

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

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### Clinical & Experimental Allergy

#### Summary

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

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

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

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

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

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

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#### Introduction

Although the majority of asthma patients can obtain good control of asthma, an important subgroup of patients remains symptomatic, despite high-dose treatment. This subgroup is called difficult-to-treat asthma (DTA) [1]. Although the prevalence of this subgroup is considered to be relatively low in the general asthma population, this subgroup is of high concern for health-care providers, particularly in tertiary hospitals, because

of the high risks of emergency department visit and hospital admission and high mortality. Patients with severe asthma are also known to account for a considerable portion of direct and indirect health care costs [2–4]. However, the mechanism and risk factors associated with DTA have not yet been established.

When we consider numerous epidemiological evidence of the association between an increased body mass index (BMI) and new onset of asthma [5–7], it has been hypothesized that obesity may also be associated

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

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

## Methods

### Subjects

We studied successive patients who visited Sagamiara National Hospital for the first time, one of the largest tertiary hospitals for allergic diseases located in central Japan, between 2000 and 2006. Their medical records were reviewed by their physician, 24 months after their first visit, and their demographical and clinical parameters, disease control and anti-asthma medication use were registered in an electronic database. Data of patients who (1) received care for asthma from the hospital for at least 24 months, (2) received asthma treatment at more than step 4 in the Global Initiative for Asthma (GINA) 2009 guideline (step 4 treatment in the

GINA 2009 guideline is a medium or high dose of an inhaled glucocorticosteroid (ICS) with one or more controllers such as a long-acting beta agonist (LABA), a leukotriene receptor antagonist (LTRA) or theophylline), (3) showed good adherence to anti-asthma medication (determined from the pharmacy prescription records by their physicians), (4) did not have any comorbid cardio-pulmonary disease (bronchiectasis, chronic bronchitis, old tuberculosis, interstitial pneumonitis, chronic eosinophilic pneumonia, Churg-Strauss syndrome or cardiac diseases), (5) did not have a smoking history greater than 30 pack-years and (6) were 75 years old or younger, were analysed in this study. Among the 3551 registered asthma patients, 1541 received asthma treatment at Step 4 or more. After the exclusion of 369 patients who did not meet the above criteria and 65 patients who had missing data on BMI, onset age, smoking status, atopic status or comorbidity [aspirin intolerance, allergic rhinitis (AR) and atopic dermatitis], 1107 patients were finally included in the analysis. This study was approved by the Ethics Committee of National Sagamiara Hospital, and all the patients provided written informed consent.

### Definition of difficult-to-treat asthma

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

### Potential risk factors and atopic phenotype

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

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

### Statistical analysis

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

### Results

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

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

Table 1. Characteristics of study patients

	Difficult-to-treat asthma (N = 486)	Controlled severe asthma (N = 621)	P-value
Age, mean ± SD (years)	52.6 ± 14.7	47.9 ± 15.0	<0.001
Gender, no. (%)			n.s.
Men	194 (40)	224 (36)	
Women	292 (60)	397 (64)	
Duration of asthma, mean ± SD, years	24.7 ± 15.5	19.6 ± 13.6	<0.001
Early-onset asthma (≤12 years), no. (%)	136 (28)	183 (30)	n.s.
Smoking status, no. (%)			
Non-smoker	264 (54)	354 (57)	n.s.
Past smoker	136 (28)	145 (23)	
Current smoker	86 (18)	122 (20)	
Smoking history (pack-years), no. (%)*			n.s.
0	264 (55)	354 (57)	
>0–<10	114 (24)	132 (21)	
≥10	103 (21)	132 (21)	
Body mass index (kgm <sup>2</sup> ), 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 <sup>†</sup>	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. (%) <sup>‡</sup>			
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<sup>2</sup> compared with patients with BMI: 18.5–24.9 kg/m<sup>2</sup>; 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<sup>2</sup> were younger than those with normal BMI) and inhaled corticosteroid (dose of ICS in women with BMI  $\geq 30$  kg/m<sup>2</sup> 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<sup>2</sup> and DTA was observed only in women with OR of 2.76, whereas the prevalence of BMI  $\geq 30$  kg/m<sup>2</sup> 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

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 ( $\leq 12$ 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 <sup>2</sup> )				
<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
$\geq 30.0$	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.

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<sup>2</sup> 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<sup>2</sup> 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 3. Patient characteristics according to body mass index categories

	Body mass index (kg/m <sup>2</sup> )				P-value
	<18.5 (n = 25)	18.5–24.9 (n = 283)	25.0–29.9 (n = 92)	≥30.0 (n = 18)	
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)	

of 1.39 in atopic patients, and 5.49 in non-atopic patients. The interaction between BMI  $\geq 30$  kg/m<sup>2</sup> 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  $\geq 30$  kg/m<sup>2</sup>  $\times$  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  $\geq 30$  kg/m<sup>2</sup> and OR of 26.22 for aspirin intolerance. A significant association between BMI  $\geq 30$  kg/m<sup>2</sup> 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

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 <sup>2</sup> )				
<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 <sup>2</sup> )				
<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 <sup>†</sup>	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 <sup>‡</sup>	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.

<sup>†</sup>Statistical significance in interaction term of BMI  $\geq 30$  kg/m<sup>2</sup>  $\times$  women;  $P$ -interaction = 0.11

<sup>‡</sup>Statistical significance in interaction term of aspirin intolerance  $\times$  women;  $P$ -interaction = 0.07

association between BMI  $< 18.5$  kg/m<sup>2</sup> 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  $\geq 30$  kg/m<sup>2</sup> 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  $\leq 18.5$  kg/m<sup>2</sup> 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 <sup>2</sup> )				
<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 <sup>2</sup> )				
<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 <sup>†</sup>	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 <sup>‡</sup>	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.

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

<sup>‡</sup>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<sup>2</sup> × women, aspirin intolerance × women or BMI ≥ 30kg/m<sup>2</sup> × 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<sup>2</sup> × women, aspirin intolerance × women, BMI ≥ 30kg/m<sup>2</sup> × 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 <sup>2</sup> )					
		<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		
	Non-atopic (n = 101)	Body mass index (kg/m <sup>2</sup> )					
		<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		
Women (n = 689)	Atopic (n = 518)	Body mass index (kg/m <sup>2</sup> )					
		<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		
	Non-atopic (n = 171)	Body mass index (kg/m <sup>2</sup> )					
		<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		
Present	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 ≥ 30 kg/m<sup>2</sup> × 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 circumference or waist-to-hip ratio [28]. Although there was no statistical significant association between

BMI  $\geq 30$  kg/m<sup>2</sup> 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 patient'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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### References

- 1 GINA Report, Global Strategy for Asthma Management and Prevention 2009 (update). Available at <http://www.ginasthma.com> (accessed 25 October 2010).
- 2 Antonicelli L, Bucca C, Neri M *et al.* Asthma severity and medical resource utilisation. *Eur Respir J* 2004; 23:723–9.
- 3 Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. *Eur Respir J* 2002; 19:61–7.
- 4 Serra-Batllés J, Plaza V, Morejon E, Comella A, Brugués J. Costs of asthma according to the degree of severity. *Eur Respir J* 1998; 12:1322–6.



- 5 Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005; 115:897–909; quiz 910.
- 6 Coogan PF, Palmer JR, O'Connor GT, Rosenberg L. Body mass index and asthma incidence in the Black Women's Health Study. *J Allergy Clin Immunol* 2009; 123:89–95.
- 7 Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol* 2002; 155:191–7.
- 8 The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J* 2003; 22:470–7.
- 9 Wenzel SE, Busse WW. Severe asthma: lessons from the Severe Asthma Research Program. *J Allergy Clin Immunol* 2007; 119:14–21; quiz 22–13.
- 10 Moore WC, Meyers DA, Wenzel SE *et al*. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010; 181:315–23.
- 11 Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; 894: i–xii, 1–253.
- 12 Mita H, Endoh S, Kudoh M *et al*. Possible involvement of mast-cell activation in aspirin provocation of aspirin-induced asthma. *Allergy* 2001; 56:1061–7.
- 13 Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005; 171:334–9.
- 14 WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363:157–63.
- 15 Nakagami T, Qiao Q, Carstensen B *et al*. Age, body mass index and Type 2 diabetes-associations modified by ethnicity. *Diabetologia* 2003; 46:1063–70.
- 16 Nagaya T, Yoshida H, Takahashi H, Kawai M. Increases in body mass index, even within non-obese levels, raise the risk for Type 2 diabetes mellitus: a follow-up study in a Japanese population. *Diabet Med* 2005; 22: 1107–11.
- 17 Olafsdottir IS, Gislason T, Thjodleifsson B *et al*. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax* 2005; 60:451–4.
- 18 Mascia K, Haselkorn T, Deniz YM, Miller DP, Bleecker ER, Borish L. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2005; 116:970–5.
- 19 Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000; 16:432–6.
- 20 Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002; 89: 474–8.
- 21 Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992; 3:452–6.
- 22 Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000; 320:827–32.
- 23 Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000; 118:1315–21.
- 24 Maniscalco M, Zedda A, Faraone S *et al*. Weight loss and asthma control in severely obese asthmatic females. *Respir Med* 2008; 102:102–8.
- 25 Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol* 1996; 98:751–8.
- 26 Rozsasi A, Polzehl D, Deutsche T *et al*. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy* 2008; 63:1228–34.
- 27 Dolan CM, Fraher KE, Bleecker ER *et al*. Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2004; 92:32–9.
- 28 Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol* 2006; 118:1284–91.
- 29 De Smet BD, Erickson SR, Kirking DM. Self-reported adherence in patients with asthma. *Ann Pharmacother* 2006; 40:414–20.