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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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 $\leq$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 $\geq$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

Association between obesity and asthma in Japanese preschool children

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Abstract

Obesity may increase the risk of subsequent asthma. We have previously reported that there is a clear association between obesity and asthma in Japanese school-aged children.

To evaluate whether a similar association exists in younger children, a nationwide cross-sectional questionnaire-based survey was performed focusing on children aged 4–5 yr. A child who had experienced wheezing during the past 12 months and had ever been diagnosed with asthma by a physician was defined as having current asthma. Overweight and underweight were defined as BMI ≥90th percentile and ≤10th percentile, respectively, according to the reference values for Japanese children from 1978 to 1981.

After excluding 2547 children because of incomplete data, 34,699 children were analyzed. 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 $p < 0.001$). Even after adjusting for other variables, such as gender, other coexisting allergic diseases, and parental history of asthma, there was an association between overweight and current asthma (adjusted odds ratio: 1.23, 95% CI: 1.10–1.38, $p < 0.001$).

Even in preschool children, obesity is already associated with asthma, and there was no gender effect on this association. Physicians should consider the impact of obesity when managing asthma in younger children.

In the past few decades, the prevalence of both asthma and obesity has been increasing dramatically. In Japanese school-aged children, the prevalence of asthma and the prevalence of obesity have increased 2.1 times (1) and 2.5–2.6 times (2, 3), respectively, over the past 20 yr. Asthma and obesity often coexist, and obesity appears to worsen asthma control and increase asthma severity, resulting in increased numbers of prescribed medications and decreased quality of life for patients (4). Recently, many studies have shown a positive association between both disorders in school-aged children, adolescents, and adults (5–6). In contrast, there have been only a few studies performed to evaluate the association between obesity and asthma in preschool children. It has been recognized that both asthma and obesity have their beginnings in early life and that the effects of these disorders continue throughout later life (7). For instance, despite the difficulty in diagnosing asthma in young children, the available data suggest that approximately 80% of childhood asthma is diagnosed by the age of 6 yr (1). Similarly, it was reported that one-third of obese preschool children were still obese as adults (8). Therefore, it is important to examine the associations between both disorders in early life.

When evaluating younger children, there have been methodological issues that made it difficult to clarify the association between asthma and obesity. One of the issues is a lack of a standard definition of asthma in preschool children (9). A questionnaire used by the International Study of Asthma and Allergy in Childhood (ISAAC), which has been widely used as a standard questionnaire for studying the prevalence of childhood asthma, was validated for use in the school-aged

children. Another issue is that a variety of definitions of child obesity have been used (10–11). Furthermore, most of the data regarding the impact of obesity on asthma were obtained from western countries, and few data from Asian countries have been reported. 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 (12, 13).

To evaluate whether there is a relationship between obesity and asthma in Japanese preschool children, we conducted a nationwide survey, in which asthma was defined as parent-reported, physician-diagnosed asthma, and overweight was defined according to the reference values of BMI for Japanese children. We also assessed the effects of potential confounders such as gender, personal history of other allergic diseases, and parental history of asthma on the association between obesity and asthma.

Methods

Study population

This study was a cross-sectional and questionnaire-based survey performed in 3- to 6-yr-old children in Japan and carried out from April through July 2008. In order to perform a nationwide survey, kindergarten classes were randomly selected from all the prefectures. The total number of children recruited was 50,959, corresponding to approximately 2% of the pediatric population, according to the data provided by the National Institute of Population and Social Security Research. This study protocol was approved by the independent review board of the National Center for Child Health and Development.

Questionnaire

The survey used a Japanese version of the ISAAC questionnaire (5, 14), which was distributed through teachers of the participating kindergartens. The questionnaires were filled by the parents. The questionnaire also included questions regarding demographics, the latest data regarding the child's height and weight, the physician's diagnosis of allergic diseases, and the parental history of asthma. Current wheeze was defined as a positive answer to the question 'Has your child had wheezing or whistling in the chest during the last 12 months?' Among the current wheezers, a child whose parent answered positively to the question 'Has your child ever been diagnosed with asthma by a physician?' was defined as having current asthma. In Japan, asthma diagnosis in preschool children is commonly based on the following criteria described in the Japanese pediatric asthma guideline (15): (i) three or more episodes of airway obstruction that was documented by wheezing, decreased air entry, and dyspnea and/or (ii) improvement of airway obstruction following bronchodilator use.

Definition of underweight and overweight

The child's weight and height were determined by 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 determined during the 1978–1981 period (16). Children who were at the 10th percentile and less were defined as underweight, those at the >10th to <90th percentile were assigned to normal weight, and those with BMI $\geq$90th percentile were defined as overweight.

Statistical analyses

The chi-square test was used to evaluate the gender differences and compare the prevalence of current asthma between groups. Multivariable analysis was performed to estimate the effects of body composition and other confounding factors on current asthma. A p value <0.05 was considered to be statistically significant. All analysis was performed using the statistical package of SPSS for Windows version 17.0J (SPSS Inc, Chicago, IL, USA).

Results

Of the 50,959 children aged 3–6 yr, 47,291 replied to the questionnaire (response rate: 92.8%). Because this population was mainly composed of 4- and 5-yr-old children, 37,246 children aged 4–5 yr were selected (78.9% of the enrolled children). Finally, after omitting incomplete data, 34,699 children were analyzed (Fig. 1). The baseline characteristics of the study population are shown in Table 1. According to the reference values of BMI for Japanese children obtained in the 1978–1981 period (16), 19.5% were categorized as underweight and 10.0% were defined as overweight, showing an increasing trend in the prevalence of underweight over the past few decades. There were gender differences; both underweight and overweight were more prevalent in boys. Boys were also more likely to have ever been diagnosed with

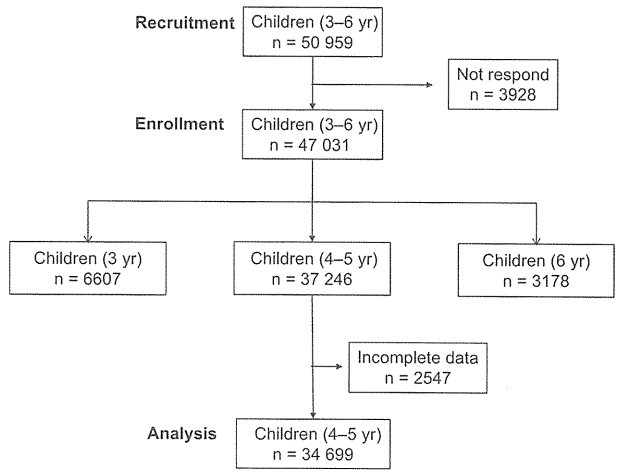

Figure 1 Participants in the cross-sectional and questionnaire-based survey.

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).

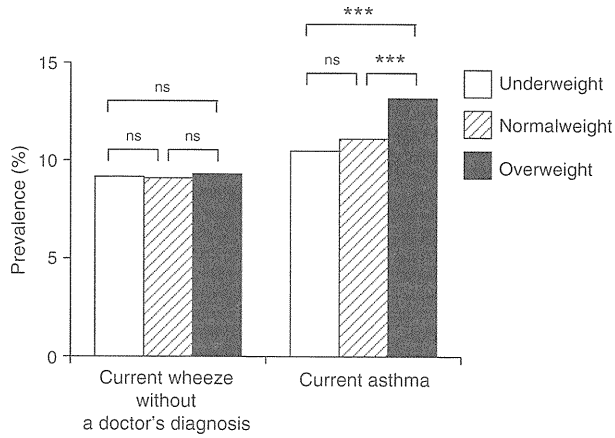

Figure 2 Effects of body composition on the prevalence of current wheeze in children without a doctor's diagnosis of asthma and current asthma. NS, not significant; ***$p < 0.001$.

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

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.