Table 1 Baseline characteristics of the study participants

	Total (n = 34,699)	Boys (n = 17,569)	Girls (n = 17,130)	p Value*
Body composition				
Underweight	6751 (19.5)	3517 (20.0)	3234 (18.9)	0.004
Overweight	3479 (10.0)	1852 (10.5)	1627 (9.5)	0.001
Ever diagnosed with				
Bronchial asthma	5574 (16.1)	3389 (19.3)	2185 (12.8)	<0.001
Atopic dermatitis	5535 (16.0)	3046 (17.3)	2489 (14.5)	<0.001
Allergic rhinitis	6099 (17.6)	3574 (20.3)	2525 (14.7)	<0.001
Food allergy	3163 (9.1)	1905 (10.8)	1258 (7.3)	<0.001
Parental history				
Bronchial asthma	7283 (21.0)	3756 (21.4)	3527 (20.6)	0.037
Current wheeze	7058 (20.3)	4168 (23.7)	2890 (16.9)	<0.001
Current asthma	3883 (11.2)	2406 (13.7)	1477 (8.6)	<0.001

Data represent number (percentage).
*Chi-square analysis for evaluating gender differences.

bronchial asthma as well as atopic dermatitis, allergic rhinitis, and food allergy. Parents of more than 20% of the children had past or present history of bronchial asthma. During the previous 12 months, 20.3% of the children had experienced wheezing. According to our definition, 11.2% of the children were categorized as having current asthma. Compared with children with current wheeze who did not have a doctor's diagnosis of asthma, children with current asthma were significantly more likely to have comorbid allergic diseases other than asthma (18.0% vs. 31.4% for atopic dermatitis, 23.8% vs. 30.2% for allergic rhinitis, and 11.1% vs. 22.2% for food allergy; $p < 0.001$ for all, Table 2). A higher prevalence of parental history of asthma was also found in children with current asthma compared with children with current wheeze who did not have a doctor's diagnosis of asthma (27.7% vs. 43.0%, $p < 0.001$).

Current asthma was significantly more prevalent in overweight children compared with underweight and normal weight children (13.2% for overweight vs. 10.5% for underweight and 11.1% for normal weight; both $p < 0.001$). In contrast, there was no modifying effect of body composition on the prevalence of current wheeze without a doctor's diagnosis of asthma (Fig. 2). Additional factors other than body composition, such as gender, comorbidities of other allergic diseases, and parental history of asthma, are also known to be associated with the prevalence of current asthma. After adjusting for these confounders, multivariable logistic regression analysis revealed that obesity was still significantly associated with current asthma (adjusted odds ratio: 1.23, 95% CI: 1.10–1.38, $p < 0.001$). Furthermore, after stratified by gender, this association was still seen in both genders (Table 3).

Table 2 Comorbidity of other allergic diseases and parental history of asthma in children with current wheeze

	Current wheeze without a doctor's diagnosis (n = 3175)	Current asthma (n = 3883)	p Value
Ever diagnosed with			
Atopic dermatitis	573 (18.0)	1218 (31.4)	<0.001
Allergic rhinitis	755 (23.8)	1174 (30.2)	<0.001
Food allergy	351 (11.1)	861 (22.2)	<0.001
Parental history			
Bronchial asthma	881 (27.7)	1669 (43.0)	<0.001

Data represent number (percentage).

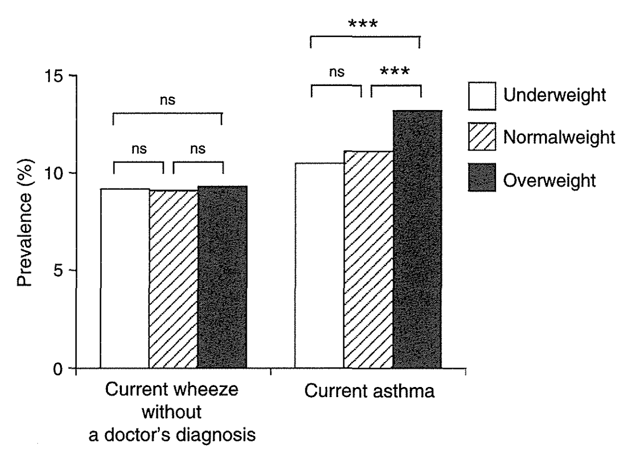

Figure 2 Effects of body composition on the prevalence of current wheeze in children without a doctor's diagnosis of asthma and current asthma. NS, not significant; ***$p < 0.001$.

Table 3 Association of underweight or overweight with current asthma

	Prevalence (%)	p Value	Adjusted OR	95% CI
Total*				
Underweight	10.5	0.099	0.93	0.85–1.02
Normal weight	11.1		1	
Overweight	13.2	<0.001	1.23	1.10–1.38
Boys**				
Underweight	12.5	0.124	0.91	0.81–1.03
Normal weight	13.7		1	
Overweight	15.6	0.015	1.19	1.04–1.38
Girls**				
Underweight	8.3	0.450	0.95	0.82–1.09
Normal weight	8.5		1	
Overweight	10.5	0.008	1.27	1.06–1.52

OR, odds ratio; CI, confidence interval.
*Adjusted for sex, parental history of asthma, lifetime diagnosis of atopic dermatitis, allergic rhinitis, and food allergy.
**Adjusted for parental history of asthma, lifetime diagnosis of atopic dermatitis, allergic rhinitis, and food allergy.

Discussion

We have previously reported that there is a clear association between obesity and current asthma in school-aged children (5). In this study, we also found a similar association between both disorders, even in preschool children. A paucity of adequate questionnaires is one of the obstacles encountered in evaluating the prevalence of asthma in young children, and this problem makes it difficult to clarify the association between asthma and obesity in this age population. Tai et al. (17) performed a survey of 1509 children aged 4–5 yr in South Australia using the ISAAC questionnaire and found a significant association between obesity and lifetime prevalence of doctor-diagnosed asthma, but the association with current symptoms (wheezing in the previous 12 months) was marginal. von Kries et al. (18) reported similar results from a survey of 9357 German children aged 5 and 6 yr using the ISAAC-based questionnaire. They found that an association with obesity was significant for lifetime prevalence of doctor-diagnosed asthma only. For current symptoms of asthma, only a trend was observed, but this was not significant. Although the ISAAC questionnaire has been used for many epidemiological studies in children, it was not validated for use in preschool children. Symptom-based core questions of the ISAAC questionnaire are not highly specific for asthma in this age group, because it has been well known that there are several phenotypes of wheezing. Hederos et al. (19) compared the parental assessment of asthma among their children aged 1–6 yr in response to a questionnaire with the corresponding medical records in Sweden and found that when adding one question regarding asthma diagnosis by a physician to the original ISAAC questionnaire, the sensitivity and specificity of the questionnaire for detecting clinically diagnosed asthma registered in the medical record were high (98% and 77%, respectively). In this study, we defined current asthma as having been diagnosed with asthma by a doctor among children who had experienced wheezing in the previous 12 months. Children with current asthma were more likely to have comorbid allergic diseases other than asthma and a parental history of asthma compared with children with current wheeze who did not have a doctor's diagnosis of asthma, suggesting that current asthma is predominately atopic in nature, while children with current wheeze who did not have a doctor's diagnosis of asthma are generally non-atopic in nature. Therefore, the definition used for asthma in this study might be more accurate for evaluating the prevalence of current asthma in young children compared with the original ISAAC definition. Furthermore, we found an association between obesity and current symptoms only in children with current asthma and not in children with current wheeze who did not have a doctor's diagnosis of asthma. Possible mechanisms underlying the relationship between asthma and obesity include mechanical changes associated with obesity, chronic systematic inflammation, and atopy (4). Inconsistent with our results, several studies have found that obesity was more strongly related to non-atopic than to atopic asthma in adults (20) and children (21). Additional studies are needed to clarify the relationship between obesity and atopy.

There are several other factors affecting the prevalence of asthma, such as gender, personal history of other allergic diseases, and parental history of asthma. In this study, even after adjustment for these factors, obesity was still associated with current asthma. There have been several reports showing gender difference in the impact of obesity on asthma. Cross-sectional data on 5- and 6-yr-old German children showed a 2.9-fold higher prevalence of doctor-diagnosed asthma in obese children compared with children with normal weight in girls but not in boys (18). In 517 preschool children of Hispanic national origin who lived in New York, the association between obesity and asthma was confined to girls (22). A similar gender-specific association was shown in school-aged children and adolescents (23, 24). In contrast, we did not find any evidence of effect modification by gender. Furthermore, in our previous study that showed an association of obesity with current asthma in school-aged children, the association was not different for boys and girls (5). These discrepancies between our findings and other published results might be explained by differences in subject ethnicities or socioeconomic status.

In the subjects of this study who aged 4–5 yr, 19.5% were categorized as underweight. Our previous study utilized the same reference values and showed that the prevalence rates of underweight by age were as follows: 15.3% in children aged 6–7 yr, 8% in children aged 13–14 yr, and 9.1% in children aged 16–17 yr (5). These data indicate that the increasing trend in the prevalence of underweight observed over the past few decades only occurred in younger children. In this study, there was no association between underweight status and current asthma. However, among children aged 2–11 yr in the United States, a U-shaped association between BMI and the probability of having asthma was reported for boys, but not for girls (25). Thus, future studies should focus not only on obesity, but also on underweight status as a risk factor for asthma.

One of the limitations of our study is that the cross-sectional study does not allow for the determination to be made as to whether obesity precedes the development of asthma or vice versa. A prospective study of children who were born in the United States and followed for up to 14 yr showed that, in 4393 children who were asthma-free during the first 24 months of life, a high BMI (> 85th percentile) at age of 2–3 yr was a risk factor for subsequent asthma development in boys but not in girls (26). Another longitudinal study conducted in the Netherlands demonstrated that a high BMI at 6–7 yr was associated with an increased risk of dyspnea and bronchial hyper-reactivity at 8 yr (27); notably, children with a high BMI at a young age who developed a normal BMI at 6–7 yr did not have an increased risk of dyspnea or bronchial hyper-reactivity at 8 yr. Another cohort study that recruited children at high risk of asthma showed that late onset of obesity (being overweight at the age of 5 yr but not at the age of 1 yr) was associated with a high risk for asthma at the age of 6 and 8 yr (28). These findings suggest that there are complex relationships between gender, age, obesity, and asthma. Further studies will be needed to understand the mechanisms underlying the association of obesity with asthma in children.

Another limitation of this study was that we failed to account for several important confounding factors, such as birth weight, gestational age, birth order, day care attendance before 1 yr of age, parental tobacco smoking, socioeconomic status, medications for asthma and other allergic diseases, and atopic status. These factors might affect the association between obesity and asthma in young children. An additional limitation of this study is that body weights and heights were parent-reported. A systematic review showed trends of under-reporting for weight and BMI and over-reporting for height in the adult population, reflecting body-image concerns (29). A cohort study showed that at 4 yr of age, parents of children with a low BMI tended to over-report body weight, whereas parents of children with a high BMI tended to under-report body weight, although the difference between measured and parent-reported weight and height was small (30). These tendencies might have affected the association between obesity and asthma.

In conclusion, together with our previous findings (5), there was a clear association between obesity and current asthma in all age group from preschool childhood to adolescence in Japan, and there was no gender effect on this association. Further studies will be needed to understand the mechanisms underlying the association of obesity with asthma in children.

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Conflict of interest

All authors declare that we have no conflict of interest.

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ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

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

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asthma; children; conjunctivitis; pollen; rhinitis.

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Abstract

Background: Patients allergic to pollen have been known to become more symptomatic during pollen season compared with the nonpollen 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 three 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.

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 hypothesized 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 sensitization 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 past 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 two prefectures in which the pollen counts were measured by different methods. The data from these three prefectures were excluded, and the data from the 44 remaining prefectures 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 sensitized 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 two types of tree pollen and the two 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 <0.05 were considered to indicate statistical significance. All analyses were performed using the statistical package 'SPSS for Windows version 19' (SPSS Inc., Chicago, IL, USA).

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 2967 counts/cm^2 (range, 34–7912 counts/cm^2) and 1245 counts/cm^2 (range, 1–6048 counts/cm^2), respectively. Cedar pollen counts were higher in prefectures in eastern Japan (Fig. 1A), and cypress pollen counts were higher in prefectures on the Pacific side than along the Sea of Japan (Fig. 1B).

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

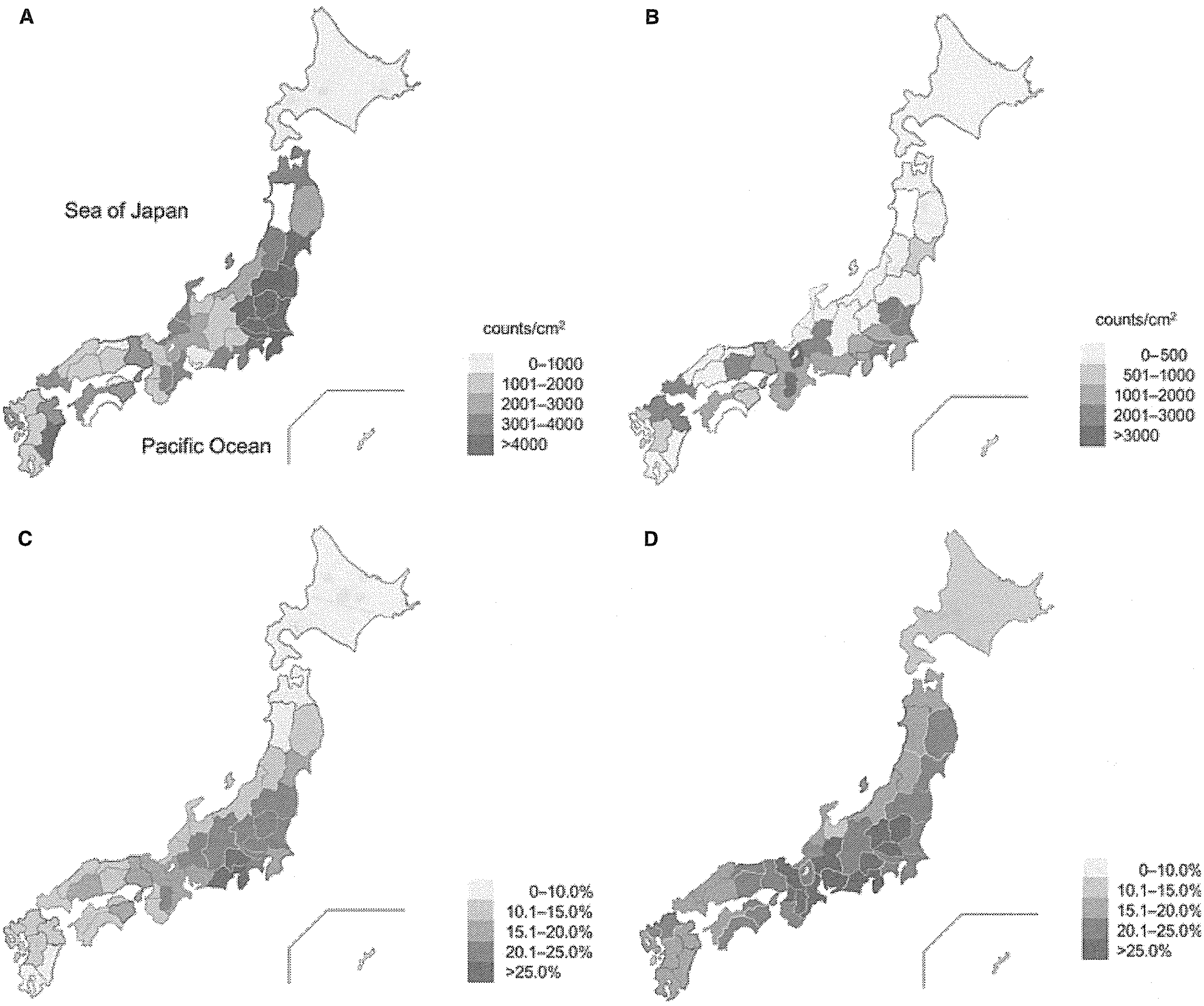

Figure 1 Maps of pollen counts and the prevalence of allergic rhinoconjunctivitis in Japan. (A) Japanese cedar pollen counts. (B) Japanese cypress pollen counts. (C) The prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children. (D) The prevalence of allergic rhinoconjunctivitis in 13-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

eastern Japan (Fig. 1C), 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. 1D). 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. 2A) but not in 13- to 14-year-old children ($R = 0.18$, $P = 0.24$) (Fig. 2B). 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. 2C,D). 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 ($P = 0.29$).

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 two age groups was inversely associated with the prevalence of allergic rhinoconjunctivitis in the younger children ($R = -0.52$, $P < 0.001$) (Fig. 3A). Therefore, we analysed the association between the pollen counts and the differences in the prevalence of allergic rhinoconjunctivitis between the two age groups. Differences in the prevalence of allergic rhinoconjunctivitis were inversely associated with cedar pollen counts ($R = -0.50$, $P = 0.001$) (Fig. 3B) but not with cypress pollen counts ($R = -0.28$, $P = 0.86$) (Fig. 3C).

We next analysed the associations between pollen counts and the prevalence of asthma (Table 1). After adjustment for

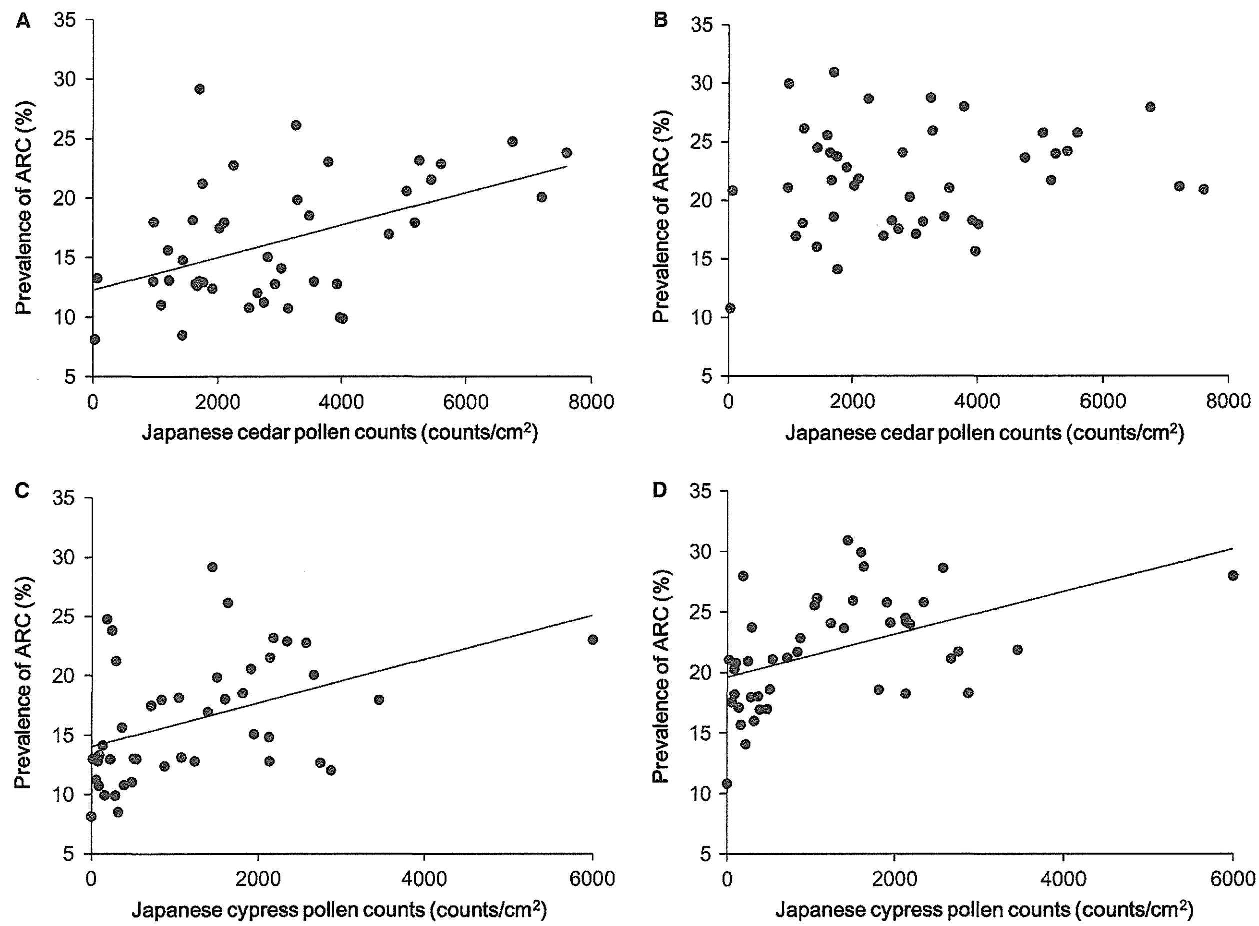

Figure 2 Pollen counts and the prevalence of allergic rhinoconjunctivitis (ARC). (A) Positive association between cedar pollen counts and the prevalence of ARC in 6- to 7-year-old children ($R = 0.48$, $P = 0.001$). (B) No association between cedar pollen counts and the prevalence of ARC in 13- to 14-year-old 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 ($R = 0.47$, $P = 0.001$).

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 sensitization 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 two 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 sensitized to at least one pollen by the age of 3 years and that the sensitization 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 sensitized 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.

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

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

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 two 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 sensitization 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.

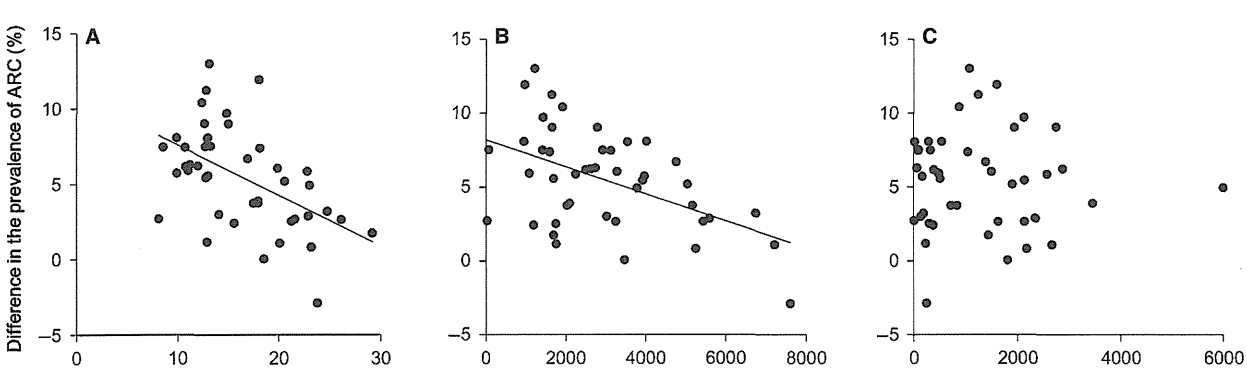

Figure 3 Differences in the prevalence of allergic rhinoconjunctivitis (ARC) between 6- to 7-year-old children and 13- to 14-year-old children. (A) Inverse association between the prevalence of ARC in 6- to 7-year-old children and the difference in the prevalence of ARC between the two age groups ($R = -0.52$, $P < 0.001$). (B) Inverse association between cedar pollen counts and the difference in the prevalence of ARC between the two 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 two age groups ($R = -0.03$, $P = 0.86$).

The strength of our study is that it addresses the associations between two types of tree pollen and the prevalence of allergic diseases in children in two different age groups. One limitation is that our study was a questionnaire-based survey without testing for sensitization. Estimation of the prevalence of allergic rhinoconjunctivitis by a questionnaire only may be not very sensitive in young children (31). However, sensitization 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.

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Author contributions

Koichi Yoshida analysed the data and wrote the article. Yuichi Adachi and Akira Akasawa designed the study protocol and cowrote the article. 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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Association between Body Mass Index and Asthma among Japanese Adults: Risk within the Normal Weight Range

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Key Words
Asthma · Obesity · Body mass index · Japan · Prevalence

Abstract
Background: Increasing amounts of data have shown that some Asian populations are more susceptible to increased weight and development of noncommunicable disease than Western populations. However, little is known about the association between increased weight, particularly within the normal range, and the development of asthma among Asian populations. ***Methods:*** To examine the association between increased body mass index (BMI) and asthma among Japanese adults, data from a nationwide population-based cross-sectional survey of asthma prevalence in Japan were analyzed (n = 22,962; age range 20–79 years). BMIs were classified into 7 categories considering WHO recommendations (cutoff points: 17.00, 18.50, 23.00, 25.00, 27.50 and 30.00), and the association between BMI and the prevalences of asthma as well as asthma symptoms were assessed by multivariate logistic regression. ***Results:*** The prevalences of obesity (BMI ≥30.00) in this population were relatively low (males 3.0%, females 2.3%). BMI categories of 25.00 or higher in both genders were significantly associated with an increased risk of asthma compared with the reference category (BMI 18.50–22.99). Even in females with a BMI of 23.00–24.99, the prevalence of asthma significantly increased (adjusted odds ratio 1.49, 95% confidence interval 1.16–1.92) compared with that in the reference category. ***Conclusions:*** An increase in the prevalence of asthma among Japanese females starts at a BMI of 23.00, which was relatively lower than those reported from Western countries. This finding suggests that the Japanese population is likely to have asthma with a lesser degree of obesity than Western populations.

Introduction

Obesity and asthma are prevalent disorders worldwide and the prevalences of both diseases have increased in the last few decades. Recently, increasing amounts of data have suggested an association between obesity and asthma [1]. Many cross-sectional or prospective studies have

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shown an increased prevalence of asthma among subjects with a body mass index (BMI) higher than 25.00 or 30.00 compared with normal-weight subjects [1–7].

Obesity is also a key risk factor for other noncommunicable diseases such as type 2 diabetes and cardiovascular diseases. On the basis of the association between BMI and mortality revealed by studies conducted mainly on Western populations, the World Health Organization (WHO) has classified a BMI of 25.00 or higher as being overweight and a BMI of 30.00 or higher as being obese [8–10]. However, there is increasing evidence that there is a difference in susceptibility to obesity among ethnic groups. Some Asian populations are known to develop type 2 diabetes and cardiovascular diseases even in the upper level of the normal BMI range, and are more likely to develop these diseases than Western populations with an identical BMI [11, 12]. Therefore, WHO consultation has added further potential action points (23.0, 27.5, 32.5, 37.5) to the principal cutoff points after considering the observed lower BMI cutoff points for overweight or obesity among Asian populations [11, 13].

Indeed, previous studies have shown that the Japanese population is susceptible to obesity and is likely to develop noncommunicable diseases. The DECODE-DECODA study shows that the increase in the prevalence of type 2 diabetes starts at a BMI between 23.00 and 24.00 in the Japanese population, but in European populations it starts at 25.00 [12]. Follow-up studies in Japanese adults aged 30–59 years have also shown that an increased BMI, even within the nonobese level, is a risk factor for diabetes mellitus [14].

However, the association between obesity and asthma among Asian populations has not been well established. Most studies that have revealed the association between obesity and asthma have been performed in Western countries. Considering the association of BMI with type 2 diabetes and cardiovascular diseases, the BMI threshold for an increased prevalence of asthma may be lower in Asian populations. The Japanese population is suitable for research on ethnic characteristics among Asian populations, because the ethnic background in Japan is relatively homogeneous. To examine the association between obesity and asthma among Japanese adults, we performed a nationwide cross-sectional, population-based study on 22,962 Japanese adults aged 20–79 years. On the basis of the WHO additional BMI cutoff points [13], we further divided the normal range of BMIs (18.50–24.99) into two narrower categories (18.50–22.99 and 23.00–24.99), and investigated the association between asthma and increased BMI even within the normal range.

Methods

Study Design

We analyzed data obtained in a nationwide population-based cross-sectional study conducted on residents aged 20–79 years, living in 10 different areas of Japan in 2006. The methods of this study have been described elsewhere [15]. In brief, subjects were asked to complete the Japanese version of the ECRHS one-page questionnaire [16], which is a highly validated questionnaire for asthma symptoms and asthma diagnosis [17]. The questionnaire also included possible risk factors for asthma, that is height and weight, smoking status, living environment, current pet ownership as well as allergic rhinitis. In this study, after excluding subjects who did not complete questions on height and weight, data from 22,962 subjects (11,237 males and 11,725 females) were analyzed. This study was approved by the Ethics Committee of Sagamihara National Hospital.

Body Mass Index

BMI was used as a measure of relative weight. BMI was calculated as self-reported weight in kilograms divided by the square of self-reported height in meters. BMIs were classified into 7 categories considering WHO classifications with additional cutoff points [13]: underweight ≤16.99 and 17.00–18.49; normal range 18.50–22.99 and 23.00–24.99; overweight 25.00–27.49 and 27.50–29.99; obese ≥30.00 kg/m^2.

Outcome Variables

Current asthma and respiratory symptoms indicative of asthma were used as outcome variables. Current asthma was defined as meeting the following two criteria: (1) an affirmative response to the question 'Have you ever had asthma?' followed by 'Was this confirmed by a doctor?' and (2) having at least 1 asthma-related symptom in the last 12 months [18]. A subject who was considered to have asthma-related symptoms was one who answered in the affirmative to at least 1 of the following 4 questions: (1) 'Have you had wheezing or whistling in your chest at any time in the last 12 months?'; (2) 'Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?'; (3) 'Have you been woken up by an attack of shortness of breath at any time in the last 12 months?'; (4) 'Have you been woken up by an attack of coughing at any time in the last 12 months?'

Statistical Analysis

The collected data were analyzed using SPSS 11.0 for Windows (SPSS Japan Inc.). In this study, we considered the BMI category of 18.50–22.99 as the reference BMI, and the prevalences of asthma and respiratory symptoms of subjects classified into the other BMI categories were compared with those of subjects classified into the reference category. Multivariate logistic regression models were separately developed by gender to adjust the risks of current asthma and respiratory symptoms associated with BMI for age groups (20–29, 30–39, 40–49, 50–59, 60–69, 70–79 years), smoking status, allergic rhinitis and pet ownership. Because the ECRHS questionnaire is originally designed for subjects aged 20–44 years and is highly validated in this population, a similar analysis was repeated after separating subjects by age group (20–44 and 45–79 years).

Results

The prevalences of wheeze in the last 12 months and current asthma in this study population were 10.2 and 4.2%, respectively. The proportions of subjects in all BMI categories are shown in table 1. The prevalences of obesity (BMI ≥30.00) among both genders were low, that is, 3.0% among males and 2.3% among females. Although more than 70% of the subjects were classified into the BMI category of normal range (18.50–24.99), the majority of them were included in the lower normal BMI category of 18.50–22.99.

Table 2 shows the gender-specific association of BMI categories with current asthma and respiratory symptoms. Generally, the associations of BMI with current asthma and respiratory symptoms in both genders were J-shaped, with the prevalence of the reference category (BMI 18.50–22.99) observed at the bottom of the J-shaped curve. After adjustment for age group, smoking status, allergic rhinitis, and pet ownership, BMI categories greater than 25.00 (25.00–27.49, 27.50–29.99 or ≥30.00) were associated with significantly increased risks of current asthma and respiratory symptoms in both genders when compared with the reference category, except for the association between current asthma and a BMI of 25.00–27.49 in males. Among females, the BMI category of 23.00–24.99 was also associated with increased risks of current asthma and respiratory symptoms compared with the reference category (current asthma: odds ratio, OR, 1.49, 95% confidence interval, CI, 1.16–1.92; wheeze: OR 1.34, 95% CI 1.11–1.61; wheeze with breathlessness: OR 1.29, 95% CI 1.02–1.63; wheeze without a cold: OR 1.46, 95% CI 1.17–1.84).

We repeated the same multivariate analysis after stratification by age group (table 3). The association between increased weight and current asthma and asthma symptoms was not significantly different between the two age groups in both genders. The BMI category of 23.00–24.99 in females aged 45–79 years was also significantly associated with increased risks of current asthma and respiratory symptoms with ORs of about 1.5. That in females aged 20–44 years was also associated with increased risks of current asthma and respiratory symptoms with ORs of about 1.4, whereas this association did not reach statistical significance, probably because of the limited sample size. However, two age groups showed a significant difference in the association of BMI categories lower than 18.50 with current asthma and asthma symptoms in both genders. A significant association between leaner BMI categories and an increased risk of asthma was observed only in subjects aged 45–79 years. This association did not change when the same analysis was repeated after the limitation of subjects to lifetime nonsmokers (data not shown).

Table 1. Proportions of subjects in all BMI categories

BMI category	Males (n = 11,237)		Females (n = 11,725)	
	n	%	n	%
Underweight				
≤16.99	121	1.2	283	2.4
17.00–18.49	394	3.5	1,064	9.1
Normal range				
18.50–22.99	5,272	46.9	6,479	55.3
23.00–24.99	2,648	23.6	1,955	16.7
Overweight				
Pre-obese				
25.00–27.49	1,806	16.2	1,165	9.9
27.50–29.99	659	5.9	512	4.4
Obese				
≥30.00	337	3.0	267	2.9

Discussion

In this study, not only BMI categories greater than 25.00 but also a BMI category of 23.00–24.99 in females was significantly associated with increased risks of current asthma and respiratory symptoms compared with the reference BMI category (18.50–22.99). Although there are numerous studies showing the association between BMI and the risk of asthma, most of them were conducted on non-Asian populations and showed that a BMI greater than 25.00 or 30.00 is associated with an increased risk of asthma or respiratory symptoms [2–7]. However, to the best of our knowledge, none of the studies except one prospective study on nurses in the USA [19] has shown such a low BMI threshold in terms of an increased risk of asthma. This finding suggests that Asian populations are susceptible to an increased weight in association with the risk of asthma as well as other noncommunicable diseases.

In this study, we used the Japanese version of the ECRHS questionnaire, which is a highly validated questionnaire for asthma and respiratory symptoms [17]. The original ECRHS questionnaire has been used on young adults mainly in European countries, and has also shown the association of BMI with asthma and respiratory symptoms [6]. Using a cutoff point of 25.00, men with a BMI of 25.00–30.00 are more likely to have wheeze with shortness of breath or wheeze in the absence of a cold

Table 2. Prevalences (%) and adjusted odds ratios (95% CI) for current asthma and respiratory symptoms associated with body mass index categories

	Males (n = 11,237)		Females (n = 11,724)	
	prevalence, %	OR	prevalence, %	OR
Current asthma				
BMI category				
≤16.99	5.8	1.23 (0.49–3.11)	6.4	1.62 (0.97–2.68)
17.00–18.49	6.9	2.07 (1.34–3.22)	3.6	0.89 (0.63–1.27)
18.50–22.99	3.5	1	3.7	1
23.00–24.99	3.6	1.11 (0.86–1.44)	5.0	1.49 (1.16–1.92)
25.00–27.49	3.9	1.22 (0.92–1.63)	5.7	1.85 (1.38–2.49)
27.50–29.99	6.1	1.94 (1.35–2.78)	5.7	1.83 (1.21–2.76)
≥30.00	10.1	3.31 (2.23–4.92)	9.0	3.02 (1.92–4.74)
Wheeze				
BMI category				
≤16.99	15.7	1.47 (0.86–2.59)	12.0	1.55 (1.06–2.28)
17.00–18.49	14.0	1.48 (1.09–2.02)	7.4	0.96 (0.75–1.24)
18.50–22.99	9.8	1	7.6	1
23.00–24.99	10.8	1.16 (0.99–1.36)	9.7	1.34 (1.11–1.61)
25.00–27.49	12.5	1.36 (1.14–1.62)	12.2	1.78 (1.44–2.19)
27.50–29.99	15.8	1.88 (1.49–2.39)	14.3	2.12 (1.60–2.79)
≥30.00	17.5	2.24 (1.64–3.04)	20.6	3.42 (2.47–4.73)
Wheeze with breathlessness				
BMI category				
≤16.99	9.1	1.27 (0.63–2.57)	8.2	1.72 (1.10–2.71)
17.00–18.49	9.4	1.66 (1.14–2.43)	4.8	1.03 (0.76–1.41)
18.50–22.99	5.8	1	4.6	1
23.00–24.99	6.7	1.24 (1.02–1.51)	5.8	1.29 (1.02–1.63)
25.00–27.49	7.2	1.30 (1.04–1.62)	7.0	1.67 (1.28–2.18)
27.50–29.99	9.0	1.82 (1.35–2.45)	8.5	2.11 (1.49–2.98)
≥30.00	14.3	3.20 (2.27–4.50)	11.8	2.94 (1.95–4.42)
Wheeze without a cold				
BMI category				
≤16.99	13.2	1.82 (1.02–3.27)	9.2	1.94 (1.26–3.00)
17.00–18.49	9.8	1.54 (1.06–2.22)	5.3	1.11 (0.82–1.50)
18.50–22.99	6.5	1	4.6	1
23.00–24.99	7.2	1.21 (0.98–1.46)	6.4	1.46 (1.17–1.84)
25.00–27.49	8.5	1.42 (1.15–1.75)	8.0	1.92 (1.49–2.48)
27.50–29.99	10.7	1.98 (1.49–2.61)	8.3	1.96 (1.38–2.80)
≥30.00	11.9	2.29 (1.59–3.30)	10.6	2.73 (1.79–4.16)

Figures in parentheses are 95% CI.
Adjusted for age group, smoking status, allergic rhinitis and pet ownership.

than those with a BMI of 20.00–25.00 with an OR of 1.26 (95% CI 1.07–1.49) or 1.22 (95% CI 1.05–1.42). However, among females, a BMI of 25.00–30.00 is not significantly associated with respiratory symptoms compared with a BMI of 20.00–25.00, and only a BMI greater than 30.00 is associated with respiratory symptoms. Data from the National Health and Nutrition Examination Survey in the USA [2] also shows that a BMI of 25.0–29.9 is not associated with an increased risk of asthma compared with the reference BMI group (18.5–24.9); only a BMI higher than 30.0 is associated with asthma with an OR of 1.43 (95% CI 1.07–1.92). Compared with these findings from large-

Table 3. Prevalences and adjusted odds ratios for current asthma and respiratory symptoms associated with BMI categories stratified by age group

	Males				Females			
	20–44 years (n = 4,241)		45–79 years (n = 6,832)		20–44 years (n = 4,269)		45–79 years (n = 7,347)	
	prevalence, %	OR	prevalence, %	OR	prevalence, %	OR	prevalence, %	OR
Current asthma								
BMI category								
≤16.99	3.1	0.63 (0.08–4.73)	7.1	1.74 (0.61–4.99)	5.2	0.91 (0.41–2.02)	7.4	2.85 (1.47–5.52)
17.00–18.49	4.9	1.13 (0.56–2.29)	8.3	3.61 (2.05–6.34)	3.8	0.74 (0.46–1.17)	3.2	1.24 (0.70–2.20)
18.50–22.99	4.7	1	2.7	1	5.0	1	2.7	1
23.00–24.99	4.6	1.05 (0.71–1.54)	3.1	1.21 (0.85–1.72)	7.0	1.40 (0.93–2.12)	4.2	1.60 (1.16–2.22)
25.00–27.49	5.1	1.15 (0.74–1.79)	3.4	1.33 (0.91–1.96)	9.8	2.00 (1.23–3.37)	4.8	1.86 (1.29–2.70)
27.50–29.99	5.9	1.40 (0.81–2.43)	6.1	2.60 (1.66–4.25)	9.5	2.08 (1.00–4.31)	4.8	1.85 (1.11–3.07)
≥30.00	12.4	3.07 (1.90–4.97)	7.2	3.58 (1.78–7.21)	12.9	3.04 (1.54–5.99)	7.2	2.96 (1.61–5.46)
Wheeze								
BMI category								
≤16.99	9.4	1.02 (0.30–3.41)	18.8	1.69 (0.93–3.08)	9.7	1.04 (0.57–1.91)	14.2	2.15 (1.32–3.52)
17.00–18.49	9.3	1.05 (0.62–1.78)	18.1	1.85 (0.25–2.72)	6.4	0.76 (0.54–1.09)	8.8	1.26 (0.88–1.82)
18.50–22.99	9.3	1	10.1	1	8.0	1	7.2	1
23.00–24.99	9.5	1.08 (0.82–1.43)	11.3	1.23 (1.01–1.49)	10.2	1.31 (0.92–1.84)	9.3	1.37 (1.10–1.70)
25.00–27.49	8.8	0.99 (0.71–1.39)	14.3	1.58 (1.28–1.94)	17.6	2.50 (1.67–3.73)	10.9	1.65 (1.29–2.12)
27.50–29.99	10.7	1.15 (0.75–1.77)	19.6	2.45 (1.84–3.28)	15.8	2.29 (1.27–4.16)	13.6	2.12 (1.54–2.91)
≥30.00	18.6	2.38 (1.60–3.54)	15.1	1.84 (1.12–3.03)	17.6	2.64 (1.45–4.80)	22.1	3.84 (2.61–5.67)
Wheeze with breathlessness								
BMI category								
≤16.99	3.1	0.56 (0.08–4.20)	11.8	1.55 (0.73–3.31)	6.8	1.15 (0.57–2.36)	9.5	2.39 (1.33–4.29)
17.00–18.49	5.5	1.10 (0.56–2.15)	12.8	2.13 (1.34–3.38)	4.3	0.82 (0.54–1.26)	5.6	1.38 (0.88–2.16)
18.50–22.99	5.5	1	6.0	1	5.1	1	4.2	1
23.00–24.99	6.5	1.31 (0.93–1.84)	6.8	1.24 (0.97–1.58)	6.2	1.24 (0.80–1.91)	5.4	1.33 (1.00–1.76)
25.00–27.49	5.1	1.01 (0.66–1.57)	8.1	1.45 (1.12–1.89)	10.3	2.21 (1.34–3.63)	6.3	1.57 (1.14–2.16)
27.50–29.99	5.9	1.21 (0.70–2.08)	11.2	2.25 (1.56–3.23)	9.7	2.19 (1.05–4.5)	8.1	2.13 (1.44–3.17)
≥30.00	16.5	3.81 (2.47–5.86)	10.1	2.23 (1.25–4.00)	9.6	2.15 (0.99–4.63)	12.8	3.41 (2.10–5.55)
Wheeze without a cold								
BMI category								
≤16.99	6.3	1.07 (0.25–4.60)	16.5	2.11 (1.11–4.02)	7.5	1.28 (0.65–2.54)	10.8	2.83 (1.62–4.95)
17.00–18.49	7.2	1.34 (0.74–2.44)	12.1	1.69 (1.06–2.69)	4.3	0.80 (0.52–1.23)	6.5	1.63 (1.07–2.50)
18.50–22.99	5.9	1	6.9	1	5.3	1	4.1	1
23.00–24.99	6.7	1.26 (0.90–1.76)	7.5	1.20 (0.96–1.52)	7.6	1.49 (1.00–2.22)	5.8	1.50 (1.14–1.98)
25.00–27.49	6.2	1.17 (0.78–1.75)	9.7	1.55 (1.21–1.98)	11.7	2.46 (1.53–3.95)	7.1	1.86 (1.36–2.53)
27.50–29.99	7.4	1.44 (0.88–2.67)	13.1	2.33 (1.66–3.28)	9.6	2.02 (0.97–4.21)	7.6	2.03 (1.35–3.06)
≥30.00	13.4	2.75 (1.74–4.36)	8.7	1.62 (0.87–3.01)	10.8	2.40 (1.15–5.00)	10.6	2.92 (1.74–4.90)

Figures in parentheses are 95% CI. Adjusted for age group, smoking status, allergic rhinitis, and pet ownership.

scale studies performed on Western populations, it can be said that the association between BMI and asthma in our study was more apparent.

Females in this study presented a consistently lower BMI threshold for an increased risk of asthma than males. This susceptibility of overweight females to asthma is compatible with the findings of previous studies [1, 3, 4]. Some studies have suggested that sex hormones play a role in modulating the association between obesity and the risk of asthma. Castro-Rodríguez et al. [20] have shown that the risk of developing asthma in girls who gain weight is also particularly high in those with early menarche. Varraso et al. [21] found a possible role of sex hormones in modulating the relationship between obesity and asthma severity: the association between BMI and asthma severity is stronger in women with early menarche than in those without early menarche.

The J-shaped association between BMI and asthma as well as respiratory symptoms was observed in both genders in the analysis of all the studied subjects (age range 20–79 years). This finding is compatible with reports from the USA and China [7, 22]. However, after stratification by age group, although the relationship between increased weight and asthma was not significantly different between the two age groups, the significant association between leaner BMI categories and an increased risk of asthma/respiratory symptoms was observed only in the subjects aged 45–79 years. A significant association between leaner BMI categories and asthma was not observed in the subjects aged 20–44 years of both genders. This finding suggests the possibility that some asthma patients lose weight because of the burden of their diseases, and this is more pronounced in older patients. However, a temporal relationship between weight loss and the development of asthma is unknown because this study is cross sectional.

One possible reason for the low BMI threshold for an increased risk of asthma among the Japanese population may be related to the differences in body fat content and distribution of fat between ethnic groups. Asian populations have a higher fat content and a more pronounced visceral adiposity than Western populations at an identical BMI [11, 23, 24]. An association between visceral adiposity and an increased risk of asthma has been reported. Sarah et al. [25] showed, using data from South Australia, that not only BMI but also waist circumference and waist-to-hip ratio are associated with asthma. A cross-sectional study on women in California has shown that a large waist circumference (>88 cm) is associated with an increased asthma prevalence, even among women with a normal BMI [26]. Therefore, an increased visceral adiposity at an identical BMI in the Japanese population may be related to the low BMI threshold for an increased risk of asthma. However, because body fat content, waist circumference and waist-to-hip ratio were not measured in this study, the direct relationship between visceral adiposity and the risk of asthma in the Japanese population was not assessed.

Not only an increased visceral adiposity at an identical BMI but also a common genetic background associated with susceptibility to both adiposity and asthma may explain the low BMI threshold for an increased risk of asthma in the Japanese population. Hallstrand et al. [27] have reported that, based on an analysis of 1,001 monozygotic and 383 dizygotic same-sex twin pairs, covariation between obesity and asthma is predominantly caused by shared genetic risk factors for both conditions. Some specific gene polymorphisms may contribute to both obesity and development of asthma. Some studies performed in Japan have shown that a polymorphism in the β3- or β2-adrenergic receptor gene is associated with weight gain, insulin resistance and development of type 2 diabetes [28–31]. Polymorphism in the β2-adrenergic receptor gene has also been associated with asthma phenotype, severity and response to β-agonists [32–34]. However, there has been no study exploring the direct relationship between specific gene polymorphisms and risks of both asthma and obesity, and the confounding effect of ethnicity on this relationship. Further examination is required in this field.

One of the advantages of this study is the sufficiently large sample size for determining the association between the narrow BMI categories and the prevalence of asthma. The major limitation of this study is that the weight and height in this study were self-reported, which is less accurate than measured weight and height. However, because our study was performed using the anonymous questionnaire, we do not assume that self-reported weight and height had a significant impact on the association between BMI and the prevalences of asthma and respiratory symptoms. Another limitation of this study is that we did not have data regarding complications and medications for diseases other than asthma such as endocrinological, metabolic and renal diseases, which influence BMI. However, the potential impact of these diseases on the relationship between BMI and asthma prevalence is limited because the prevalences of these diseases are relatively low in both asthmatic patients and the general population.

In conclusion, this cross-sectional study of the Japanese population showed that the increases in the prevalences of current asthma and respiratory symptoms among females start at a BMI of 23.00. This finding suggests that the BMI threshold for the increased risk of asthma among Asian populations may be lower than that for Western populations. Further studies from other Asian populations are required to explore the effect of ethnicity on the relationship between obesity and asthma.

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ORIGINAL ARTICLE Asthma and Rhinitis

Obesity and aspirin intolerance are risk factors for difficult-to-treat asthma in Japanese non-atopic women

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Clinical & Experimental Allergy

Summary

Background Asthma is a clinical syndrome characterized by variabilities in disease expression and severity. The pathophysiological mechanism underlying anti-asthma treatment resistance is also assumed to be different between disease phenotypes.

Objective To elucidate the effect of gender and atopic phenotype on the relationship between clinical factors and the risk of treatment resistance.

Methods We compared outpatients with difficult-to-treat asthma (DTA; n = 486) in a tertiary hospital for allergic diseases in central Japan with those with controlled severe asthma (n = 621) with respect to clinical factors including body mass index (BMI) and aspirin intolerance using multivariate logistic regression analysis stratified by gender and atopic phenotype.

Results When analysis was performed on the entire study populations, obesity (BMI $\geq$ 30 kg/m^2; adjusted odds ratio (OR) 1.92; 95% confidence interval (95% CI: 1.07–3.43) and aspirin intolerance (OR: 2.56, 95% CI: 1.44–4.57) were found to be the significant risk factors for DTA. However, after the stratification by gender and atopic phenotype, the association between obesity and DTA was significant only in women (OR: 2.76, 95% CI: 1.31–5.78), but not in men (OR: 1.03, 95% CI: 0.38–2.81), and only in non-atopics (OR: 4.03, 95% CI: 1.15–14.08), but not in atopics (OR: 1.54, 95% CI: 0.79–3.02). The similar gender and phenotypic differences were also observed in the association between aspirin intolerance and DTA: namely, the association was significant only in women (OR: 3.96, 95% CI: 1.84–8.50), but not in men (OR: 1.19, 95% CI: 0.46–3.05); and only in non-atopics (OR: 5.49, 95% CI: 1.98–15.19), but not in atopics (OR: 1.39, 95% CI: 0.65–2.98).

Conclusions and Clinical Relevance Significant associations of obesity and aspirin intolerance with DTA were observed only in women and in non-atopics. These findings suggest that a phenotype-specific approach is needed to treat patients with DTA.

Keywords aspirin intolerance, asthma phenotype, difficult-to-treat asthma, gender difference, obesity

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Introduction

Although the majority of asthma patients can obtain good control of asthma, an important subgroup of patients remains symptomatic, despite high-dose treatment. This subgroup is called difficult-to-treat asthma (DTA) [1]. Although the prevalence of this subgroup is considered to be relatively low in the general asthma population, this subgroup is of high concern for healthcare providers, particularly in tertiary hospitals, because of the high risks of emergency department visit and hospital admission and high mortality. Patients with severe asthma are also known to account for a considerable portion of direct and indirect health care costs [2–4]. However, the mechanism and risk factors associated with DTA have not yet been established.

When we consider numerous epidemiological evidence of the association between an increased body mass index (BMI) and new onset of asthma [5–7], it has been hypothesized that obesity may also be associated with severe asthma. However, studies on this association are limited, and there are conflicting reports on this association. The European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) has shown that BMI is associated with asthma severity in women, but not in men [8], whereas results of the Severe Asthma Research Program (SARP) study did not show a difference in BMI in relation to the degree of asthma severity [9]. Inconsistency in the association between BMI and DTA may result from the heterogeneity of the phenotypic presentation of severe asthma. Indeed, from the dataset of the SARP study, Moore et al. have reported that an unsupervised hierarchical cluster analysis identified five distinct clinical phenotypes of asthma, and the prevalence of obese patients is also different between these phenotypes [10]. Therefore, stratified analyses by asthma phenotype are required to establish the potential relationship between BMI and DTA. Furthermore, differences in the ethnic/genetic background among the studied populations may also be a cause of this inconsistency. However, studies on the association between obesity and asthma severity among Asian populations have been limited.

The aim of this study was to determine the phenotypic differences in risk factors associated with DTA in Japanese adult patients with severe persistent asthma. Atopy is a well-documented indicator of asthma phenotype. Therefore, we compared the risk factors for DTA in atopic patients with those in non-atopic patients. The gender difference in the risk factor was also examined in this study, because gender is one of the most important clinical/epidemiological parameters that determine disease expression and phenotype. A study in Japan may have the advantage of having a relatively homogenous ethnic/racial population; therefore, the association between risk factors and DTA can be determined without considering the ethnic/racial difference in the studied patients.

Methods

Subjects

We studied successive patients who visited Sagamihara National Hospital for the first time, one of the largest tertiary hospitals for allergic diseases located in central Japan, between 2000 and 2006. Their medical records were reviewed by their physician, 24 months after their first visit, and their demographical and clinical parameters, disease control and anti-asthma medication use were registered in an electronic database. Data of patients who (1) received care for asthma from the hospital for at least 24 months, (2) received asthma treatment at more than step 4 in the Global Initiative for Asthma (GINA) 2009 guideline (step 4 treatment in the GINA 2009 guideline is a medium or high dose of an inhaled glucocorticosteroid (ICS) with one or more controllers such as a long-acting beta agonist (LABA), a leukotriene receptor antagonist (LTRA) or theophylline), (3) showed good adherence to anti-asthma medication (determined from the pharmacy prescription records by their physicians), (4) did not have any comorbid cardiopulmonary disease (bronchiectasis, chronic bronchitis, old tuberculosis, interstitial pneumonitis, chronic eosinophilic pneumonia, Churg-Strauss syndrome or cardiac diseases), (5) did not have a smoking history greater than 30 pack-years and (6) were 75 years old or younger, were analysed in this study. Among the 3551 registered asthma patients, 1541 received asthma treatment at Step 4 or more. After the exclusion of 369 patients who did not meet the above criteria and 65 patients who had missing data on BMI, onset age, smoking status, atopic status or comorbidity [aspirin intolerance, allergic rhinitis (AR) and atopic dermatitis], 1107 patients were finally included in the analysis. This study was approved by the Ethics Committee of National Sagamihara Hospital, and all the patients provided written informed consent.

Definition of difficult-to-treat asthma

Patients with DTA were defined as those meeting any of the following two criteria: (1) having 'uncontrolled' asthma symptoms in the recent 4 weeks and (2) having one or more unscheduled visits/hospitalizations or rescue steroid bursts in the recent 12 months. Patients with 'uncontrolled' asthma symptoms were defined as those meeting any of the following: having daytime symptoms more than twice/week, having any limitation of activity, having any nocturnal symptoms/awaking or having used a reliever more than twice/week. Patients who did not meet any of these criteria were considered as having controlled asthma.

Potential risk factors and atopic phenotype

Body mass index, duration of asthma, smoking status, atopic phenotype, aspirin intolerance and comorbidity of AR, atopic dermatitis and sinusitis were considered as potential risk factors for DTA. Weight and height were measured by a medical technologist, and BMI was calculated. BMIs were categorized according to the World Health Organization classification [11]: underweight, $<18.5\ kg/m^2$; normal range, $18.5–24.9\ kg/m^2$; overweight, $25.0–29.9\ kg/m^2$; obese, $\geq 30.0\ kg/m^2$. Aspirin intolerance was defined as being 'present' if a patient shows positive results in a provocation test or has an apparent history of severe exacerbation induced by the ingestion of non-steroidal anti-inflammatory drugs. The aspirin provocation test was performed as