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, ≥ 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

previously reported [12]. In brief, doubling doses (25, 50, 100 and 200 mg equivalent to aspirin) of lysine aspirin were intravenously administered to patients in a stable condition. Provocation was stopped at appearance of a positive reaction. A positive reaction in the airways was defined as when the forced expiratory volume in 1 s fell 20% or more from the baseline. Considering the frequent overdiagnosis and underdiagnosis of aspirin intolerance, all the patients suspected of having aspirin-intolerant asthma in our hospital are advised to undergo the aspirin provocation test. Consequently, 32 of 61 patients with aspirin-intolerant asthma in this study were diagnosed on the basis of positive results of the provocation test. Patients with a suspicious history of aspirin intolerance, but not confirmed by the provocation test were classified as 'suspicious'. Patients who showed one or more positive results in a skin test or serum-specific IgE test for eight screened allergens, namely, mite, Japanese cedar pollen, grass pollen, ragweed pollen, cat dander, dog dander, alternaria and aspergillus, were considered as atopic. Others were considered as non-atopic.

Statistical analysis

Descriptive statistics were generated by comparing DTA and controlled asthma patients. Significance testing was performed using Chi-squared analysis for categorical variables and Student t-test or ANOVA for continuous variables. Descriptive statistics comparing BMI categories were also generated for each gender. Adjusted odds ratio (OR) with 95% confidence interval (95% CI) was estimated using multivariate logistic regression analysis with adjustment where necessary for potential confounding variables. The effects of gender and atopic phenotype on the relationship between risk factors and DTA were assessed using repeating multivariate logistic regression analysis after stratifying patients by gender and atopic phenotype. The statistical interactions of gender and atopic phenotype in the relationship between risk factors and DTA were analysed by including interaction terms in logistic regression analysis.

Results

Among 1107 patients studied, 486 were considered as having DTA, and 621 were considered as having controlled severe asthma. The characteristics of the patients are shown in Table 1. DTA patients were more likely than controlled severe asthma patients to be older, have aspirin intolerance and a longer duration of asthma, and be non-atopic. They were similar with respect to other demographical and clinical factors.

Multivariate logistic regression analysis was performed to identify risk factors associated with DTA.

Table 1. Characteristics of study patients

	Difficult-to-treat asthma (N = 486)	Controlled severe asthma (N = 621)	P-value
Age, mean ± SD (years)	52.6 ± 14.7	47.9 ± 15.0	<0.001
Gender, no. (%)			n.s.
Men	194 (40)	224 (36)	
Women	292 (60)	397 (64)	
Duration of asthma, mean ± SD, years	24.7 ± 15.5	19.6 ± 13.6	<0.001
Early-onset asthma (≤12 years), no. (%)	136 (28)	183 (30)	n.s.
Smoking status, no. (%)			
Non-smoker	264 (54)	354 (57)	n.s.
Past smoker	136 (28)	145 (23)	
Current smoker	86 (18)	122 (20)	
Smoking history (pack-years), no. (%)*			n.s.
0	264 (55)	354 (57)	
>0–<10	114 (24)	132 (21)	
≥10	103 (21)	132 (21)	
Body mass index (kgm^2), no. (%)			n.s.
<18.5	41 (8)	44 (7)	
18.5–24.9	324 (67)	429 (69)	
25.0–29.9	90 (19)	125 (20)	
≥30.0	31 (6)	23 (4)	
Atopic phenotype, no. (%)			0.014
Atopy	349 (72)	486 (78)	
Non-atopy	137 (28)	135 (22)	
Aspirin intolerance			<0.001
Absent	431 (89)	588 (95)	
Suspicious	14 (3)	14 (2)	
Present	41 (8)	19 (3)	
Comorbidity, no. (%)			
Allergic rhinitis	271 (56)	402 (65)	0.003
Atopic dermatitis	45 (9)	81 (13)	n.s.
Sinusitis	87 (18)	108 (17)	n.s.
Medication use			
Dose of ICSs, mean±SD, μg/day†	1377 ± 643	1197 ± 485	<0.001
LABA, no. (%)	329 (68)	419 (68)	n.s.
LTRA, no. (%)	170 (35)	199 (32)	n.s.
Theophylline, no. (%)	328 (68)	363 (59)	0.002
Maintenance OCS use (mg), no. (%)‡			
0	398 (82)	587 (95)	<0.001
1–5	63 (13)	27 (4)	
6–10	22 (5)	6 (1)	
≥11	3 (1)	1 (0)	
Uncontrolled asthma symptoms, no. (%)	305 (63)	0 (0)	<0.001
Frequency of unscheduled visits or hospitalization per year, no.			<0.001

(continued)

Table 1 (continued)

	Difficult-to-treat asthma (N = 486)	Controlled severe asthma (N = 621)	P-value
0	214 (44)	621 (100)	
1–2	177 (36)	0 (0)	
3–5	64 (13)	0 (0)	
≥6	31 (6)	0 (0)	

SD, standard deviation; ICSs, inhaled corticosteroids; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; OCSs, oral corticosteroids.

*Numbers may not add to total because of missing data.

†Doses of ICSs are shown as beclometasone equivalent.

‡Doses of OCSs are shown as prednisone equivalent.

First, we included in the analysis, clinically important factors such as age, gender, smoking status, BMI, atopic phenotype and other factors that were found to be statistically significant using univariate analysis (model 1; Table 2). Obesity (patients with BMI ≥ 30 kg/m^2 compared with patients with BMI: 18.5–24.9 kg/m^2; OR: 1.92; 95% CI: 1.07–3.43), aspirin intolerance (OR: 2.56; 95% CI: 1.44–4.57) and disease duration (every 10 years; OR: 1.33; 95% CI: 1.17–1.51) were found to be risk factors for DTA.

To elucidate the potential confounding factor for the association between BMI and DTA, we compared the proportions of patients with atopy and aspirin intolerance between BMI categories (Table 3). The proportions of patients with atopy and aspirin intolerance were not significantly different between BMI category groups. The other potential confounders [smoking status, maintenance oral corticosteroids (OCS) and use of LABA, LTRA and theophylline] were not differently distributed over BMI category groups (data not shown), with the exceptions of age (patients with BMI ≥ 30 kg/m^2 were younger than those with normal BMI) and inhaled corticosteroid (dose of ICS in women with BMI ≥ 30kg/m^2 was slightly higher than that in women with normal BMI). Moreover, to adjust the potential confounding effects of maintenance OCS use and dose of ICSs on the association between risk factors and DTA, they were also included in this multivariate model (model 2; Table 2). Even after this adjustment, the associations of obesity, aspirin intolerance and disease duration with DTA remained significant.

To explore gender difference in the associations of BMI and aspirin intolerance with DTA, we performed the analysis after stratification by gender (Table 4). A statistically significant association between BMI ≥ 30 kg/m^2 and DTA was observed only in women with OR of 2.76, whereas the prevalence of BMI ≥ 30 kg/m^2 in men was similar in DTA and in controlled severe asthma with OR of 1.03. Gender difference was also observed in the association between aspirin intolerance and DTA, with ORs of 1.19 in men and 3.96 in women. The statistical interactions of gender with BMI ≥ 30 kg/m^2 and aspirin intolerance were borderline significant (P interaction, 0.11, and 0.07, respectively). The proportion of current smokers was significantly different between genders (data not shown). To exclude the potential confounding effect of current smoking on the gender difference in risk factor for DTA, we also repeated the same multivariate analysis after the restriction of patients to lifetime non-smokers. This analysis showed an almost similar gender difference to the above analysis, indicating that these gender differences in risk factor for DTA is not confounded by the gender difference in smoking status.

The analysis was also repeated after stratification by atopic phenotype (Table 5). A strong association between BMI ≥ 30 kg/m^2 and DTA was observed only in non-atopic patients (OR: 4.03; 95% CI: 1.15–14.08). A phenotypic difference was also observed in the relationship between aspirin intolerance and DTA, with ORs

Table 2. Adjusted odds ratios and 95% confidence intervals for difficult-to-treat asthma according to risk factors

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Age (every 10 years)	1.12	0.99–1.27	1.10	0.97–1.24
Gender				
Men	1		1	
Women	0.92	0.70–1.20	0.92	0.70–1.20
Duration of asthma (every 10 years)	1.33	1.17–1.51	1.26	1.11–1.44
Early-onset asthma (≤12 years)	0.70	0.45–1.11	0.76	0.48–1.21
Smoking status				
Non-smoker	1		1	
Past smoker	1.21	0.89–1.64	1.10	0.80–1.50
Current smoker	1.26	0.89–1.78	1.23	0.87–1.76
Body mass index (kg/m^2)				
<18.5	1.33	0.83–2.13	1.29	0.80–2.10
18.5–24.9	1		1	
25.0–29.9	0.89	0.64–1.22	0.89	0.64–1.23
≥30.0	1.92	1.07–3.43	1.87	1.03–3.38
Atopic phenotype				
Atopy	1		1	
Non-atopy	1.13	0.82–1.55	1.13	0.82–1.56
Allergic rhinitis	0.80	0.62–1.04	0.83	0.64–1.08
Aspirin intolerance				
Absent	1		1	
Suspicious	1.12	0.54–2.57	1.13	0.51–2.51
Present	2.56	1.44–4.57	2.27	1.26–4.11
Medication use				
Maintenance OCS				
No			1	
Yes			2.65	1.71–4.10
Dose of ICSs (every 100μg)			1.04	1.02–1.07

ICSs, inhaled corticosteroids; OCSs, oral corticosteroids.

Table 3. Patient characteristics according to body mass index categories

	Body mass index (kg/m^2)				
	<18.5 (n = 25)	18.5–24.9 (n = 283)	25.0–29.9 (n = 92)	≥30.0 (n = 18)	P-value
Men					
Atopic phenotype, no. (%)					n.s
Atopy	19 (76)	216 (76)	68 (74)	14 (78)	
Non-atopy	6 (24)	67 (24)	24 (26)	4 (22)	
Aspirin intolerance					n.s
Absent	22 (88)	262 (95)	87 (96)	18 (100)	
Suspicious	0 (0)	7 (3)	1 (1)	0 (0)	
Present	3 (12)	14 (5)	4 (4)	0 (0)	
	(n = 60)	(n = 470)	(n = 123)	(n = 36)	P-value
Women					
Atopic phenotype, no. (%)					n.s
Atopy	48 (80)	357 (76)	88 (72)	25 (69)	
Non-atopy	12 (20)	113 (24)	35 (29)	11 (31)	
Aspirin intolerance					n.s
Absent	51 (92)	437 (95)	112 (91)	30 (84)	
Suspicious	4 (7)	11 (2)	2 (2)	3 (8)	
Present	5 (8)	22 (5)	9 (7)	3 (8)	

Table 4. Associations of body mass index and aspirin intolerance with risk of difficult-to-treat asthma stratified by gender

	Difficult-to-treat asthma N (%)	Controlled severe asthma N (%)	OR*	95% CI
Men (n = 418)				
Body mass index (kg/m^2)				
<18.5	15 (8)	10 (5)	1.91	0.80–4.59
18.5–24.9	135 (70)	148 (66)	1	
25.0–29.9	36 (19)	56 (25)	0.69	0.42–1.14
≥30.0	8 (4)	10 (5)	1.03	0.38–2.81
Aspirin intolerance				
Absent	178 (92)	211 (94)	1	
Suspicious	4 (2)	4 (2)	0.93	0.22–4.25
Present	12 (6)	9 (4)	1.19	0.46–3.05
Women (n = 689)				
Body mass index (kg/m^2)				
<18.5	26 (9)	34 (9)	1.17	0.66–2.07
18.5–24.9	189 (65)	281 (71)	1	
25.0–29.9	54 (19)	69 (17)	1.02	0.66–1.55
≥30.0	23 (8)	13 (3)	2.76†	1.31–5.78
Aspirin intolerance				
Absent	253 (87)	377 (95)	1	
Suspicious	10 (3)	10 (3)	1.27	0.50–3.21
Present	29 (10)	10 (3)	3.96‡	1.84–8.50

OR, odds ratio; 95% CI, 95% confidence interval.

*Adjusted for age, duration of asthma, early-onset asthma, smoking status, atopic phenotype and allergic rhinitis.

†Statistical significance in interaction term of BMI ≥ 30kg/m^2 × women; P-interaction = 0.11

‡Statistical significance in interaction term of aspirin intolerance × women; P-interaction = 0.07

of 1.39 in atopic patients, and 5.49 in non-atopic patients. The interaction between BMI ≥ 30 kg/m^2 and atopic phenotype was not statistically significant (P interaction = 0.20), probably because of the limited sample size (only 15 non-atopic obese patients). However, OR of interaction term of BMI ≥ 30 kg/m^2 × non-atopy was relatively high (OR: 2.49; 95% CI: 0.61–10.10; data not shown). On the other hand, the interaction between aspirin intolerance and atopic phenotype was statistically significant (P interaction = 0.02).

To elucidate the effects of gender and atopic phenotype on the association between risk factors and DTA, further stratification was performed by combining with gender and atopic phenotype, and the logistic regression analysis was repeated (Table 6). Among these four groups, that is, atopic men, non-atopic men, atopic women and non-atopic women, the strongest associations of BMI and aspirin intolerance with DTA were observed in the group of non-atopic women, with OR of 4.50 for BMI ≥ 30 kg/m^2 and OR of 26.22 for aspirin intolerance. A significant association between BMI ≥ 30 kg/m^2 and DTA was also observed in the group of atopic women. On the other hand, there was no significant association between BMI and DTA in the atopic and non-atopic men. Conversely, the significant association between BMI < 18.5 kg/m^2 and DTA was observed in atopic men.

Discussion

In this analysis on 1107 outpatients with severe asthma in one of the largest tertiary hospitals for allergic diseases in Japan, we have identified the risk factors for DTA as obesity, aspirin intolerance and a long disease duration. Furthermore, after stratification by gender and atopic phenotype, obesity and aspirin intolerance were found to be significant risk factors for DTA only in women and in non-atopics. These findings suggest that the pathophysiological mechanism underlying treatment resistance is different between disease phenotypes.

Women with BMI ≥ 30 kg/m^2 were about three times more likely to have DTA than those with normal BMI, whereas no significant association between BMI and DTA was observed in men. On the other hand, lean atopic men with BMI ≤ 18.5 kg/m^2 were more likely to have DTA than atopic men with normal BMI with OR of 2.78, indicating that there is a small subgroup of lean atopic male DTA patients. This finding supports

Table 5. Associations of body mass index and aspirin intolerance with risk of difficult-to-treat asthma stratified by atopic phenotype

	Difficult-to-treat asthma *N* (%)	Controlled severe asthma *N* (%)	OR*	95% CI
Atopics (n = 835)				
Body mass index (kg/m^2)				
<18.5	30 (9)	37 (8)	1.36	0.80–2.31
18.5–24.9	238 (68)	335 (69)	1	
25.0–29.9	61 (18)	95 (20)	0.87	0.60–1.27
≥30	20 (6)	19 (4)	1.54	0.79–3.02
Aspirin intolerance				
Absent	326 (93)	462 (95)	1	
Suspicious	8 (2)	10 (2)	1.03	0.39–2.72
Present	15 (4)	14 (3)	1.39	0.65–2.98
Non-atopics (n = 272)				
Body mass index (kg/m^2)				
<18.5	11 (8)	7 (5)	1.53	0.52–4.57
18.5–24.9	86 (63)	94 (70)	1	
5.0–29.9	29 (21)	30 (22)	1.02	0.53–1.96
≥30	11 (8)	4 (3)	4.03†	1.15–14.08
Aspirin intolerance				
Absent	105 (77)	126 (93)	1	
Suspicious	6 (4)	4 (3)	1.52	0.37–6.17
Present	26 (19)	5 (4)	5.49‡	1.98–15.19

OR, odds ratio; 95% CI, 95% confidence interval.

*Adjusted for age, gender, duration of asthma, early-onset asthma, smoking status and allergic rhinitis.

†Statistical significance in interaction term of BMI ≥ 30 kg/m^2 × non-atopy; P-interaction = 0.20.

‡Statistical significance in interaction term of aspirin intolerance × non-atopy; P-interaction = 0.02.

the need for stratified analysis by genders, because the incorporation of these lean male DTA patients may confuse the overall relationship between obesity and DTA. The mechanism underlying the relationship between gender and risk of severe asthma associated with BMI is as yet unclarified. A study by Varraso et al. suggests the possible role of sex hormones in modulating the relationship between obesity and asthma. They found that the association between BMI and asthma severity is stronger in women with early menarche than in those without early menarche [13].

This study was performed on a population with a relatively homogeneous ethnic/racial/genetic background. More than 95% of the patients studied were considered to be Japanese Mongoloid. Some reports have shown that the association between obesity and non-communicable diseases such as type 2 diabetes or cardiovascular diseases is different between ethnic groups [14, 15]. In particular, Japanese individuals are reported to be more vulnerable to obesity and the development of type 2 diabetes than American and European individuals [16]. There may be such an ethnic/racial difference in the risk of severe asthma, and this difference may be one of the causes of the inconsistency in the association between obesity and DTA in previous studies.

Although non-atopy itself was not an independent risk factor, the association between obesity and DTA was stronger in non-atopic patients than in atopic patients. This finding suggests that obesity and non-atopy may share similar inflammatory characteristics that can make asthma difficult to control. Studies on the interaction between atopy and obesity as a risk factor for severe asthma are as yet limited. Olafsdottir et al. have shown that the level of high sensitive C-reactive protein is elevated in obese patients, and is also associated with the risk of non-atopic asthma [17].

Many studies have shown that aspirin intolerance is a risk factor for severe/DTA [8, 9, 18, 19]. Our data also confirmed the strong relationship between DTA and aspirin intolerance as determined using a provocation test and/or an apparent episode, and this relationship was significant in women, but not in men, and in non-atopics, but not in atopics. About 50% of the aspirin-intolerant patients in our study were diagnosed on the basis of positive results of a provocation test. Therefore, the diagnosis of aspirin intolerance and the association between definitively diagnosed aspirin intolerance and DTA shown in this study were considered to be more accurate than those in the previous reports. Unfortunately, we do not have information on how many patients were advised to undergo the provocation test and how many patients did not undergo the test. We assumed that the proportion of non-respondents to the invitation was about 40%. However, we consider that there was no selection between the patients who underwent the provocation test and those who did not. Few studies have also shown a gender difference in the association between aspirin intolerance and asthma severity [19]. Aspirin intolerance is also more prevalent in female patients than in male patients [19, 20]. Sex hormones are assumed to play some role in the development of aspirin intolerance and have an interactive effect on asthma severity. Recent evidence has shown that the prevalence of atopy in patients with aspirin-intolerant asthma is similar to that in the general population [19]; therefore, the atopic condition is not supposed to affect the development of aspirin intolerance. However, our data showed that the relationship between aspirin intolerance and the risk of DTA was stronger in non-atopics than in atopics.

The combined effect of BMI ≥ 30kg/m^2 × women, aspirin intolerance × women or BMI ≥ 30kg/m^2 × non-atopy as risk factors for DTA was significant in the stratified analysis, but did not gain statistical significance on a multiplicative scale. To evaluate additive interaction of BMI ≥ 30kg/m^2 × women, aspirin intolerance × women, BMI ≥ 30kg/m^2 × non-atopy or aspirin

Table 6. Associations of body mass index and aspirin intolerance with risk of difficult-to-treat asthma stratified by gender and atopic phenotype

Gender	Phenotype	Risk factor	Difficult-to-treat asthma *N* (%)	Controlled severe asthma *N* (%)	OR*	95% CI
Men (n = 418)	Atopic (n = 317)	Body mass index (kg/m^2)				
		<18.5	12 (9)	7 (4)	2.78	1.01–7.64
		18.5–24.9	99 (70)	117 (67)	1	
		25.0–29.9	25 (18)	43 (24)	0.69	0.38–1.24
		≥30	5 (4)	9 (5)	0.73	0.22–2.43
		Aspirin intolerance				
		Absent	134 (95)	170 (97)	1	
		Suspicious	3 (2)	1 (1)	3.55	0.34–36.87
		Present	4 (3)	5 (3)	0.84	0.21–3.42
	Non-atopic (n = 101)	Body mass index (kg/m^2)				
		<18.5	3 (6)	3 (6)	0.85	0.13–5.73
		18.5–24.9	36 (68)	31 (65)	1	
		25.0–29.9	11 (21)	13 (27)	1.15	0.38–3.46
		≥30	3 (6)	1 (2)	3.10	0.27–35.10
		Aspirin intolerance				
		Absent	44 (83)	41 (92)	1	
		Suspicious	1 (2)	3 (6)	0.20	0.02–2.70
		Present	8 (15)	4 (8)	1.59	0.41–6.23
Women (n = 689)	Atopic (n = 518)	Body mass index (kg/m^2)				
		<18.5	18 (9)	30 (10)	1.06	0.55–2.02
		18.5–24.9	139 (67)	218 (70)	1	
		25.0–29.9	36 (17)	52 (17)	1.04	0.64–1.71
		≥30	15 (7)	10 (3)	2.52	1.07–5.97
		Aspirin intolerance				
		Absent	192 (92)	292 (94)	1	
		Suspicious	5 (2)	9 (3)	0.72	0.23–2.28
		Present	11 (5)	9 (3)	1.81	0.71–4.59
	Non-atopic (n = 171)	Body mass index (kg/m^2)				
		<18.5	8 (10)	4 (5)	2.35	0.54–10.15
		18.5–24.9	50 (60)	63 (72)	1	
		25.0–29.9	18 (21)	17 (20)	0.92	0.37–2.26
		≥30	8 (10)	3 (3)	4.50 †	1.00–21.36
		Aspirin intolerance				
		Absent	61 (73)	85 (98)	1	
		Suspicious	5 (6)	1 (1)	8.68	0.67–113.73
		Present	18 (21)	1 (1)	26.22 ‡	3.21–213.96

OR, odds ratio; 95% CI, 95% confidence interval.

*Adjusted for age, duration of asthma, early-onset asthma, smoking status and allergic rhinitis.

†Statistical significance in interaction term of BMI ≥ 30kg/m^2 × women × non-atopy; P-interaction = 0.40.

‡Statistical significance in interaction term of aspirin intolerance × women × non-atopy; P-interaction = 0.01.

intolerance × non-atopy, we also estimated the relative excess risk due to interaction (RERI) [21] (data not shown). All the RERI values were greater than 0 (1.34, 1.98, 0.92 and 1.03, respectively), indicating that there are important biological interactions between them.

Many studies have shown that pathophysiology-specific treatment can improve asthma control. For example, weight reduction in obese patients with asthma has shown to improve disease control [22–24]. Some studies also have shown that patients with aspirin intolerance benefits from aspirin desensitization [25, 26]. These pathophysiology-specific treatments are valuable particularly in patients who are resistant to conventional anti-asthma medications, namely, DTA. Our findings are important in

that they suggest the possibility that non-atopic women are more likely to benefit from weight reduction than other patients, and that non-atopic women with aspirin-intolerant asthma may be good candidates for aspirin desensitization.

In this study, we defined DTA considering the description of the GINA 2009 guideline, in which DTA is defined as follows: 'Patients who do not reach an acceptable level of control at Step 4 can be considered to have difficult-to-treat asthma'. We defined 'not reaching an acceptable level of control' as 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; namely, current level of control and exacerbation in the recent 12 months. There has been no universally accepted definition of severe/DTA in the literature. Indeed, large-scale clinical studies of severe/DTA, such as SARP [9], ENFUMOSA [8] and TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) [27] studies, have used different definitions of severe/DTA. However, they are similar with each other in terms of inclusion of both current control status and exacerbations in the recent 1 year as an indicator of asthma severity and treatment resistance. Therefore, the definition of DTA in our study was also similar to those of these large-scale clinical studies.

The major limitation of this study is related to its design. The causal relationship between risk factors and DTA is unclear from this study, because this study did not evaluate longitudinal changes in disease control with time in relation to risk factors. The subjects of this study were patients from a single centre. A single-centre study has less external validity than a multicentre study. However, a single-centre study has an advantage in terms of the relatively high internal validity, if it was performed in a large tertiary hospital whose clinical information is reliable.

Another limitation is related to the method of measurement of obesity. We used only BMI as a marker of obesity. However, BMI is not a sensitive marker for central obesity when compared with measures of central obesity such as waist circumstance or waist-to-hip ratio [28]. Although there was no statistical significant association between BMI $\geq$ 30 kg/m^2 and DTA in men, there is a possibility that more sensitive methods of measurement of central obesity can reveal obesity-DTA relationship also in men.

The limited sample size may be another limitation. The total sample size of this study was not small, but the sample size was insufficient for the analysis of the interaction between the risk factors. In particular, we were unable to elucidate whether there was an interaction between obesity and aspirin intolerance as risk factors for DTA, because there were only three obese aspirin-intolerant patients, which was small for statistical analysis.

We recruited only patients with good adherence to anti-asthma medications to participate in the study. The physician of each patient evaluated the patent's adherence to anti-asthma medications from pharmacy records on how many prescriptions were actually filled; we did not measure adherence rate by more objective methods such as using an electric measuring device. Therefore, there is a possibility that the actual adherence rate was slightly lower than that evaluated by the physicians. However, a study showed an increased medication adherence rate with increasing severity of asthma, suggesting that the adherence rate of severe persistent asthma is relatively high [29]. We also do not believe that potential unrecognized poor adherence to anti-asthma medications (even if it exists) confounds the gender and phenotypic difference in the relationship of obesity and aspirin intolerance with DTA.

In conclusion, we found obesity and aspirin intolerance to be risk factors for DTA. The associations of obesity and aspirin intolerance with DTA were significant in women, but not in men, and in non-atopics, but not in atopics. These findings suggest that a phenotype-specific approach is needed to treat patients with DTA.

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ORIGINAL ARTICLE

Age-related Prevalence of Allergic Diseases in Tokyo Schoolchildren

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ABSTRACT

Background: The International Study of Asthma and Allergies in Childhood (ISAAC) has reported the prevalence of asthma and allergic diseases in many countries.

Methods: We used the ISAAC core written questionnaire to examine the prevalence of asthma and allergic diseases in 6- to 14-year old schoolchildren in Tokyo. In 2005, we conducted a cross-sectional survey of all schoolchildren in all public schools located in the Setagaya area of Tokyo.

Results: Data were collected from 27,196 children in 95 schools. Prevalence ranged from 10.5% to 18.2% for asthma symptoms and from 10.9% to 19.6% for atopic dermatitis, with both conditions tending to decrease with age. As has been previously reported for all age groups, significantly higher rates of current asthma are observed in boys than in girls. The prevalence of allergic rhinoconjunctivitis exhibited a different pattern from that of asthma and atopic dermatitis, peaking at the age of 10 (34.8%). Prevalence of allergic rhinoconjunctivitis was 1.5 to 2-fold higher than the previous ISAAC studies that were performed in Tochigi and Fukuoka. In all age groups, symptoms of allergic conjunctivitis were more frequent from February to May, which coincides with the Japanese cedar pollen season, and were less frequent between June to September.

Conclusions: The prevalence of asthma and atopic dermatitis was higher in younger schoolchildren. Tokyo schoolchildren appear to have extremely high prevalence rates of seasonal allergic rhinoconjunctivitis.

KEY WORDS

asthma, atopic dermatitis, ISAAC, prevalence, rhinitis

INTRODUCTION

Asthma and allergic diseases are common in children. Urbanization has led to an increase in allergic diseases, and thus, this has become an important health problem in today's society.

Many countries have conducted large prevalence surveys of asthma and allergic diseases. In 1991, the International Study of Asthma and Allergic diseases in Childhood (ISAAC) established a standardized methodology to compare the prevalence and severity of asthma and atopic diseases in children.[1] Since starting the study in 1993, the ISAAC Phase One study group has examined the prevalence rates of asthma in children around the world and found that over a 12-month period, the highest rates were for children living in the UK, Australia, and New Zealand, while the lowest were in children residing in Eastern Europe, the Asia-Pacific, and Africa.[2] In contrast, the highest prevalence rates of symptoms related to allergic rhinoconjunctivitis occurred in countries that were scattered across the world. Moreover, the prevalence of allergic rhinoconjunctivitis in children aged 13-14 years was higher than those aged 6-7 years in all of the countries studied around the world. Interestingly, this pattern was not seen for asthma.

The Japanese Ministry of Education, Culture, Sports, Science and Technology has announced that the prevalence of doctor-diagnosed asthma in children has doubled from 1994 to 2004. They also reported that schoolchildren are more likely than other age groups to develop asthma.[3]

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In Japan, ISAAC surveys have been conducted in Fukuoka, the eighth largest city in Japan, and in Tochigi, which is an average-sized city. In Tochigi in 1995, the prevalence of allergic rhinoconjunctivitis in children aged 13-14 was 21.5%.[4] In Fukuoka, the 12-month prevalence of allergic rhinoconjunctivitis among children aged 6-7 increased from 7.8% in 1994 to 10.6% in 2002, while over the same period of time in children aged 13-14, it increased from 14.9% to 17.6%.[5] Similar trends were also seen in many other Asia-Pacific countries and in India. In contrast, the prevalence of asthma, however, did not notably increase in any of these countries or in Japan.

Children born in urban areas are expected to have higher prevalences of allergic diseases than those born in rural areas.[6] Although Tokyo is the largest city in Japan, and thereby, would be expected to have the highest prevalence of allergic diseases, previous ISAAC surveys have never been done in this city. Thus, there were two aims of the present study. First, the ISAAC protocol was used to determine whether age-related differences are responsible for the prevalence of allergic symptoms observed among Tokyo schoolchildren. Based on these findings, the second part of the study was designed to compare these results with the findings of previous ISAAC studies in Japan and determine if there were differences between large urban areas and other areas that were less populated/more rural in nature.

METHODS

SUBJECTS

The survey was conducted from May to June, 2005, in accordance with the ISAAC protocol.[7] The present survey was part of an investigation by the Japanese Asthma Survey Group (JASG), and was aimed at surveying the prevalence of allergic diseases in all age groups at various places throughout Japan.

Setagaya was chosen as the research zone for this study, as it is located in the center of Tokyo. During the study period, this was the biggest geographical region within the Greater Tokyo Area. Setagaya has a population density that is close to the Tokyo average, with 830,000 inhabitants living in about 58 km^2 (22 square miles).

In Japan, compulsory education consists of nine grades (years). In April of each year, children who have reached the age of 6 enroll in an elementary school that has six grades. After graduating from elementary school, students enter junior high school, which has three grades. The current survey covered all of the schoolchildren in these nine grades. During the study period, Setagaya had 64 public elementary schools and 31 public junior high schools, with approximately 80% of the children attending these public schools. With the help of the Setagaya City Board of Education, we were able to investigate all public elementary and junior high school students.

QUESTIONNAIRE

We used the ISAAC written questionnaire for 6-7 year olds for the elementary school children and the questionnaire for 13-14 year olds for the junior high school children. Our group previously translated the ISAAC written questionnaire from English into Japanese and then back into English to confirm its accuracy. An explanatory note for eczema and rash was added, as the Japanese language does not normally differentiate between the two. The questionnaire was distributed at all of the schools, with the children then taking it home to be filled out. Prior to filling out the questionnaire, all participants in the study provided informed consent. For the younger age group, the children's parents completed the questionnaire, while the children in the older age group completed it on their own. After completing the form, the questionnaires were taken back to the schools for collection.

Based on the questionnaire answers, we evaluated the 12-month point prevalences of asthma, allergic rhinoconjunctivitis, and atopic dermatitis.[7] To define current asthma and examine wheezing during the previous 12 months, we asked the following question, "Have you (has your child) had wheezing or whistling in the chest in the last 12 months?". If current asthma was present, the questionnaire further assessed the frequency and severity of the episodes. Questions pertaining to allergic rhinoconjunctivitis included those regarding sneezing or a running or blocked nose (in the absence of flu) that was associated with itchy-watery eyes over the last 12 months. The monthly frequency among children who had symptoms of allergic rhinoconjunctivitis was evaluated by asking, "In which of the past 12 months did this nose problem occur? (please tick any which apply)." Atopic dermatitis was considered to be present when there was an itchy, relapsing skin rash that affected the flexural areas during the preceding 12 months.

ETHICAL CONSIDERATIONS

The ethics committee of the National Center for Child Health and Development approved the study protocol. The older children directly provided informed consent. However, since parents completed the questionnaire for the younger children, parental informed consent was obtained in this group.

STATISTICAL ANALYSIS

Analyses focused on changes in the 12-month prevalence of the symptoms, which included asthma, rhinitis and dermatitis. Data were analyzed using SPSS 15.0J (SPSS Inc., Chicago, IL, USA), with a p-value of <0.05 defined as being statistically significant. Proportions between the two groups were compared using chi-squared tests. The interrelationship between age and the 12-month point prevalence was evaluated by Pearson's correlation.

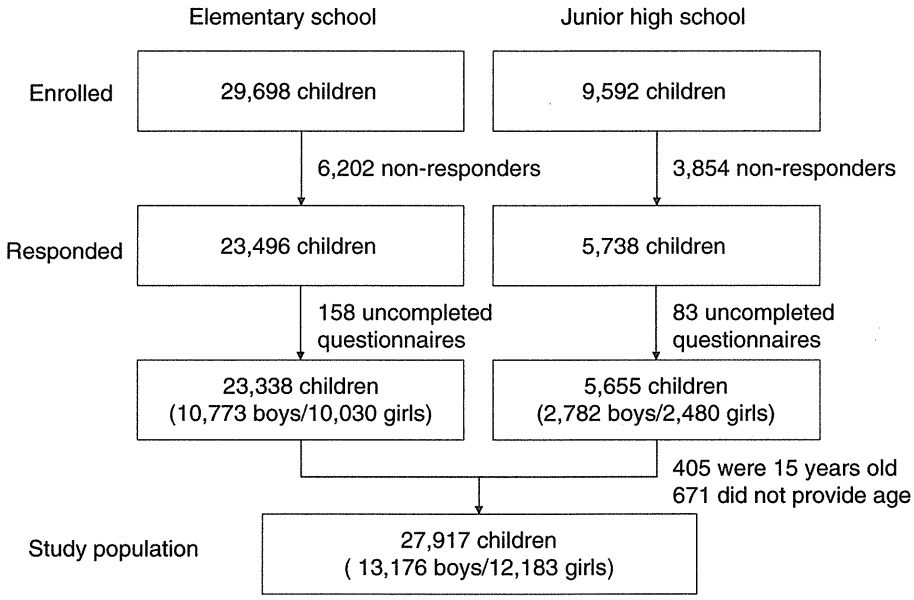

Fig. 1 Study subjects and the study protocol. All students in all public schools in Setagaya from May through June of 2005 were enrolled in the study, with more than 70% of all children aged 6-14 years at these schools included in the analyses.

RESULTS

Of the 95 schools approached, all agreed to participate, which resulted in a target population of 39,290 children (Fig. 1). Out of this population, a total of 23,338 elementary school children (78.6%), aged 6 to 12 years, and 5,655 junior high school children (59.0%), aged 12 to 15 years, completed questionnaires. For the 15-year-old children, numbers were quite small and thus, we excluded this group from the analyses. Of the 27,917 children aged 6 to 14 that we were able to analyze, 13,176 (47.2%) were boys, and 12,183 (43.7%) were girls. In 2,558 children, we were not able to determine the gender.

Current asthma prevalence ranged from 10.5% to 18.2% among all age groups (Table 1), with the highest found in the younger children. There was a strong inverse correlation between the age and prevalence (r = -0.956, P < .001). When boys were compared to girls in all of the age groups, boys had significantly higher rates of current asthma (P < .001 for ages 6 to 12, P < .05 for ages 13 and 14). While frequent wheezing and sleep disturbance were more common in younger children and in boys, exercise-induced wheezing during the last 12 months was more common in older children of both sexes and in younger boys.

In contrast to the asthma findings, the prevalence of allergic rhinoconjunctivitis tended to be higher in older children (Table 2), increasing rapidly from age 6 to 10. By the age of 10, the prevalence of allergic rhinoconjunctivitis was 34.8%. In all age groups, symptoms of allergic rhinoconjunctivitis were more frequent from February to May, and less frequent from June to September (Fig. 2). On a day-to-day basis, moderate or severe interference due to rhinoconjunctivitis was more common in older children of both sexes and in boys.

Similar to the asthma findings, the prevalence of atopic dermatitis was highest in younger children, with analyses showing a significant inverse correlation with age (r = -0.983, P < .001) (Table 2). However, severe symptoms of atopic dermatitis were more often observed in older children. There were no gender differences noted for the prevalence or severity of atopic dermatitis.

Among the 27,389 children aged 6 to 14 years who completed questionnaires about their current asthma, allergic rhinoconjunctivitis and atopic dermatitis symptoms, 14.0% had current asthma. Of these children, 41.6% and 31.3% had the symptoms of allergic rhinoconjunctivitis and atopic dermatitis, respectively. While 43.1% of the children in this study had ≥1 of the symptoms during the past 12 months, only 2.2% had all three symptoms (Fig. 3). Table 3 shows the overlap of the current symptoms for three diseases based on age among the 27,389 children.

DISCUSSION

In 2005 we examined the prevalence of asthma, allergic rhinoconjunctivitis and atopic dermatitis in a large sample of schoolchildren who resided in the Tokyo metropolitan area of Setagaya. The prevalence of current asthma and atopic dermatitis was inversely correlated with age, whereas that of allergic rhinoconjunctivitis showed an age-dependent increase until

Table 1 Prevalence (%) and severity of asthma symptoms in 6 to 14 year old children

Symptoms	Age (years)								
	6	7	8	9	10	11	12	13	14
Current wheeze									
Total	18.2	15.7	15.6	13.3	14.5	11.9	12.0	10.3	10.5
Boys	***21.4	***17.8	***17.8	***16.0	***17.4	***14.7	***14.9	*12.0	*12.0
Girls	14.5	13.5	12.9	10.9	10.9	9.3	9.3	8.6	8.8
Wheezing attacks ≥ 4 /12 months									
Total	5.1	3.7	4.4	3.7	4.0	3.3	3.1	3.3	3.1
Boys	*6.0	**4.6	**5.5	*4.4	*4.6	*4.2	*4.0	4.1	3.1
Girls	4.3	2.8	3.2	2.9	3.0	2.7	2.3	2.7	3.0
Awakened by wheezing ≥ 1 /wk									
Total	2.4	2.3	2.0	2.0	1.6	1.3	1.2	0.6	1.2
Boys	3.0	2.4	2.2	2.1	1.8	*1.6	1.7	0.6	*2.0
Girls	2.0	2.2	1.7	1.9	1.2	0.8	0.9	0.7	0.5
Speech limitation									
Total	2.4	1.7	1.5	1.8	1.2	1.2	1.4	0.9	1.8
Boys	**3.3	2.0	1.8	2.2	*1.7	***1.8	***2.0	1.2	1.9
Girls	1.6	1.6	1.1	1.5	0.8	0.5	1.0	0.7	2.0
Exercised-induced wheezing									
Total	5.8	6.0	6.2	6.7	7.6	7.1	11.7	13.2	14.4
Boys	***7.6	***7.3	6.6	**7.9	7.8	7.9	12.0	13.6	*14.3
Girls	4.1	4.6	5.7	5.3	6.8	6.4	12.1	13.1	15.0

Comparisons were performed between boys and girls for each symptom and age. *$P < .05$, **$P < .01$, ***$P < .001$.

Table 2 Prevalence (%) and severity of allergic rhinoconjunctivitis and atopic dermatitis symptoms in 6 to 14 year old children

Symptoms	Age (years)								
	6	7	8	9	10	11	12	13	14
Allergic rhinoconjunctivitis									
Total	19.7	22.5	25.1	26.9	34.8	32.5	33.8	27.8	29.1
Boys	*21.2	23.1	26.3	27.1	35.6	33.0	35.2	29.3	27.0
Girls	17.7	22.3	23.9	25.4	34.5	31.9	32.3	27.1	30.1
Moderate to severe interference by rhinitis									
Total	10.2	11.9	14.1	14.6	21.4	19.9	21.5	18.1	20.6
Boys	11.2	*13.1	**16.1	15.1	*23.4	*21.1	*23.8	18.9	20.6
Girls	9.5	10.7	12.3	13.3	20.6	18.1	19.4	15.9	19.8
Atopic dermatitis									
Total	19.6	17.4	16.9	16.6	15.3	15.0	13.6	11.9	10.9
Boys	19.9	17.0	17.3	17.7	15.6	14.8	13.3	10.7	10.3
Girls	19.7	18.5	16.2	15.6	14.8	15.0	14.1	12.8	11.4
Kept awake by rash ≥1/wk									
Total	1.6	1.7	1.7	1.5	1.5	1.3	1.9	2.5	2.5
Boys	1.5	1.8	1.9	1.6	1.2	1.2	2.1	2.0	2.7
Girls	1.8	1.6	1.4	1.5	1.4	1.5	1.6	2.9	2.2

Comparisons were performed between boys and girls for each symptom and age. *$P < .05$, **$P < .01$, ***$P < .001$.

reaching the age of 10. These correlations also showed an overlap of the prevalences for the three diseases in accordance with age. These findings suggest that the peak prevalence of asthma and atopic dermatitis may occur at or before the age of 5, similar to that previously reported. In an Australian study, the frequency of atopic dermatitis increased and reached a maximum prevalence by the age of 1, after which it decreased in an age-dependent manner in a group of preschool-age children.[8] For asthma, the

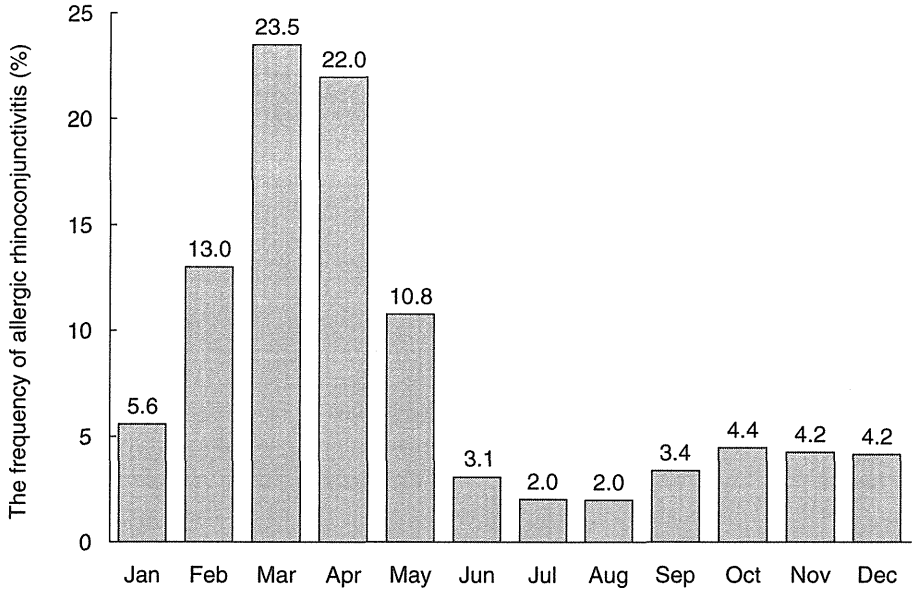

Fig. 2 Monthly frequency of allergic rhinoconjunctivitis in all subject age groups.

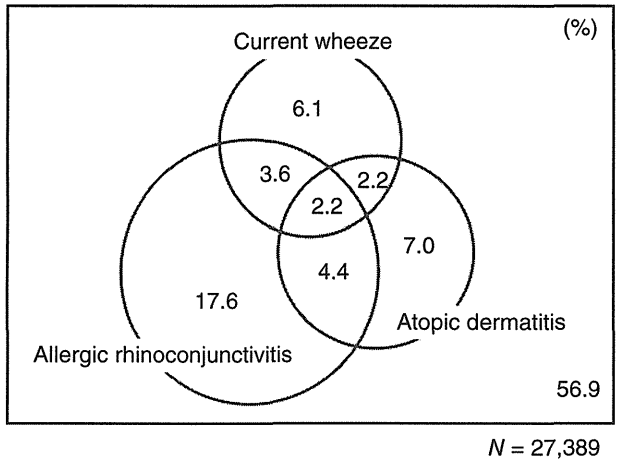

Fig. 3 Venn diagram showing overlap of the current asthma, allergic rhinoconjunctivitis and/or atopic dermatitis symptoms among children aged 6 to 14 who completed questionnaires that gathered symptom prevalence data over a 12-month period.

prevalence in boys was higher than that in girls in each age group of the present study. This supports the findings of previous ISAAC studies, including one that was performed in Fukuoka. This study demonstrated that 6-7 year olds had higher prevalences of asthma and atopic dermatitis and a lower prevalence of allergic rhinoconjunctivitis when compared to 13-14 year olds. The study also showed that the prevalence of asthma was higher in boys.[2]

In the present study, the prevalence of atopic dermatitis also decreased with increasing age. On the other hand, older children were more likely to have severe symptoms. This suggests that even though mild dermatitis appears to have been completely resolved, severe dermatitis actually became exacerbated with increased age. While results of previous ISAAC studies have been mixed with regard to these findings, most Asian studies have shown a similar pattern. Therefore, atopic dermatitis rates in Setagaya, as in other Asian cities, might be influenced by exposure to irritant gases such as car exhaust fumes or by high concentrations of house dust mites.[9]

The prevalence rates of allergic rhinoconjunctivitis in children aged 6-7 and 13-14 in the present study were extremely high as compared to those in the 2002 Fukuoka study, even though the asthma rates were similar. It should also be noted that the prevalence of allergic rhinoconjunctivitis in Tokyo children aged 6-7 was one of the highest that has been documented among all of the ISAAC Phase Three populations.[6] Tokyo has the highest per-capita income in Japan, and thus, our findings are consistent with previous reports that have shown that the prevalence of allergic rhinoconjunctivitis is higher in high-income versus low-income countries.[10]

We compared the present results from Tokyo with those obtained using the same questionnaire several years previously in Fukuoka and Tochigi. These ISAAC Phase Three surveys revealed that the prevalence of allergic diseases in Fukuoka and other Asian areas did not change markedly from Phase One.[11] This suggests that the prevalence of allergic disease in Tokyo is also likely to have remained relatively constant during this period, hence comparisons between the present and previous studies can provide meaningful information.

Table 3 Overlap prevalence (%) of asthma, allergic rhinoconjunctivitis and/or atopic dermatitis symptoms in children 6 to 14 years of age

Symptoms	Age (years)								
	6	7	8	9	10	11	12	13	14
BA (+), ARC (+), AD (+)	2.6	2.1	2.9	2.6	2.2	1.9	1.7	1.6	1.6
BA (+), ARC (+), AD (-)	3.2	3.9	3.4	3.4	4.9	3.4	4.2	2.4	2.5
BA (+), ARC (-), AD (+)	3.5	2.9	2.5	2.1	1.7	1.6	1.3	1.5	1.2
BA (-), ARC (+), AD (+)	3.8	4.0	4.1	4.5	5.5	5.5	5.1	2.7	2.6
BA (+), ARC (-), AD (-)	8.9	6.7	6.8	5.3	5.8	5.0	5.0	4.6	5.1
BA (-), ARC (+), AD (-)	10.0	12.5	14.7	16.4	22.3	21.7	22.9	20.9	22.5
BA (-), ARC (-), AD (+)	9.6	8.4	7.4	7.3	5.9	6.0	5.5	6.1	5.4
BA (-), ARC (-), AD (-)	58.4	59.4	58.1	58.4	51.8	54.8	54.4	60.2	59.1

BA, current wheeze; ARC, allergic rhinoconjunctivitis; AD, atopic dermatitis.

Asthma is more prevalent in urbanized areas, as air pollution is one of environmental factors that can exacerbate asthma. It is well known that components of diesel exhaust particles worsen respiratory symptoms through a variety of mechanisms.[12] In Tokyo, the number of diesel-powered automobiles is heavily regulated by prefectural ordinances that were put in place in 2003 in order to control the severe air pollution. Pollution concentration differences might explain why the prevalence of current wheezing in the present study was higher in Tokyo than in Tochigi, which is a less populated area.

Compared to Fukuoka, Tokyo has higher pollen levels. Thus, the higher exposure to pollen in Tokyo might contribute to the higher prevalence of allergic diseases that are seen as compared to Fukuoka. However, it is unclear as to why Tochigi, which has higher recorded pollen counts would have a lower prevalence of allergic diseases as compared to Tokyo.[13] Braun-Fahrländer suggested that there may be factors associated with occupations related to agriculture, and thus parents who farm, may pass on a reduced risk to their children for producing specific IgE antibodies to aeroallergens, thereby preventing the development of clinical symptoms of allergic rhinitis.[14] Therefore, we speculate that Tochigi's higher farming population might account for this discrepancy.

The prevalence of allergic rhinoconjunctivitis was higher in older children, and there were no clear gender differences noted. In all age groups, the peak prevalences were observed during March and April, a period that coincides with the release of Japanese cedar pollen, which is one of the most common spring pollen antigens in Japan. Therefore, it is highly likely that the main pediatric seasonal pollen allergy that is seen in Tokyo is due to the Japanese cedar tree. When the monthly prevalence of allergic rhinoconjunctivitis was examined, it was found to be similar to the high prevalence that is seen in older children (data not shown). As seasonal rhinoconjunctivitis is a strong indicator of IgE-mediated allergy in children, our study results suggest that older children have a higher prevalence of IgE-mediated allergy than younger children.

Interestingly, the highest pollen counts during the past two decades were recorded in Tokyo during the same time when the present 10-year-old children were in their first year of life. A Swedish study that examined sensitization found that children born during a year of exceptionally high birch pollen counts had a higher prevalence of birch pollen sensitivity at ages 4 to 5.[15] In contrast, Burr showed an inverse association between grass pollen counts and the prevalence of allergic rhinitis symptoms.[16] However, they analyzed grass pollen counts in European countries, Australia, and Kuwait, and thus, their results might not be applicable to the present study in Japan.

In the current study, parents of elementary schoolchildren under the age of 11 along with a few elementary schoolchildren who were 12 years old completed the questionnaires. All of the junior high school children completed the questionnaires by themselves, which included some 12-year-old junior high school students. When reporting symptoms, answers provided by the parents and the children often differed, with the children appearing to be more valid reporters than their parents. However, the respondent differences could be ignored in the present study, as the age differences over the 12-month examination period for the three diseases did not significantly change for those who were 12 years old. Nevertheless the prevalence of exercise-induced wheezing and sleep disturbance caused by eczema more increased after the age of 11. While it is feasible that the differences were mainly because of the respondents, these differences might actually mean that some parents incorrectly judged the symptoms present in their children. Therefore, the actual prevalence of exercise-induced wheezing and sleep disturbance caused by eczema in the younger age groups could be higher than what was actually reported in the current re-

sults.

In addition to the point discussed above, other limitations of this study might include the time period that was covered by the survey. The study period covered the time between May and June, which corresponded to the time immediately after the peak months of exposure to Japanese cedar pollens. The ISAAC protocols recommend that studies on allergic rhinoconjunctivitis should not use surveys in which 50% of the surveyed population is studied in the months that precede the allergy season. However, it was unclear in our study as to whether or not Japanese cedar pollen was the main allergen that causes allergic problems in Tokyo schoolchildren. In Japanese adults, in addition to Japanese cedar pollen, the major allergens associated with allergic rhinoconjunctivitis include grass and ragweed pollens, which are released at the beginning of the summer and continue to be released until autumn. In addition, it should also be noted that when conducting these types of surveys in public schools, the seasons when the surveys can be conducted are dictated by when schools are in session, and thus, they cannot be done year round.

In conclusion, the present study demonstrated the prevalence of asthma, allergic rhinoconjunctivitis, and atopic dermatitis in school-age children. Our findings indicate that the prevalence of asthma and atopic dermatitis was higher in younger children, while the prevalence of allergic rhinoconjunctivitis was much higher than that which has been reported in previous surveys of other Asian cities. To prevent onset and exacerbation of symptoms along with improving the quality of life of schoolchildren affected by asthma and allergic diseases, additional studies that investigate allergic disease prevalence in preschool children will need to be undertaken in the future.

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CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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Original Article

Association of overweight with asthma symptoms in Japanese school children

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Abstract ***Background***: Most studies regarding the association of obesity with asthma have been performed in the Western countries. This study is a nationwide survey conducted in Japan.

Methods: A cross-sectional and questionnaire-based survey was performed among children aged 6–7, 13–14, and 16–17 years, using the ISAAC questionnaire. Overweight was defined as BMI ≥ 90th according to the reference values for Japanese children obtained during 1978–1981.

Results: Of a total of 179 218 children, 149 464 replied to the questionnaire (response rate 83.4%). After omitting incomplete data, 139 117 were analyzed. In all the age groups, being overweight was associated with current asthma after adjustment for confounding factors (adjusted OR: 1.24 in children 6–7 years of age, 1.31 in those 13–14 years, and 1.32 in those 16–17 years). These tendencies were observed in both genders. Overweight was a risk factor for nocturnal cough, independent of current asthma in the older age groups (adjusted OR: 1.21 in children 13–14 years, and 1.17 in those 16–17 years).

Conclusions: There is a clear association between obesity and current asthma in Japanese school-aged children. Mechanisms through which obesity related with nocturnal cough might be different from those of obesity-associated asthma.

Key words asthma, obesity, overweight, school children.

In the past few decades, the prevalence of both asthma and obesity has been increasing dramatically. In Japan, there is a 2.1 times increase in the prevalence of asthma[1] and a 2.5–2.6 times increase in the prevalence of obesity[2] in school-aged children during the past 20 years. Recently there have been a lot of studies evaluating the association between both disorders, but these data are inconsistent. Furthermore, most of them were reported from the Western countries, and little data have been reported from Asian countries. It has been known that there are ethnic differences in body composition including body mass index (BMI), body fat mass and fat distribution between Asian and Caucasian children.[3,4] These differences might affect the association between obesity and asthma. Age and gender are other factors that influence the relationship between obesity and asthma.[5] Therefore, we conducted a nationwide survey to evaluate the relationship between asthma and obesity in Japanese children of three different age groups: 6–7 years, 13–14 years, and 16–17 years of age.

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Methods

Study population

This study was a cross-sectional, questionnaire-based survey among 6–7-year-old, 13–14-year-old, and 16–17-year-old school children in Japan, and was carried out from April to July 2008. In order to perform a nationwide survey schools were randomly selected from all the prefectures, and the total number of children recruited was 179 218, corresponding to approximately 2% of the population, according to the data of the National Institute of Population and Social Security Research. Because the mainlands of Japan run from northeast to southwest, the climate varies between regions. In this study, Japan was geographically divided into two regions: northeast and southwest.

Questionnaire

The survey used a Japanese version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire,[6,7] which was distributed through teachers of the participating schools. The questionnaires for 6–7-year-old children were completed by their parents, and those for older children were answered by the children. The questionnaire also included questions regarding demographics, height and weight.

Current asthma was defined as answering positively to the question "Have you (or your child) had wheezing or whistling in the chest during the past 12 months?". Exercise-induced wheezing (EIW) was defined when the question "In the past 12 months, have your (or your child's) chest sounded wheezy during or after exercise?" was answered "yes". Night cough was defined as a positive response to the question "In the past 12 months, have you (or your child) had a dry cough at night, apart from a cough associated with a cold or chest infection?"

Definition of underweight and overweight

The child's weight and height were requested in the questionnaire. BMI was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). The subjects were categorized into three groups based on the 10th and 90th percentiles, according to the reference values of BMI for Japanese children, which were obtained in 1978–1981 period.[8] Children who were at the 10th percentile and less were defined as underweight, those at the greater than 10th to less than the 90th percentile were assigned to normoweight, and those at the 90th percentile and more were defined as overweight.

Statistical analyses

The χ^2 test was used to evaluate differences in BMI distribution for the regions and genders. Multivariate logistic regression analysis was performed to estimate the effects of BMI and other covariates on respiratory symptoms (current asthma, exercise-induced wheezing, and night cough) in subjects with current asthma. Kappa statistics were used to compare the level of inter-individual agreement between current asthma and respiratory symptoms (EIW and nocturnal cough). Kappa scores >0.41 are considered to show moderate agreement: >0.61, good agreement, and >0.81, very good agreement.[9] A value of $P < 0.05$ was considered to be statistically significant. All analysis was performed using the statistical package of SPSS for Windows version 17.0J.

Ethics

This study protocol was approved by the independent review board (IRB) of the National Center for Child Health and Development.

Results

Of the 179 218 children, 149 464 replied to the questionnaire (response rate 83.4%). After omitting incomplete data, 139 117 were analyzed (Fig. 1). Background characteristics of the study population are shown in Table 1. Approximately 14% of the subjects were categorized as overweight and the prevalence of overweight was higher in the northeast region compared with the southwest region in each age group (Table 1). The youngest age group included more children categorized as underweight than the older age groups. There were gender differences in the prevalence of overweight and underweight in each age group. There was a tendency that boys were more slender than girls in the children aged 6–7 years, but this tendency changed with age. In the children aged 16–17 years, the prevalence of overweight in boys was higher than that in girls, and more girls were categorized as underweight. There were age differences in the prevalence of respiratory symptoms (Table 2). The prevalence of current asthma in the youngest age group was higher (13.6%) than that of the older age groups (9.5% in children aged 13–14 years and 8.3% in children 16–17 years old). In contrast, only a very low percentage of children aged 6–7 years old (4.3%) had current episodes of EIW, while approximately 15% of the older age group had such episodes (16.5% in children aged 13–14

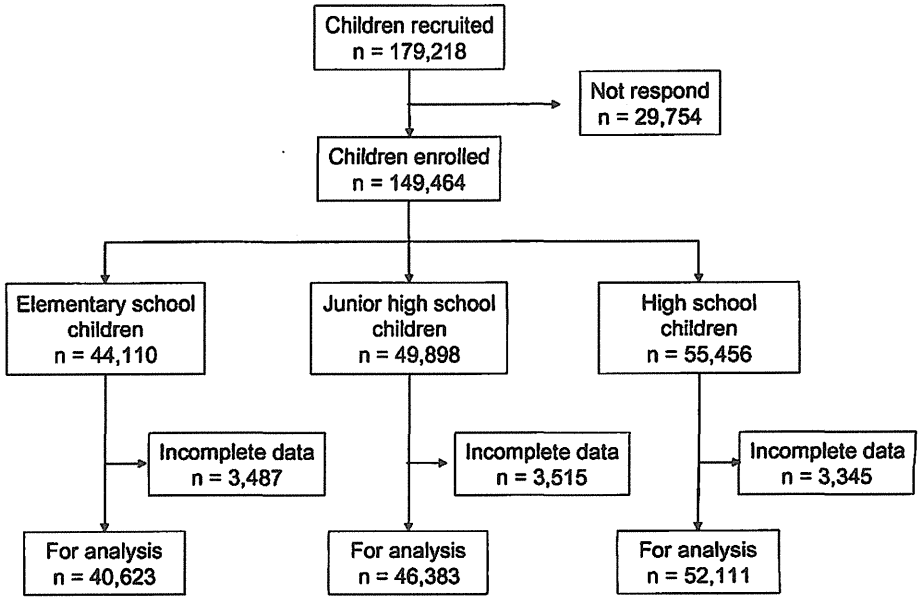

Fig. 1 Participants of the cross-sectional and questionnaire-based survey.