has your child ever had asthma?" Rhinitis in the past 12 months was defined by a positive response to the question, "In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he or she did not have a cold or the flu?" In children with rhinitis in the past 12 months, allergic rhinoconjunctivitis in the past 12 months was defined by a positive response to the question, "In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?" Pollinosis ever was defined by a positive response to the question, "Has your child ever had pollinosis?" Eczema in the past 12 months was defined by positive responses to the questions, "Has your child had this itchy rash at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?" Eczema ever was defined by a positive response to the question, "Has your child ever had eczema?" Furthermore, a few additional questions to evaluate symptoms in the past month were included.

Statistical Analyses

Demographic differences between participants were examined using χ^2 tests or analyses of variance. The χ^2 test for heterogeneity was used to evaluate the overall monthly or seasonal effects on the responses to the questions about allergic diseases. A significance level at a P value less than .01 was chosen because of the large number of comparisons. When the results of χ^2 tests were statistically significant, the residual analyses were used to determine which month or season produced the statistically significant differences. Adjusted standardized residuals greater than 2.58 or less than −2.58 were considered statistically significant because these values correspond to P values less than .01. All analyses were performed using SPSS 19 for Windows (IBM, Armonk, New York).

Results

Study Population

In total, 24,850 children 6 to 12 years old (8.9 ± 2.0 years, 49.9% girls) of 18,829 parents were included in the analyses. The response rate was 87.2%. The characteristics of the study population are presented in Table 1. Age and sex did not vary significantly across the 12 surveys ($P = .31$ and $P = .67$, respectively). Furthermore, the percentages of the parents who answered for at least 2 children did not differ significantly across the 12 surveys ($P = .35$).

Monthly Variations in Responses to Asthma Questions

The overall χ^2 analysis showed a significant fluctuation in positive responses regarding wheezing in the past 12 months ($P < .001$), but no fluctuation was present in the positive responses regarding exercise-induced wheezing in the past 12 months and asthma ever ($P = .75$ and $P = .15$, respectively; Table 2). There also was a significant variation in the positive responses regarding wheezing in the past month ($P < .001$), but no variation was found in the positive responses regarding exercise-induced wheezing in the past month ($P = .03$).

The positive responses regarding wheezing in the past 12 months and wheezing in the past month exhibited similar patterns (Fig 1A). Moreover, there was a significant positive relation between positive responses regarding wheezing in the past 12 months and in the past month ($R^2 = 0.73$; Fig 1B). Residual analysis indicated that positive responses regarding wheezing in the past 12 months were significantly lower in July (12.8%; adjusted standardized residual −2.93) and higher in November (18.0%; adjusted standardized residual 4.25) compared with the expected values.

Seasonal Variations in Responses to Rhinitis and Eczema Questions

The overall χ^2 analysis showed significant variations in positive responses regarding rhinitis and allergic rhinoconjunctivitis in the past 12 months and pollinosis ever ($P = .002$, $P < .001$, and $P < .001$, respectively; Table 3). There also was a significant variation in positive responses regarding rhinitis in the past month ($P < .001$). In contrast, there were no significant variations in positive responses regarding eczema in the past 12 months, eczema ever, and eczema in the past month ($P = .33$, $P = .55$, and $P = .13$, respectively).

Residual analyses showed significantly higher rates of positive responses to the questions about rhinitis in the past 12 months (59.4%), allergic rhinoconjunctivitis in the past 12 months (24.3%), and

Table 1
Characteristics of study participants

	Children			Respondents
	Subjects analyzed	Age (y), Average ± SD	Girls, n (%)	Parents answering for ≥2 children, n (%)
February	2,033	9.0 ± 2.0	1,024 (50.4)	461 (30.0)
March	2,085	8.9 ± 2.0	1,029 (49.4)	497 (32.1)
April	2,068	8.9 ± 2.0	1,011 (48.9)	467 (29.8)
May	1,968	8.9 ± 2.0	1,025 (52.1)	434 (28.8)
June	2,101	8.8 ± 2.0	1,070 (50.9)	466 (29.2)
July	2,224	8.9 ± 2.0	1,129 (50.8)	527 (31.9)
August	2,054	8.9 ± 2.0	1,007 (49.0)	457 (29.1)
September	2,115	8.9 ± 2.0	1,044 (49.4)	464 (28.7)
October	2,065	8.9 ± 2.0	1,025 (49.6)	457 (29.2)
November	2,102	8.8 ± 2.0	1,026 (48.8)	488 (30.7)
December	2,008	8.9 ± 2.0	1,003 (50.0)	440 (28.7)
January	2,027	8.9 ± 2.0	1,014 (50.0)	447 (28.8)

Table 2
Monthly variations in responses to asthma questions

	Positive response, % (adjusted standardized residual)												P value
	February	May	April	May	June	July	August	September	October	November	December	January	
Wheezing in past 12 mo	15.2 (0.36)	14.0 (−1.17)	13.8 (−1.40)	14.5 (−0.45)	13.8 (−1.51)	12.8 (−2.93)	13.9 (−1.33)	15.1 (0.28)	16.6 (2.31)	18.0 (4.25)	16.4 (1.98)	14.7 (0.30)	<.001
EIW in past 12 mo	6.6 (−0.41)	6.0 (−0.75)	6.0 (−0.83)	6.3 (−0.24)	6.2 (−0.47)	6.1 (−0.72)	6.5 (0.09)	6.1 (−0.73)	7.0 (1.15)	6.7 (0.46)	7.5 (1.99)	6.3 (−0.31)	.75
Asthma ever	19.2 (1.88)	16.0 (−2.11)	16.7 (−1.28)	17.7 (0.03)	17.0 (−0.84)	16.9 (−1.10)	18.5 (0.92)	17.5 (−0.21)	17.9 (0.26)	19.4 (2.13)	18.1 (0.45)	17.7 (−0.06)	.15
Wheezing in past month	5.5 (−0.03)	5.2 (−0.61)	4.2 (−2.64)	5.0 (−1.00)	4.8 (−1.50)	4.3 (−2.51)	5.6 (0.36)	3.9 (−3.27)	6.9 (3.03)	8.1 (5.60)	6.6 (2.36)	5.6 (0.31)	<.001
EIW in past month	2.6 (−0.43)	2.8 (0.07)	2.5 (−0.70)	2.2 (−1.47)	2.4 (−1.10)	2.4 (−1.12)	2.9 (0.33)	2.0 (−2.26)	3.4 (1.98)	3.0 (0.84)	3.6 (2.37)	3.3 (1.57)	.03

Abbreviation: EIW, exercise-induced wheezing.

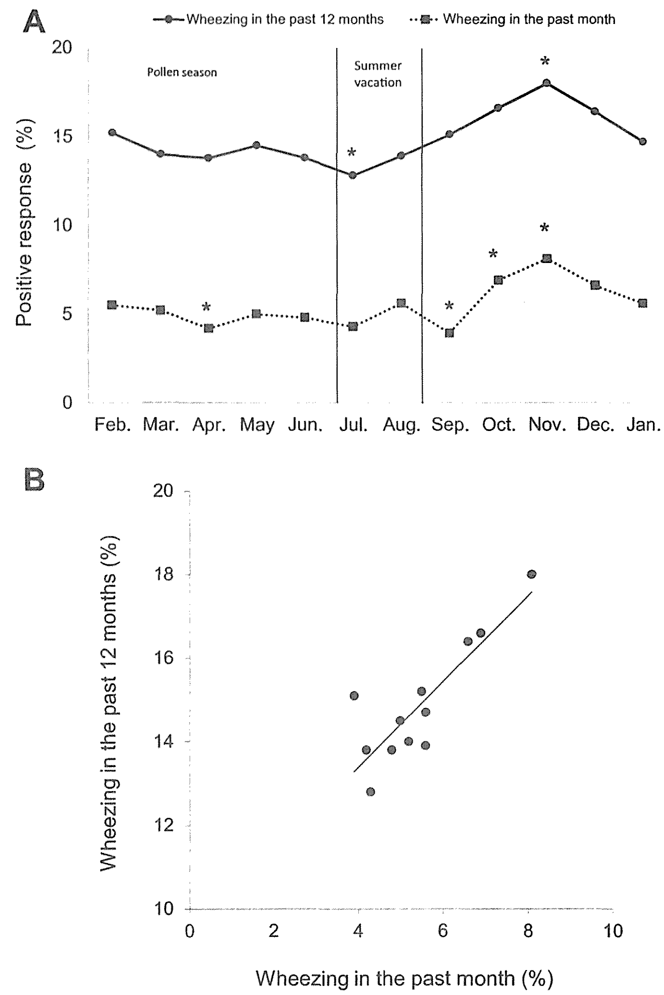

Figure 1. Responses to questions about wheezing. *(A)* Monthly fluctuations in positive responses to questions about wheezing in the past 12 months and the past month. *Adjusted standardized residual higher than 2.58 or lower than −2.58. *(B)* Relation between positive responses to questions about wheezing in the past month and the past 12 months ($R^2 = 0.73$, $P < .01$).

pollinosis ever (33.2%) in spring compared with the expected values (adjusted standardized residuals 3.69, 6.46, and 2.77, respectively).

Discussion

This study showed that the timing of data collection affected the responses to questions about wheezing in the past 12 months in a Web-based survey. Furthermore, the responses to questions about wheezing in the past 12 months were strongly associated with the responses to questions about wheezing in the past month, which suggests that the recall of wheezing in the past 12 months was influenced by more recent wheezing. The results of the present study are inconsistent with those of a study performed using the ISAAC written questionnaire in New Zealand.[3] The New Zealand study analyzed 21,437 schoolchildren 6 to 7 and 13 to 14 years old and found no seasonal variations; the positive responses to the question about wheezing in the past 12 months in children 6 to 7 years old occurred at rates of 25.7% in spring through early summer, 24.4% in late summer through autumn, and 24.8% in winter ($P =$ .54); in adolescents 13 to 14 years old, these rates were 28.4% in spring through early summer, 27.9% in late summer through autumn, and 31.9% in winter ($P = .13$).

One possible reason for the discrepancies between the results of the aforementioned study and the present study is that the periods of the comparisons differed. The present study investigated

Table 3
Seasonal variations in responses to rhinitis and eczema questions

	Prevalence, % (adjusted standardized residual)				
	Winter	Spring	Summer	Autumn	*P* value
Rhinitis in past 12 mo	54.1 (−1.78)	59.4 (3.69)	55.6 (−0.27)	54.3 (−1.58)	.002
Allergic rhinoconjunctivitis in past 12 mo	16.1 (−4.22)	24.3 (6.46)	20.2 (1.09)	16.9 (−3.23)	<.001
Pollinosis ever	27.2 (−3.97)	33.2 (2.77)	32.9 (2.43)	29.7 (−1.20)	<.001
Rhinitis in past month	36.5 (2.63)	38.0 (4.10)	28.7 (−6.00)	33.5 (−0.68)	<.001
Eczema in past 12 mo	14.6 (−0.86)	16.0 (1.14)	15.5 (0.48)	14.7 (−0.74)	.33
Eczema ever	54.5 (−1.15)	54.7 (0.89)	57.0 (1.49)	56.0 (0.53)	.55
Eczema in past month	10.9 (−0.57)	12.2 (1.56)	11.9 (1.00)	10.1 (−1.95)	.13

monthly variations in responses, whereas the study conducted in New Zealand compared responses across 3 seasons, not including summer vacation season. In many countries in the Northern Hemisphere, hospital admissions, emergency department visits, and unscheduled physician consultations for childhood asthma generally reach a trough in summer and drastically increase in September,[8,9,13] indicating the role of viral respiratory tract infection in asthma exacerbation.[14] In the present study, positive response rates regarding wheezing in the past 12 months decreased to the lower levels in July and August, which are months of summer vacation. Pollen season may be a concern when considering the time-dependent variation because some studies have reported that tree pollen induces asthma exacerbations.[15,16] However, pollen season owing to Japanese cedar and cypress,[11] which is spring in Japan, did not affect the positive responses to wheeze in the past 12 months in the present study, in line with findings from the New Zealand study.

Another possible reason for this discrepancy may be the differences in data collection. Web-based questionnaires are returned more rapidly than postal questionnaires, and most respondents of Web-based questionnaires complete the surveys within a few days of receiving a request.[5,17] Okupa et al[18] compared the value of a daily symptom diary with a retrospective questionnaire for assessing asthma symptoms and found that retrospective symptom recall through the questionnaire was more affected by recent symptoms. Shorter periods of data collection, which is an advantage of Web-based surveys, might make time-dependent variations more obvious. Timing of data collection in Web-based childhood asthma surveys should be designed with consideration of the annual cycle of exacerbations.

In contrast, the rates of positive responses to the questions about exercise-induced wheezing in the past 12 months and the past month were not affected by the timing of data collection. Some studies have reported that exercise-induced wheezing in children and adults with asthma is associated with climate and pollen conditions. Korean studies have shown that the prevalence of exercise-induced asthma in patients with asthma is higher in the spring, autumn, and winter than in the summer and that this prevalence is significantly related to temperature and humidity.[19,20] A Danish study showed that the occurrence of exercise-induced bronchospasm increases significantly during pollen season in schoolchildren with hay fever and asthma but not in schoolchildren with hay fever alone.[21] A study in Finland showed that exercise-induced asthma is aggravated during the birch pollen season in men with asthma and an allergy to birch pollen.[22] Although these studies have reported seasonal effects on symptoms of exercise-induced wheezing in patients with asthma, this relation remains unclear in population-based studies.

This study showed that the responses to the rhinitis questions varied across the seasons, which is consistent with the study that was conducted in New Zealand.[3] These 2 studies showed a relation between pollen seasons and responses to the rhinitis questions. In contrast to questions about respiratory symptoms, the responses to the eczema questions, which included eczema in the past month, did not depend on the season. These findings are consistent with those from the study conducted in New Zealand.[3] Although some ecologic studies have reported that climate and latitude are associated with the prevalence of eczema,[23–26] few population-based time-series studies have evaluated the association between the prevalence of eczema and the seasons. A German population-based study of 1,673 6-year-old children reported summer-type and winter-type patterns of eczema symptoms; the severity of eczema in children with the summer-type pattern was associated with exposure to outdoor grass pollen, and the severity of eczema in children with the winter-type pattern was associated with lower temperatures.[27] A Japanese nationwide cross-sectional study conducted from 2007 to 2008 showed that the number of outpatients with atopic dermatitis was positively associated with temperature.[28] This inconsistency might be due to differences in study populations, climates, and latitudes.

One limitation of the present study is that the study participants were limited to Internet users. However, the Information and Communications Statistics Database of the Ministry of Internal Affairs and Communications in Japan (http://www.soumu.go.jp/johotsusintokei/english/) found that more than 90% of people 20 to 49 years old can access the Internet, which indicates that most parents of schoolchildren in Japan currently use the Internet; thus, the selection bias should be small. Another limitation is that this study did not include adolescents, which is the age group that showed seasonal variation in responses to asthma question in the study in New Zealand.[3] Further studies of adolescents using Web-based questionnaires are needed.

In conclusion, this study suggests that the timing of data collection in a Web-based study affects responses to questions about wheezing and rhinitis in schoolchildren. Taking this in account will allow the Web-based ISAAC questionnaire to become a more useful research tool for epidemiologic studies. Furthermore, physicians and asthma caregivers should consider a recall bias when they assess patients' allergic symptoms during a particular period.

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In summary, in this large, nationally representative sample of more than 600 asthmatic patients, we found that triclosan exposure was associated with a more than 70% increased risk of reporting an asthma exacerbation in the last year. Exposure to triclosan may directly lead to asthma exacerbations, or elevated triclosan levels may be a marker for poor asthma control. Future prospective studies are needed to determine whether triclosan exposure has a role in the development and maintenance of allergy and allergic respiratory disease.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2013.11.017.

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Test-retest reliability of the International Study of Asthma and Allergies in Childhood questionnaire for a web-based survey

Epidemiologic surveys are essential for providing fundamental insight into allergic diseases. However, in epidemiologic studies that use traditional approaches, such as paper questionnaires and interviews, the response rates have decreased in the past decades. This issue was even raised by the International Study of Asthma and Allergies in Childhood (ISAAC).[1] The median response rates of active consents in the 6- to 7-year age group decreased from 84% in phase 1 to 78% in phase 3, which was conducted 7 years after phase 1.[2] Another approach to data collection using the Internet is increasing in academic research.[3] However, web-based surveys accounted for only 1% of epidemiologic articles in the 7 high-impact general medical and epidemiologic journals from 2008 to 2009.[3] One of the reasons for this finding might be that there are few studies that investigate the reliability of the data collected via the Internet. Thus, this study aims to evaluate the reliability of the web-based ISAAC questionnaire.

This study was conducted using the Macromill online research system (Macromill Inc, Tokyo, Japan), which maintains one of the largest research panels in Japan. Among the 2,598 monitors who resided in the Kyushu region and had children aged 6 to 12 years based on their background data, we randomly selected 958 parents to participate in the survey in September 2011 (time 1 survey). If a parent had 2 or more children aged 6 to 12 years, they were asked to complete the questionnaire for each child, and 1,254 children were recruited. For the test-retest study, we randomly selected 200 children from the children who participated in the time 1 survey and asked their parents to complete the same questionnaire in October 2011 (retest survey).

We used the web-based ISAAC questionnaire based on the Japanese version of the written questionnaire. It was a multiple-page design and automatically skipped questions that were irrelevant to the respondent. We estimated the prevalence of allergic symptoms based on the responses to the ISAAC core questions.[1] Demographic differences among the study participants were compared using the χ^2 test or the Mann-Whitney test. $P < .05$ was considered statistically significant. Reliability was assessed using the proportion of agreement and the κ coefficient. All analyses were performed using SPSS statistical software, version 19 (IBM, Armonk, New York). The study protocol was approved by the independent review board of the Tokyo Metropolitan Children's Medical Center.

A total of 184 study participants (93 boys and 91 girls; mean [SD] age, 8.8 [1.8] years) were analyzed for the assessment of test-retest reliability. The respondent characteristics between the time 1 survey and the retest survey were not significantly different. Life-long prevalence of allergic symptoms, especially skin symptoms, tended to be higher than the current prevalence (Table 1). The proportion of agreement for the questions on asthma and nose and/or eye symptoms was more than 90%, whereas that for the questions on eczema was less than 90%. The questions on current symptoms had κ coefficients between 0.55 and 0.64. Of interest was that the κ coefficients for the question on current eczema was lower than that for the question on eczema ever, which was opposite of those for respiratory symptoms.

This study found that the web-based ISAAC questionnaire was reliable for the epidemiologic survey. Population-based studies using

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Table 1
Prevalence of allergic symptoms, proportion of agreement, and κ coefficients

Variable	Prevalence, %		Proportion of Agreement, %	κ Coefficient (95% Confidence Interval)
	Time 1	Retest		
Current wheeze	12.5	14.7	91.3	0.63 (0.46-0.80)
Asthma ever	18.5	19.0	94.0	0.80 (0.69-0.92)
Current allergic rhinoconjunctivitis	13.6	14.7	91.3	0.64 (0.48-0.80)
Pollinosis ever	15.2	14.1	94.6	0.78 (0.65-0.91)
Current eczema	13.0	13.6	89.7	0.55 (0.37-0.73)
Eczema ever	39.7	41.8	75.0	0.48 (0.35-0.61)

the ISAAC written questionnaire have produced similar κ coefficients to our results. A test-retest study of the ISAAC written questionnaire conducted in Malaysian children aged 7 to 12 years after a 1-month interval demonstrated that the κ coefficients for the questions on asthma, rhinitis, and eczema were 0.63 to 0.81, 0.49 to 0.52, and 0.34 to 0.83, respectively.[4] In an Italian study performed 3 months apart in adolescents, the ISAAC written questionnaire revealed κ coefficients between 0.41 and 0.86 for the questions on asthma.[5] Furthermore, a randomized study that compared web-based and written ISAAC questionnaires on respiratory symptoms found that both questionnaires yielded equal results in adolescents.[6]

For the questions regarding respiratory or nose and/or eye symptoms, the questions using "ever" as a reference period tended to have higher reliability than those using "in the past 12 months." Similar results were found in the Malaysian and Italian studies.[4,5] In contrast, the reliability of the question on eczema ever tended to be lower than that on current eczema. The prevalence of current eczema was one-third of that of eczema ever, which means that many children diagnosed as having eczema in infancy outgrow it when they reach school age. Although recalling symptoms experienced during a lifetime might be easier than recalling symptoms during specific intervals, recalling the symptoms only seen in infancy might be less likely to be reliable in a study conducted in schoolchildren. Compared with higher reliability of the questions on respiratory and nose and/or eye symptoms, reliability of the questions on eczema was lower, consistent with the results of the Malaysian study.[4] This lower reliability might be explained by languages and cultural backgrounds. The ISAAC phase 3 study group reported that some English terms were difficult to translate into other languages despite a detailed protocol.[7] Terms such as *itchy rash* and *eczema* might have their own interpretation problems in Japanese along with Bahasa Malaysia.[4] Although the Japanese version of the ISAAC questionnaire used footnotes to describe skin lesions, our results suggested that the language problems persisted.

The limitation of this study was the concern about generalizability; people who did not have access to computers with Internet connections could not participate in this study. The Ministry of Internal Affairs and Communications in Japan (http://www.soumu.go.jp/johotsusintokei/english/) revealed that the Internet diffusion rate among people aged 20 to 49 years exceeded 90%, which means that most parents of schoolchildren currently use the Internet in Japan.

The web-based ISAAC questionnaire was found to be as reliable as the written one and could become a new research tool when the target population has a high Internet penetration rate. Further studies are needed to create a web-based questionnaire using multimedia, such as sound and visual content, which would lead to further improvement in the reliability of questionnaires.

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Urinary biopyrrin: a potential inflammatory marker of atopic dermatitis

Atopic dermatitis (AD) is a chronic and relapsing eczematous disease that is generally associated with allergen-induced skin inflammation. Chronic persistent inflammation by free radicals is postulated to impair skin barrier function, leading to dry skin and sustained pruritus; therefore, excessive oxidative stress is postulated to exacerbate the inflammatory process of AD.[1] In children with AD, levels of urinary 8-hydroxydeoxyguanosine, a product of nucleic acid oxidation, are indeed elevated according to disease severity.[2]

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「アレルギー疾患の全年齢にわたる継続的疫学調査体制の
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