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 $\geq$ 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 $\geq$ 30 kg/m^2 were younger than those with normal BMI) and inhaled corticosteroid (dose of ICS in women with BMI $\geq$ 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 $\geq$ 30 kg/m^2 and DTA was observed only in women with OR of 2.76, whereas the prevalence of BMI $\geq$ 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 $\geq$ 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 $\geq$ 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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