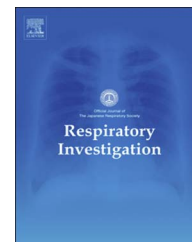




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Obesity-associated severe asthma in an adult Japanese population

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ABSTRACT

Background: Severe asthma is increasingly being recognized as an important public health issue. Obesity has been identified as a risk factor for poor asthma control and for worsening of asthma severity. However, most studies investigating obese patients with asthma have been performed in Western countries. Reports on the characteristics of obese Japanese individuals with severe asthma are lacking. Herein, we investigated the clinical characteristics of patients with obesity-associated severe asthma in a Japanese population and the association between obesity and poor asthma control.

Methods: We conducted a retrospective observational study of adult patients with severe asthma. Patients were classified into two groups based on the definition of obesity recommended by the Japan Society for the Study of Obesity: obese (OB) group (body mass index [BMI] ≥ 25 kg/m²) and non-obese (NOB) group (BMI < 25 kg/m²). The two groups were compared. The characteristics of obesity and the metabolic functions are known to differ between males and females; therefore, we analyzed male-only and female-only cohorts separately.

Results: A total of 492 patients were enrolled. Age, smoking history in terms of number of pack-years, daily controller medications use, and spirometric data were not significantly different between the OB and NOB groups in either cohort. In the female cohort, the annual exacerbation ratio and the percentage of frequent exacerbators were significantly higher in the OB group compared to the NOB group. A multivariate logistic regression analysis showed that obesity was independently associated with frequent asthma exacerbations in the female cohort.

Abbreviation: BMI, body mass index; FEF₅₀, forced expiratory flow at 50% of the vital capacity; FEF₇₅, forced expiratory flow at 75% of the vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GINA, global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; JASSO, Japan Society for the Study of Obesity; PEF, peak expiratory flow; RAST, radioallergosorbent test; WHO, World Health Organization

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Conclusions: Our study revealed that obesity, defined as a BMI ≥ 25 kg/m², was independently associated with poor asthma control (including acute exacerbations) in adult Japanese females with severe asthma.

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1. Introduction

Severe asthma is increasingly being recognized as an important public health issue. Obesity has been identified as one of the risk factors for poor asthma control in adults [1–4]. Clinical studies have indicated that there is a reduced response to corticosteroids in obese patients with asthma [5–7]. Although the characteristics of subjects with obesity-related asthma have been clarified in recently published articles, the patients who were enrolled in these studies were mainly from Western countries. In addition, obesity was defined according to the World Health Organization (WHO) classification: body mass index (BMI) ≥ 30 kg/m² [8].

Several studies in obesity research have indicated that there are differences in the characteristics of obesity and the metabolic functions between East-Asian and Western populations; for instance, the percentage of body fat has been reported to be higher in East-Asian populations than in Western populations of the same age, sex, and BMI [9]. A strong association between obesity, defined as a BMI ≥ 25 kg/m², and the incidence of diabetes mellitus has been shown among second- and third-generation Japanese living in the United States [10]. When the association between obesity-related disorders and BMI was analyzed, the optimal cut-off for BMI for maximizing the sensitivity and specificity to detect obesity-related disorders was found to be 25 kg/m² in the Japanese people [11]. Based on this finding, the Japan Society for the Study of Obesity (JASSO) has set a BMI of 25 kg/m² as the cut-off for the definition of obesity [11].

Large-scale studies of the association between obesity and asthma prevalence in Japanese populations have been published [12–14], and the association between obesity and asthma prevalence in the Japanese has become clearer. These reports have shown a higher prevalence of asthma in obese subjects compared to non-obese subjects. However, these studies did not provide enough information about the impact of obesity on severe asthma. To fill this knowledge gap, we conducted the present study to investigate the characteristics of subjects with severe asthma with a focus on the influence of obesity. We attempted to determine the clinical characteristics of patients with obesity-associated severe asthma in a Japanese population and to further clarify the association between obesity and acute exacerbations of asthma.

2. Patients and methods

2.1. Patients

We continuously enrolled patients with asthma who visited the outpatient clinic of the Department of Allergy and

Respiratory Medicine at the Fraternity Memorial Hospital (Tokyo, Japan) between October 2015 and December 2015. It is one of the largest departments for the treatment of allergic diseases in Japan and has a capacity of attending approximately 1500 patients with asthma in a month. The inclusion criteria for patients were as follows: (1) diagnosis of asthma based on the Global Initiative for Asthma (GINA) guidelines; (2) severe asthma as described previously [15]; (3) regular use of asthma medication for ≥ 2 years before the enrollment; (4) availability of spirometric data obtained in a stable health condition; and (5) absence of other respiratory diseases that can affect the spirometric data, including diffuse emphysema or previous history of tuberculosis.

2.2. Study design

We conducted a retrospective observational study. The real-life data (clinical and laboratory data) of the enrolled patients were obtained from the electronic medical records. We classified the patients into two groups based on the JASSO definition of obesity [11]: obesity (OB) group i.e. BMI ≥ 25 kg/m² and non-obesity (NOB) group i.e. BMI < 25 kg/m². We compared the groups' characteristics and data. The characteristics of obesity and the metabolic functions are known to differ between males and females; therefore, we analyzed male-only and female-only cohorts separately. This study was approved by The Fraternity Memorial Hospital Research Ethics Committee (Approval No: 94, Approval date: 23/February /2012) and was performed in accordance with the Declaration of Helsinki.

2.3. Data collection

The data on demographic characteristics, comorbidities, latest results of spirometry performed when the patient's asthma was stable, laboratory data, characteristics of asthma, type of controller medications used in a stable condition, and annual exacerbation ratio were recorded in a standardized data-collection sheet. High-dose inhaled corticosteroids (ICSs) were defined according to the GINA guidelines. The annual exacerbation ratio was defined with reference to a previous study report [16]: the total number of severe acute exacerbations $\times 12$ /total duration of the observation period (months).

We identified the number of severe acute exacerbations between the day of enrollment and the day of the visit approximately 1 year before the enrollment for each patient, and used that number to calculate the annual exacerbation ratio. Severe acute exacerbation of asthma was defined as described previously [17]. Briefly, acute asthma exacerbations necessitating an emergency room visit for treatment with systemic corticosteroids or necessitating an increase in the

dose of systemic corticosteroids from a stable maintenance dose for ≥ 3 days were defined as severe acute exacerbation. Frequent exacerbators were defined as patients who had more than three severe exacerbations within 1 year. This was based on the fact that seasonal exacerbations of asthma are generally observed three times per year in Japan: early spring (March–April), the rainy season (June), and the typhoon season (September).

2.4. Statistics

We used the Student's t-test to compare the OB and NOB groups after assessing the equality of variances for variables using the Levene's test. When the Levene's test showed significance (equal variances not assumed), the Welch's t-test was used to compare the groups. Fisher's exact test was used for comparisons of proportion in categorical variables. Multivariate logistic regression analyses were performed to adjust for confounders and to obtain the adjusted odds ratio between obesity and frequent exacerbations. A p value < 0.05 was considered significant. All statistical analyses were performed using SPSS version 24 software (IBM, Armonk, NY).

3. Results

3.1. Demographic data of the patients

We reviewed the electronic medical records of all patients with asthma who visited our department over a 3-month period (approximately 4500 patients with asthma). Among these patients, 492 patients fulfilled the inclusion criteria. The demographic characteristics of the enrolled patients are presented in Table 1. In the female cohort, 107 patients were OB, and 173

patients were NOB. In the male cohort, 104 patients were OB, and 108 patients were NOB. In both cohorts, no significant differences were detected with respect to age or the number of pack-years of smoking between the OB and the NOB groups. The percentage of patients with domestic exposure to pets and with family history of asthma did not differ significantly between the OB and the NOB group in both cohorts. A higher percentage of female patients in the OB group had diabetes mellitus. No significant association was detected between a comorbidity of any other allergic disease and obesity in both cohorts.

3.2. Characteristics of asthma and therapy

The characteristics of the patients' asthma and therapy are summarized in Table 2. Obesity was not associated with the duration of asthma, history of childhood asthma, out-grown childhood asthma, or the presence of aspirin sensitivity in either the male or the female cohort. With regard to asthma therapy, the percentage of patients with high-dose ICS use, daily use of oral corticosteroids, or omalizumab use was not significantly different between the NOB and the OB group in the male or the female cohorts.

Despite the absence of significant differences in the asthma characteristics or the type of the controller medications used at enrollment between the OB and the NOB groups, the annual exacerbation ratio was significantly ($p = 0.023$) higher in the OB group (3.3 ± 5.4) compared to the NOB group (2.0 ± 3.3) in the female cohort. In contrast, no significant difference was detected in the annual exacerbation ratio between the OB and the NOB groups in the male cohort. Additionally, the percentage of frequent exacerbators was significantly higher in the OB group (33%) compared to the NOB group (21%) in the female cohort ($p = 0.048$).

Table 1 – Demographic data of patients.

	Females			Males		
	Non-obesity	Obesity	p	Non-obesity	Obesity	p
n	173	107		108	104	
Body mass index (kg/m ²)	20.9 $\pm$ 2.2	28.4 $\pm$ 3.6	$<0.001^*$	21.8 $\pm$ 1.6	27.7 $\pm$ 3.2	$<0.001^*$
Age (yr)	55 $\pm$ 16	56 $\pm$ 15	0.478	57 $\pm$ 15	55 $\pm$ 13	0.424
Smokers (Ex & Current)	40 (26%)	19(20%)	0.285	47(54%)	48 (52%)	0.881
Pack-years	3.1 $\pm$ 7.6	2.6 $\pm$ 8.5	0.601	11.6 $\pm$ 17.9	12.5 $\pm$ 24.9	0.775
Domestic pet exposure	83(56%)	44(51%)	0.498	37(44%)	34(41%)	0.756
Family history of asthma	79(48%)	43 (45%)	0.607	46(49%)	43 (47%)	0.770
Comorbidities						
Chronic sinusitis	14(8%)	7(7%)	0.816	11(10%)	10(10%)	1.000
GERD	46(27%)	23(21%)	0.393	23(21%)	21(20%)	0.867
Diabetes mellitus	17(10%)	21(20%)	0.030*	8(7%)	16(15%)	0.083
Dyslipidemia	22(13%)	22(21%)	0.092	15(14%)	23(22%)	0.152
Hypertension	36 (21%)	26(24%)	0.554	20 (19%)	32(31%)	0.055
Comorbidities of allergic diseases						
Allergic rhinitis	125(72%)	74(69%)	0.590	78(72%)	71(68%)	0.551
Atopic dermatitis	16(9%)	13(12%)	0.545	17(16%)	16(15%)	1.000
Food allergy	17 (10%)	18(17%)	0.096	3(3%)	6(6%)	0.325
Drug allergy	19 (11%)	17(16%)	0.271	2(2%)	4(4%)	0.439

Data are presented as mean $\pm$ SD or n (%).*: Statistically significant ($p < 0.05$)

GERD: Gastroesophageal reflux disease.

Table 2 – Characteristics of asthma and its treatments.

	Females			Males		
	Non-obesity	Obesity	p	Non-obesity	Obesity	p
Duration of asthma	21 ± 15	22 ± 16	0.642	25 ± 16	24 ± 15	0.787
History of childhood asthma	47(28%)	27(26%)	0.780	41(39%)	42(42%)	0.670
Out-grow of childhood asthma	16(35%)	9(32%)	1.000	13(33%)	11(26%)	0.627
Aspirin sensitivity	6(3%)	9(8%)	0.100	4(4%)	6(6%)	0.532
Asthma therapy						
GINA therapy step 4	135 (78%)	87(81%)	0.547	91 (84%)	87(84%)	1.000
GINA therapy step 5	38 (22%)	20(19%)		16%	17(16%)	
High-dose ICS	166(96%)	106(99%)	0.160	103(95%)	100(96%)	1.000
Daily use of OCS	24(14%)	13 (12%)	0.720	15(14%)	13 (13%)	0.841
Dose of daily OCS (mg/day) ⁺	3.3 ± 1.8	3.7 ± 2.5	0.572	3.7 ± 1.6	3.7 ± 2.6	0.984
Omalizumab	17(10%)	11 (10%)	1.000	4(4%)	4(4%)	1.000
Annual exacerbation ratio	2.0 ± 3.3	3.3 ± 5.4	0.023*	0.9 ± 1.9	1.6 ± 3.8	0.109
Frequent exacerbators	37(21%)	35(33%)	0.048*	16(15%)	19(18%)	0.580

Data are presented as mean ± SD or n (%). *: Statistically significant ($p < 0.05$). +: Equivalent dose to prednisolone. The mean dose of daily OCS was calculated for the patients with daily use of OCS.

GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroids; OCS: Oral corticosteroids.

Table 3 – Pulmonary function tests and laboratory tests data.

	Females			Males		
	Non-obesity	Obesity	p	Non-obesity	Obesity	p
FVC ^(L)	2.40 ± 0.68	2.33 ± 0.64	0.435	3.36 ± 0.86	3.27 ± 0.90	0.498
%FVC (%)	88.2 ± 18.5	87.4 ± 20.0	0.728	85.8 ± 17.4	82.1 ± 17.8	0.119
FEV ₁ ^(L)	1.95 ± 0.65	1.93 ± 0.60	0.715	2.56 ± 0.89	2.56 ± 0.82	0.979
%FEV ₁ (%)	87.0 ± 20.0	85.9 ± 21.7	0.688	77.9 ± 20.3	77.0 ± 19.0	0.726
FEV ₁ /FVC (%)	80.8 ± 9.6	81.8 ± 10.0	0.390	75.2 ± 12.5	78.1 ± 9.8	0.064
%PEF (%)	80.4 ± 22.4	83.5 ± 27.1	0.295	78.9 ± 23.0	77.7 ± 25.8	0.735
%FEF ₅₀ (%)	71.8 ± 34.2	78.9 ± 38.1	0.104	62.2 ± 36.2	70.8 ± 41.1	0.108
%FEF ₇₅ (%)	66.6 ± 37.1	65.1 ± 36.8	0.751	56.5 ± 38.2	57.7 ± 33.7	0.817
Peripheral blood						
Eosinophils(μL)	333 ± 356	366 ± 573	0.552	367 ± 342	395 ± 312	0.535
IgE (IU/mL)	455 ± 1077	1154 ± 4063	0.090	2135 ± 12830	878 ± 1985	0.341
RAST positive						
House dust	102(62%)	58(56%)	0.372	66(65%)	72(77%)	0.085
Mite	99(60%)	57(55%)	0.377	67(66%)	70(75%)	0.207
Cat	16(35%)	14 (45%)	0.475	15(45%)	14 (39%)	0.631
Dog	15(29%)	15 (48%)	0.101	11(34%)	7(24%)	0.414
Candida	14(23%)	10(28%)	0.632	12(33%)	9(33%)	1.000
Aspergillus	8(14%)	7(21%)	0.385	11(30%)	8(29%)	1.000

Data are presented as mean ± SD or n (%).

FVC: Forced vital capacity; FEV₁: forced expiratory volume in 1s; PEF: peak expiratory flow; FEF₅₀: forced expiratory flow at 50% of the vital capacity; FEF₇₅: forced expiratory flow at 75% of the vital capacity; IgE: Immunoglobulin E; RAST: Radioallergosorbent test.

Next, we divided the OB patients in the female cohort into two groups: obese patients whose BMI values were $<30 \text{ kg/m}^2$ (OB1) ($n = 76$) and those whose BMI values were $\geq 30 \text{ kg/m}^2$ (OB2) ($n = 31$) and compared the NOB, OB1, and OB2 groups of females. There was a significant difference in the annual exacerbation ratio among the three groups (NOB, 2.0 ± 3.3 ; OB1, 3.3 ± 5.5 ; and OB2, 3.4 ± 5.4) based on the analysis of variance (ANOVA) ($p = 0.038$). As expected, a post-hoc test revealed that the annual exacerbation ratio in the OB1 group

was significantly higher ($p = 0.028$) than that in the NOB group, and the annual exacerbation ratio in the OB2 group tended to be higher ($p = 0.081$) compared to that in of the NOB group. No significant difference in the annual exacerbation ratio was detected between the OB1 and the OB2 groups ($p = 0.863$) based on the post-hoc test. The percentage of frequent exacerbators in the OB1 (33%) and the OB2 (32%) groups was not significantly different ($p = 1.000$, Fisher's exact test). A correlation analysis showed that there were no

Table 4 – Adjusted odds ratio for frequent exacerbators.

	Females Adjusted OR (95% CI)	p	Males Adjusted OR (95% CI)	p
Obesity	2.292 (1.244 - 4.223)	0.008*	0.784 (0.316–1.945)	0.600

* Statistically significant ($p < 0.05$)

significant correlations between BMI and the acute exacerbation ratio in both the female and the male cohorts.

3.3. Pulmonary function tests and laboratory tests data

The spirometric data showed there were no significant differences between the OB and the NOB groups in the female or the male cohort (Table 3). Eosinophil counts were not significantly different between the OB and the NOB groups in the male cohort. The percentage of patients with a positive IgE radioallergosorbent (RAST) score was not associated with obesity in either cohort.

3.4. Obesity showed an independent association with frequent exacerbations

Based on the results described above, we speculated that obesity, as defined by JASSO, is one of the risk factors for frequent exacerbations. To test this speculation, we classified the enrolled patients into two groups: frequent exacerbators (FEs) and non-frequent exacerbators (non-FEs). Then, we compared these groups' variables first using a univariate analysis and then using a multivariate analysis. In the female cohort, significant differences were revealed between the FEs and non-FEs with respect to the existence of obesity, the duration of asthma, GINA therapy step, the percentage of patients using omalizumab, and the spirometric data (Suppl. Tables S1–S3). In the male cohort, significant differences were observed between the FEs and non-FEs with respect to the duration of asthma, the comorbidity of gastroesophageal reflux disease (GERD), GINA therapy step, the percentage of patients using daily oral corticosteroids, the percentage of patients using omalizumab, and the spirometry data (Suppl. Tables S1–S3).

To find the independent factors associated with frequent exacerbators, we performed a multivariable logistic regression analysis (dependent variable: frequent exacerbators). We entered the variables mentioned above (the variables that showed significant differences between the FEs and non-FEs) and obesity into a multivariable logistic regression model, and we used a backward, stepwise elimination method to make the final multivariable model (Suppl. Tables S4 and S5). The adjusted odds ratio with regard to the association between obesity and frequent exacerbators was 2.292 (95% confidence interval 1.244–4.223, $p = 0.008$) in the female cohort (Table 4), whereas no significant association was detected between obesity and frequent exacerbators in the male cohort.

3.5. Obesity showed a greater effect in female patients with late-onset asthma

Obesity-related non-eosinophilic asthma has been identified as a phenotype of asthma that is characterized by late onset, female predominance, and poor asthma control in Western populations [18,19]. To confirm the presence of this phenotype in Japanese obese patients with asthma patients, we divided the female cohort into three sub-cohorts (“carryover”, “outgrowth,” and “adult-onset”). We investigated the association between obesity and poor asthma control in the three groups. “Carryover” was defined as asthma that was first diagnosed at an age ≤ 16 years, and the symptoms had persisted or regular medications had been necessary at least until the time of enrollment in the present study. “Outgrowth” was defined as childhood asthma that had resolved at an age ≤ 16 years, and the asthma symptoms had relapsed at an age ≥ 18 years. “Adult-onset” was defined as asthma diagnosed when the patient was ≥ 18 years old, with no previous diagnosis of asthma at an age ≤ 17 years.

Our analyses revealed no significant differences between the OB and the NOB groups with respect to age, smoking status, comorbidities of allergic diseases, GINA therapy step, or daily use of oral corticosteroids among the carryover, outgrowth, and adult-onset sub-cohorts (Suppl. Table S6). In the adult-onset sub-cohort, the percentage subjects with high-dose ICS use was higher in the OB group compared to the NOB group (Suppl. Table S6). There were no significant differences in acute exacerbation rate or percentage of frequent exacerbators between the NOB and the OB groups in the carryover and the outgrowth sub-cohorts (Table 5). In contrast, the acute exacerbation rate in the OB group (3.2 ± 5.7) was significantly higher than that in the NOB group (1.7 ± 3.1) in the adult-onset sub-cohort ($p = 0.036$). There was also a significant difference in the percentage of frequent exacerbators between the OB and the NOB groups in the adult-onset sub-cohort ($p = 0.039$).

4. Discussion

We conducted a retrospective observational study of 492 patients with severe asthma. Our findings revealed that the female obese patients with asthma had a higher acute exacerbation ratio (Table 2). In addition, obesity was independently associated with frequent exacerbations of asthma (Table 4). Thus, obesity was demonstrated to be closely associated with severe acute exacerbations in a population of adult Japanese females with asthma.

While several studies using data obtained from patients in Western countries have clearly shown the association

Table 5 – Difference of obesity-related severe acute exacerbation of asthma among carryover, outgrowth and adult onset groups.

	Carryover			Outgrowth			Adult onset		
	Non- obesity	Obesity	p	Non- obesity	Obesity	p	Non- obesity	Obesity	p
Annual exacerbation ratio	3.0 ± 3.4	4.7 ± 5.3	0.235	2.4 ± 4.3	2.7 ± 3.7	0.866	1.7 ± 3.1	3.2 ± 5.7	0.036*
Frequent exacerbators	11 (37%)	8 (44%)	0.762	3 (19%)	3 (33%)	0.630	22 (18%)	24 (31%)	0.039*

* Statistically significant ($p < 0.05$).

between obesity and poor asthma control or increased asthma severity [1–4], there have been few studies on such an association in Japanese subjects. Youkou et al. conducted a questionnaire survey in patients with asthma to investigate the association between obesity and poor asthma control, and they concluded that obese patients may have decreased sensitivity to corticosteroids. However, no differences were observed in emergency department visits or hospitalization due to asthma exacerbations between obese and non-obese patients with asthma [20]. In the study by Youkou et al., more than half of the patients were at Therapy Step 1 or 2, which likely affected the results. Information regarding the impact of obesity on severe asthma, especially the association between obesity and poor asthma control in patients with severe asthma, has been lacking. The population in the present study comprised only patients with severe asthma, and the results of our analyses showed that the annual exacerbation rate was higher among obese patients with asthma than among non-obese patients with asthma.

An important finding of this study is that obesity, defined as a BMI ≥ 25 kg/m², affected the annual exacerbation ratio. No significant difference in the annual exacerbation ratio was found between OB1 group (“overweight” as defined according to the WHO, $25 \leq \text{BMI} < 30$ kg/m²) and the OB2 group (“obese” as defined according to the WHO, BMI ≥ 30 kg/m²), whereas the annual exacerbation ratios in the OB1 and OB2 groups were higher than that in the normal-weight (non-obese) group. In addition, there was no correlation between BMI and acute exacerbations. These findings suggest that the threshold of BMI is important when considering the association between BMI and asthma exacerbations. The findings also suggest that the precise definition of obesity must be considered when investigating or treating obese patients of different ethnicities with asthma.

Another important and interesting finding is that no significant difference in the spirometric data was observed between the obese and non-obese patients in the female cohort although the annual exacerbation ratio was higher in the obese patients than in the non-obese patients (Tables 2, 3). The %FVC has been shown to be decreased in obese subjects with asthma in studies from Western countries, [1,21]. These results imply that, in the Japanese female population, poor asthma control – including frequent exacerbations of asthma – was induced by metabolic factors more than by physical effects on the lung functions due to the accumulation of fat. The percentage of body fat in East-Asian populations is higher than that in Western

populations at the same BMI [9]. Therefore, the adipocytokines released from the adipose tissue and obesity-related systemic oxidative stress are thought to be higher in Japanese individuals than in Western individuals with the same BMI.

Adipocytokines released from the adipose tissue and obesity-related systemic oxidative stresses are speculated to be the potential causes of decreased steroid response in obese patients with asthma patients. Adipocytokines, including tumor necrosis factor- α (TNF- α) and interleukin (IL)-6, are elevated in obese subjects. Some of the cytokines are known to cause steroid resistance via a modification of glucocorticoid receptor subunit expression [22,23]. Oxidative stress, which is elevated in obese subjects [24], is well known to induce steroid resistance [25]. In fact, an association between oxidative stress and acute exacerbation ratio has been observed in obese patients with asthma, but not in non-obese patients with asthmatic [26].

An additional important finding of our present investigation is that, in the patients with adult-onset asthma, the acute exacerbation ratio and the percentage of frequent exacerbators were higher in obese patients compared to non-obese patients. However, the differences in these parameters were not detected between obese and non-obese patients in patients with a history of childhood asthma or a carryover of childhood asthma. These results suggest that obesity seems to have a stronger association with poor asthma control in patients with late-onset asthma. This is consistent with the reported evidence that obesity-related asthma is characterized by late onset, female predominance, and poor asthma control in Western populations [18,19].

In the male cohort of the present study, there was no significant difference in the frequency of severe acute exacerbations between obese and non-obese patients. This may be due to several reasons. First, obesity may affect asthma control less in males compared to females. Cluster analyses of asthma have shown that the obesity-related severe asthma phenotype is characterized by female predominance [19,27] despite the nearly 1:1 ratio of males to females in the prevalence of both asthma and obesity. In addition, Varrasso et al. have reported that the association between BMI and the asthma severity score was stronger in females [4]. Second, BMI-defined obesity may cause a bias in male cohorts. The fat-free mass is higher in males than in females; therefore, the body fat percentage in males is lower than that in females with the same BMI. A different result might be

obtained if obesity was defined based on the fat percentage in male cohorts.

This study used the second-largest cohort of patients with officially confirmed severe asthma [15] to investigate the clinical characteristics of subjects with obesity-associated severe asthma [1]. A key strength of our study was that all enrolled patients were diagnosed to have asthma based on the GINA guidelines by trained allergy specialists or physicians under training to become allergy specialists. However, certain limitations must be considered when interpreting our results. First, the BMI is a widely accepted marker of obesity, but it may not be the best indicator of adiposity. The body fat percentage and waist circumference may be better markers of obesity, especially in males. However, we could not obtain the patients' body fat percentages or waist circumferences in this retrospective observational study. Second, we enrolled only patients who had been regularly using medications for ≥ 2 years before the enrollment; thus, patients with poor adherence to medication were excluded. However, we could not check whether all prescribed medications were used properly by all patients. Unrecognized patients with poor adherence to medications may have been included.

5. Conclusion

The results of this study demonstrated that JASSO-defined obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$) has an independent association with poor asthma control including frequent severe acute exacerbations in female Japanese patients with severe asthma. Poor asthma control seems to be induced by obesity even without the physical influence of fat accumulation on lung functions. Our findings, especially the BMI cut-off for the definition of obesity, should be considered in efforts to improve the treatment of obese Japanese patients with severe asthma.

Disclosures

The authors have no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.resinv.2018.07.003>.

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1 Suppl. Table S6 Demographic data of the patients with carryover of asthma, outgrowth of asthma and adult onset
2 asthma
3

	Carryover			Outgrowth			Adult onset		
	Non- obesity	Obesity	p	Non- obesity	Obesity	p	Non- obesity	Obesity	p
n	30	18		16	9		122	77	
Body mass index (kg/m ²)	20.8±1.8	29.6±4.3	<0.001	20.4±2.8	28.4±4.1	<0.001	20.9±2.2	28.2±3.4	<0.001
Age (yr)	42±12	47±12	0.213	49±17	45±15	0.556	59±16	59±14	0.734
Smokers (Ex & Current)	5 (18%)	2 (14%)	1.000	3 (20%)	2(25%)	1.000	31 (29%)	15(20%)	0.225
Pack-years	1.6±4.1	1.3±3.9	0.830	2.2±5.5	1.0±1.8	0.540	3.6±8.5	3.0±9.5	0.638
Domestic pet exposure	13 (50%)	6 (46%)	1.000	8 (62%)	4 (67%)	1.000	61 (56%)	34 (52%)	0.535
Family history of asthma	19 (63%)	12 (80%)	0.321	12 (80%)	2 (25%)	0.023	47 (40%)	29 (40%)	1.000
Comorbidities of allergic diseases									
Allergic rhinitis	25 (83%)	15 (83%)	1.000	14 (88%)	6 (67%)	0.312	83 (68%)	50 (65%)	0.757
Atopic dermatitis	7 (23%)	8 (44%)	0.198	1 (6%)	2 (22%)	0.530	8 (7%)	3 (4%)	0.535
Food allergy	2 (7%)	4 (22%)	0.179	5 (31%)	3 (33%)	1.000	9 (7%)	11 (14%)	0.147
Drug allergy	2 (7%)	5(28%)	0.086	2 (13%)	0 (0%)	0.520	14 (11%)	12 (16%)	0.399
Asthma therapy									
GINA therapy step 4	23 (77%)	13 (72%)	0.743	12 (75%)	6 (67%)	0.673	96 (79%)	66 (86%)	0.263
GINA therapy step 5	7 (23%)	5 (28%)		4 (25%)	3 (33%)		26 (21%)	11 (14%)	
High-dose ICS	30 (100%)	18(100%)	NA	16 (100%)	9 (100%)	NA	115 (94%)	77 (100%)	0.045
Daily use of OCS	3 (10%)	4 (22%)	0.400	2 (13%)	1 (11%)	1.000	19 (16%)	7 (9%)	0.204
Dose of daily OCS ⁺	3.3±2.1	3.1±4.0	0.938	3.0±2.8	5	NA	3.3±1.8	4.1±1.6	0.478
Omalizumab	6 (20%)	1 (6%)	0.231	2 (13%)	2 (22%)	0.602	8 (7%)	8 (10%)	0.423

4 Data are presented as mean±SD or n (%). ⁺: Equivalent dose to prednisolone. The mean dose of daily OCS was calculated for the
5 subjects with daily use of oral OCS.

6 GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroids; OCS: oral corticosteroids; NA: Not applicable

7

Supplementary tables

Obesity-associated severe asthma in an adult Japanese population

Suppl. Tables S1 Demographic data of patients

	Females			Males		
	Non- FE	FE	p	Non- FE	FE	p
n	208	72		177	35	
Obesity	72 (35%)	35 (49%)	0.048	85 (48%)	19(54%)	0.580
Age (yr)	56±16	54±16	0.353	56±15	55±12	0.556
Smokers (Ex & Current)	49 (27%)	10 (16%)	0.089	80 (54%)	15(47%)	0.558
Pack-years	3.3±8.4	1.7±6.2	0.100	12.9±23.1	8.4±13.5	0.291
Domestic pet exposure	99 (57%)	28 (47%)	0.231	59 (42%)	12 (48%)	0.662
Family history of asthma	90 (47%)	32 (47%)	1.000	72 (46%)	17 (61%)	0.217
Body mass index (kg/m ²)	23.5±4.6	24.4±4.8	0.153	24.6±4.1	25.1±2.7	0.495
Comorbidities						
Chronic sinusitis	15 (7%)	6 (8%)	0.796	19 (11%)	2 (6%)	0.539
GERD	50 (24%)	19 (26%)	0.751	31 (18%)	13 (37%)	0.013
Diabetes mellitus	28 (13%)	10 (14%)	1.000	19 (11%)	5 (14%)	0.561
Dyslipidaemia	33 (16%)	11 (15%)	1.000	31 (18%)	7 (20%)	0.809
Hypertension	47 (23%)	15 (21%)	0.870	43 (24%)	9 (26%)	0.832
Comorbidities of allergic diseases						
Allergic rhinitis	150 (72%)	49 (68%)	0.548	123 (69%)	26 (74%)	0.687
Atopic dermatitis	22 (11%)	7 (10%)	1.000	27 (15%)	6 (17%)	0.800
Food allergy	26 (13%)	9 (13%)	1.000	8 (5%)	1 (3%)	1.000
Drug allergy	26 (13%)	10 (14%)	0.838	4 (2%)	2 (6%)	0.258

Data are presented as mean±SD or n (%).

GERD: Gastroesophageal reflux disease.

Suppl. Tables S2 Characteristics of asthma and its treatments

	Females			Males		
	Non- FE	FE	p	Non- FE	FE	p
Duration of asthma	19±15	26±17	0.001	23±15	30±17	0.029
History of childhood asthma	49 (24%)	25 (35%)	0.088	64 (38%)	19 (54%)	0.089
Out-grow of childhood asthma	19 (40%)	6 (23%)	0.201	18 (29%)	6 (33%)	0.772
Aspirin sensitivity	10 (5%)	5 (7%)	0.545	8 (2%)	5 (6%)	0.672
Asthma therapy						
GINA therapy step 4	173 (83%)	49 (68%)	0.011	154 (87%)	24 (69%)	0.011
GINA therapy step 5	35 (17%)	23 (32%)		23 (13%)	11 (31%)	
High-dose ICS	201 (97%)	71(99%)	0.684	170 (96%)	33 (94%)	0.645
Daily use of oral corticosteroids	23 (11%)	14 (19%)	0.104	19 (11%)	9 (26%)	0.027
Omalizumab	16 (8%)	12 (17%)	0.039	4 (2%)	4 (11%)	0.027

Data are presented as mean±SD or n (%).

GINA: Global Initiative for Asthma; ICS, Inhaled corticosteroids.

17 Suppl. Tables S3 Pulmonary function tests and laboratory data

18

	Females			Males		
	Non- FE	FE	p	Non- FE	FE	p
FVC (L)	2.40±0.65	2.29±0.71	0.223	3.38±0.90	3.00±0.67	0.019
%FVC (%)	89.5±18.0	83.5±21.2	0.022	85.8±17.5	75.0±16.0	0.001
FEV ₁ (L)	1.96±0.62	1.88±0.65	0.316	2.62±0.88	2.26±0.64	0.021
%FEV ₁ (%)	88.0±20.1	82.4±21.8	0.045	79.4±19.4	67.3±17.8	0.001
FEV ₁ /FVC (%)	81.1±9.5	81.5±10.5	0.766	76.9±11.7	74.9±8.8	0.319
%PEF (%)	82.2±22.3	79.6±29.4	0.437	80.6±25.0	66.6±16.9	0.002
%FEF ₅₀ (%)	74.4±34.9	74.9±38.7	0.918	69.3±40.5	51.9±25.1	0.015
%FEF ₇₅ (%)	66.2±37.2	65.5±36.3	0.887	60.0±37.8	42.5±19.8	0.008
Peripheral blood						
Eosinophils(/μL)	322±341	411±669	0.151	373±310	418±404	0.458
IgE (IU/mL)	664±2268	885±3573	0.551	779±1381	5130±22181	0.261
RAST positive						
House dust	121 (61%)	39 (57%)	0.572	109 (67%)	29 (85%)	0.040
Mite	116 (58%)	40 (58%)	1.000	109 (68%)	28 (82%)	0.145
Cat	24 (42%)	6 (30%)	0.429	23 (38%)	6 (67%)	0.152
Dog	20 (33%)	10 (48%)	0.295	15 (28%)	3 (43%)	0.411
Candida	18 (23%)	6 (30%)	0.567	16 (31%)	5 (45%)	0.483
Aspergillus	9 (13%)	6 (29%)	0.099	14 (26%)	5 (42%)	0.311

19 Data are presented as mean±SD or n (%).

20 FVC: Forced vital capacity; FEV₁: forced expiratory volume in 1 second; PEF: peak
 21 expiratory flow; FEF₅₀: forced expiratory flow at 50% of the vital capacity; FEF₇₅: forced
 22 expiratory flow at 75% of the vital capacity; IgE: Immunoglobulin E; RAST:
 23 Radioallergosorbent test.

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26 Suppl. Tables S4 Multivariate logistic regression analyses for the female cohort
27

	Odds Ratio (95% CI)	p
Obesity	2.292 (1.244 - 4.223)	0.008
Duration of asthma	1.026 (1.008- 1.045)	0.005

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33 Suppl. Tables S5 Multivariate logistic regression analyses for the male cohort
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	Odds Ratio (95% CI)	p
Obesity	0.784 (0.316- 1.945)	0.600
GERD	2.536 (1.001- 6.420)	0.050
%FEV ₁	0.969 (0.947- 0.991)	0.006

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