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ORIGINAL ARTICLE

Influence of Underweight on Asthma Control

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ABSTRACT

Background: Although the association between asthma control and body mass index (BMI) has been thoroughly investigated, most of this work has focused on the influence on asthma incidence or the effect of obesity on asthma control. To date, there have been no published studies on the influence of underweight on asthma control.

Methods: The aim of this study was to investigate the influence of underweight, as defined by the Japan Society for the Study of Obesity (JASSO), on asthma control in Japanese asthmatic patients. Using data from questionnaire surveys administered by the Niigata Asthma Treatment Study Group, we compared asthma control, as measured by the Asthma Control Test (ACT), between a normal weight group (18.5 kg/m^2 =< BMI < 25 kg/m^2) and an underweight group (BMI < 18.5 kg/m^2).

Results: Of the asthmatic patients who completed the 2008 and 2010 surveys, 1464 and 1260 cases were classified as being in the normal weight group, and 174 and 155 cases were classified as being in the underweight group. The ACT score (median, [interquartile range]) in the underweight group in 2008 (22, [19-24]) and 2010 (23, [19-25]) was significantly lower than that in the normal group in 2008 (23, [20-25]) and in 2010 (24, [21-25]).

Conclusions: This study is the first, large-scale investigation of the influence of underweight on asthma control, and we have confirmed an adverse influence in a clinical setting. A potential mechanism for this interaction was unknown. Further investigation will be required.

KEY WORDS

bronchial asthma, control of asthma, underweight

ABBREVIATIONS

ACT, asthma control test; AIA, aspirin intolerant asthma; BMI, body mass index; ED, emergency department; ICS, inhaled corticosteroid; IQR, interquartile range; JASSO, Japan Society for the Study of Obesity.

INTRODUCTION

The widespread use of inhaled corticosteroids (ICS) in the clinical setting has resulted in vast improvements in asthma control.[1-3] However, asthma prevalence and mortality are not low, leading to an estimated annual loss of 15 million disability-adjusted life years, according to the World Health Organization.[4] Asthma imposes a considerable social and economic burden and needs to be addressed urgently.[5,6] This includes measures to further improve asthma management.

An increasing body of literature suggests an interaction between body mass index (BMI) and asthma.[7] Epidemiologic studies have suggested that overweight and obesity increase asthma incidence and skew prevalent asthma towards a more difficult-to-control phenotype.[8-13] However, there are very few

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reports on the association between being underweight and asthma. Almost all of these studies focused on the influence of underweight on asthma incidence, both in children and adults.[14-20] Therefore, it remains uncertain whether underweight can influence the control of asthma in the same way as overweight or obesity.

This study used the regular questionnaire survey administered by the Niigata Asthma Treatment Study Group since 1998. This survey includes questions relating to asthma management. The subjects in this survey were adult patients with bronchial asthma who visited medical institutions in Niigata Prefecture. The attending physicians of these patients were included in the survey. On the basis of these surveys, we have previously reported the clinical characteristics of adult bronchial asthma patients,[21] elderly bronchial asthma,[22] near-fatal asthma,[23] and perimenstrual asthma.[24] We have also published results relating to exacerbation factors,[25] the selection of ICS,[26] the relationship between smoking and gender in asthmatics,[27] and changes in asthma management.[1-3] These surveys give a good indication of the actual state of asthma management in Japan. In this study, we attempted to analyze the influence of underweight on asthma control in Japanese asthmatic patients using the data from 2008 and 2010 surveys. We classified patients with asthma into a normal weight group and an underweight group. As the definitions of underweight, normal and obese, can vary by race,[28-31] we used the JASSO BMI definitions for this study.

METHODS

Participation in this study was open to all medical institutions in Niigata Prefecture who intended to join the Niigata Asthma Treatment Study Group. This study was performed with the approval of the Ethics Committee of the School of Medicine of Niigata University in Niigata Prefecture, Japan, or at the relevant participating institution, in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki). The surveys from 2008 and 2010 involved 28 and 24 large hospitals (200 beds or more), 14 and 16 small hospitals (less than 200 beds), and 62 and 56 clinics (no beds), respectively. In the 2008 and 2010 surveys, a total of 5260 and 4662 questionnaires were prepared, and 3146 and 2762 responses were received (response rate: 59.8 and 59.2%), respectively. Table 1 shows the questions used in the questionnaire (originally in Japanese). The survey was performed over 2 months from September to October in 2008 and 2010. Subjects were adult patients (aged 16 years or older) with bronchial asthma who regularly visited the participating institutions for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves. Therefore, individual patients were expected to understand technical terms such as "attack" or "unconsciousness" in the questionnaire (Table 1). In addition to this questionnaire, the Asthma Control Test (ACT), which has been validated as a clinical indicator of asthma control,[32,33] was carried out separately at the same time. To evaluate problems with asthma management and treatment related to normal activity levels, the questionnaires also asked patients about their satisfaction with daily life. The subjects answered by choosing 1 of 5 answers, as shown in Table 1.

In addition to monitoring their patients' completion of the questionnaire, physicians were asked to supply details on current treatment, in particular the medications used for control, the type of asthma (atopic or non-atopic) in accordance with elevation in serum total IgE or detection of specific IgE for allergens, and the severity of asthma in accordance with Asthma Prevention and Management Guideline 2006 (in Japanese) published by Japanese Society of Allergology (JSA). This definition of asthma severity is essentially the same as that used by the Global Initiative for Asthma 2006.

The results for continuous variables were expressed as arithmetic means and standard deviations. Intergroup differences in terms of continuous variables were evaluated using the Kruskal-Wallis test and Wilcoxon's rank sum test with the Bonferroni correction. A Chi-square test with the Bonferroni correction was also used to assess the significance of differences in proportions between groups. All statistical analyses were performed with the statistical software StatView 5.0 PowerPC version (SAS Institute Inc., Cary, NC, USA). For all statistical analyses, a P-value < 0.05 was considered to be significant.

RESULTS

PATIENT CHARACTERISTICS

The characteristics of patients completing the 2008 and 2010 surveys are summarized in Table 2A, B, respectively. Of the asthmatic patients who answered the questionnaire in 2008 and 2010, 1464 and 1260 were classified as being in the normal weight group ($18.5\ kg/m^2 \leq BMI < 25\ kg/m^2$) and 174 and 155 were classified as being in the underweight group ($BMI < 18.5\ kg/m^2$), respectively. The mean BMIs of the underweight groups in the 2008 and 2010 surveys were significantly lower ($17.4+/-0.9\ kg/m^2$, $17.4+/-0.9\ kg/m^2$) than those of the normal weight groups ($21.7+/-1.8\ kg/m^2$, $21.9+/-1.8\ kg/m^2$). In the 2010 survey, there were significantly more females in the underweight group than in the normal group. There were no significant differences in age, disease duration, disease type, smoking status, the rate of peak-flow meter use and disease severity between the normal and underweight groups in either survey.

ASTHMA SYMPTOMS AND CONTROL

The ACT scores (median, interquartile range [IQR])

Table 1 Questionnaire administered to asthmatic patients (original in Japanese)

Age: years old Gender: male/female

Question 1

When were you first diagnosed as having bronchial asthma? Year: Month: Day:

Question 2

1) Select which of the following applies to you:
(I do not smoke, I am an ex-smoker, I currently smoke)

2) If you are an ex-smoker, please answer followings:

At what age did you start smoking?	The age you started:
At what age did you stop smoking?	The age you stopped:
How many cigarettes did you smoke per day?	Cigarettes/day (on average):
Did you stop smoking due to your asthma?	Yes or No:

3) If you currently smoke, please answer the following:

How old were you when you started smoking?	The age you started:
How many cigarettes did you smoke per day?	Cigarettes/day (on average):

Question 3

1) Do you use a peak-flow meter? (Yes or No)

2) What was your average peak flow rate when using your meter during the last 2 weeks?

Morning: Night:

Question 4 Select one answer for each the following questions:

1) How often did you have asthma attacks during the last 12 months?
(frequent attacks, seasonal attacks, or few attacks)

2) How often did you have asthma attacks during the last 2 weeks?
(5-7/week, 3-4/week, 1-2/week, or none)

3) How severe were your asthma attacks during the last 2 weeks?
(impossible to move, impossible to lie down, possible to lie down, stridor, dyspnea upon exertion)

4) Have you ever been hospitalized due to asthma?
(yes/no)

5) Have you ever been taken by ambulance or visited an emergency room due to an attack?
(yes/no)

6) Have you ever been placed on a respirator due to an asthma attack?
(yes/no)

7) Have you ever been unconscious due to an asthma attack?
(yes/no)

8) Have you ever had an attack induced by anti-inflammatory drugs, including painkillers, antipyretics, or cold medicine?

9) Were you absent from work or school due to an asthma attack during the last 12 months?
(yes/no)

Question 5

How bad was your asthma during the last 2 weeks?
(very good, fairly good, mediocre, slightly bad, or bad)

Question 6

Describe your symptoms during the last 2 weeks:

1) In the morning
(cough, sputa, chest tightness, stridor, dyspnea, or no symptoms)

2) At night
(cough, sputa, chest tightness, stridor, dyspnea, or no symptoms)

3) Sleep disturbance
(sometimes cannot fall asleep due to dyspnea, cannot have a good sleep due to dyspnea, waking up in the night due to chest tightness, or none)

Question 7

Do you feel satisfied with your daily life?
(very satisfied, fairly satisfied, mediocre, slightly dissatisfied, or dissatisfied)

Table 2A Patient characteristics in 2008 survey

	Normal group	Underweight group
BMI (mean +/- SD: kg/m2)	21.7 +/- 1.8 (*N* = 1464)	17.4 +/- 0.9*** (174)
Age (mean +/- SD: year)	55.1 +/- 17.4 (*N* = 1460)	55.2 +/- 20.4 (*N* = 173)
Gender: male/female (%)	45.4/53.6 (*N* = 1449)	40.8/59.2 (*N* = 174)
Duration (mean +/- SD: year)	14.0 +/- 13.5 (*N* = 1316)	14.3 +/- 13.0 (*N* = 159)
Type: atopic/non-atopic (%)	69.8/24.4 (*N* = 1379)	66.1/28.7 (*N* = 165)
Severity: Step1/2/3/4 (%)	26.8/28.3/25.8/4.7 (*N* = 1253)	24.7/28.7/21.3/4.0 (*N* = 147)
Smoking status: Non/Ex/Cu (%)	50.2/31.1/15.7 (*N* = 1421)	51.7/28.1/16.1 (*N* = 167)
PEF use rate (%)	26.3	33.3

****P* < 0.001 v.s. normal group. Non, non-smoker; Ex, ex-smoker; Cu, current smoker; PEF, peak flow meter.

Table 2B Patient characteristics in 2010 survey

	Normal group	Underweight group
BMI (mean +/- SD: kg/m2)	21.9 +/- 1.8 (*N* = 1260)	17.4 +/- 0.9*** (*N* = 155)
Age (mean +/- SD: year)	56.7 +/- 16.7 (*N* = 1249)	54.5 +/- 18.7 (*N* = 153)
Gender: male/female (%)	45.3/53.3 (*N* = 1242)	25.8/72.9*** (*N* = 153)
Duration (mean +/- SD: year)	16.2 +/- 15.1 (*N* = 1137)	13.9 +/- 13.7 (*N* = 139)
Type: atopic/non-atopic (%)	70.6/24.6 (*N* = 1200)	64.5/27.7 (*N* = 144)
Severity: MdI/MdP/MoP/SP/SrP (%)	31.8/24.4/32.1/6.6/1.0 (1210)	25.2/32.3/29.7/5.2/1.9 (*N* = 146)
Smoking status: Non/Ex/Cu (%)	49.9/33.5/14.7 (*N* = 1236)	58.7/24.5/14.8 (*N* = 152)
PEF use rate (%)	23.2	25.2

****P* < 0.001 v.s. normal group. MdI, mild intermittent; MdP, mild persistent; MoP, moderate persistent; SP, severe persistent; SrP, severer persistent; Non, non-smoker; Ex, ex-smoker; Cu, current smoker; PEF, peak flow meter.

Table 3A ACT score, asthma attack rate, rates of asthma-related symptoms in morning and night, and the sleep disturbance rate during the two weeks prior to answering the survey in 2008

	Normal group (*N* = 1464)	Underweight group (*N* = 174)
ACT (median [IQR])	23 [20-25]	22 [19-24]*
Asthma attack rate (%)	22.5	26.5
ARS in morning rate (%)	41.7	44.3
ARS in night rate (%)	29.8	35.1
Sleep disturbance rate (%)	13.7	15.5

**P* < 0.05 v.s. normal group. ARS, asthma-related symptoms; IQR, interquartile range.

Table 3B ACT score, asthma attack rate, rates of asthma-related symptoms in morning and night, and the sleep disturbance rate during the two weeks prior to answering the survey in 2010

	Normal group (*N* = 1260)	Underweight group (*N* = 155)
ACT (median [IQR])	24 [21-25]	23 [19-25]*
Asthma attack rate (%)	18.4	23.9
ARS in morning rate (%)	38.3	43.9
ARS in night rate (%)	27.5	31.0
Sleep disturbance rate (%)	10.9	16.1

**P* < 0.05 v.s. normal group. ARS, asthma-related symptoms; IQR, interquartile range.

and other indicators of asthma control (asthma attack rate, frequency of asthma-related symptoms in the morning and at night, and rate of sleep disturbance during the two weeks prior to answering the survey) in the 2008 and 2010 surveys are shown in Table 3A, B, respectively. In both surveys, the ACT score in the underweight group was significantly lower than that in the normal weight group. There were no significant differences in the other indicators between the normal and underweight groups. In both surveys, there were no significant differences between the normal and underweight groups in the rate of asthma

Table 4A Asthma attacks and asthma-related work absences during the one year prior to answering the 2008 survey

	Normal group (*N* = 1464)	Underweight group (*N* = 174)
AA: frequent/seasonal/few (%)	129/500/681 (8.8/31.1/46.5)	19/66/76 (10.9/37.9/43.7)
ARWA rate (%)	8.6	12.6

AA, asthma attacks; ARWA, asthma-related work or school absences.

Table 4B Asthma attacks and asthma-related work absences during the one year prior to answering the 2010 survey

	Normal group (*N* = 1260)	Underweight group (*N* = 155)
AA: frequent/seasonal/few (%)	113/355/670 (9.0/28.2/53.2)	16/52/71 (10.9/33.5/48.5)
ARWA rate (%)	7.8	12.9*

*$P < 0.05$ v.s. normal group. AA, asthma attacks; ARWA, asthma-related work or school absences.

Table 5A Drugs/medications in 2008 survey

	Normal group (*N* = 1464)	Underweight group (*N* = 174)
ICS use rate (%)	87.0	83.9
LTRA use rate (%)	40.8	40.9
OCS use rate (%)	4.8	4.0
SML use rate (%)	35.8	37.4
p-TBL use: rate (%)	8.5	10.9
OSRT use: rate (%)	41.4	46.0

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PSL, predonisolone; SML, salmeterol; p-TBL, tulobuterol patches; OSRT, oral sustained-released theophylline.

Table 5B Drugs/medications in 2010 survey

	Normal group (*N* = 1260)	Underweight group (*N* = 155)
ICS use rate (%)	89.3	88.4
LTRA use rate (%)	42.9	38.7
OCS use rate (%)	4.0	5.8
SML use rate (%)	45.6	39.3
p-TBL use: rate (%)	5.2	4.5
OSRT use: rate (%)	36.7	30.3

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PSL, predonisolone; SML, salmeterol; p-TBL, tulobuterol patches; OSRT, oral sustained-released theophylline.

attacks during the year prior to answering the survey (Table 4A, B). In the 2010 survey, the rate of asthma-related work absences during the year prior to answering the survey in the underweight group was significantly higher than that in the normal group, although there was no significant difference in the 2008 survey (Table 4A, B).

DRUGS/MEDICATIONS AND SATISFACTION IN DAILY LIFE

The drugs/medications used by patients, and their levels of satisfaction with daily life, in the 2008 and 2010 surveys, are summarized in Table 5A, B, 6A, B, respectively. There were no significant differences in either the drugs/medications or satisfaction with daily life, between the normal and underweight groups in the two surveys.

HOSPITALIZATION, AMBULANCE USE OR EMERGENCY DEPARTMENT (ED) VISITS, ATTACKS WITH UNCONSCIOUSNESS, MECHANICAL VENTILATION AND ASPIRIN INTOLERANT ASTHMA (AIA) ATTACKS

Table 7A, B, show the rates of hospitalization, ambulance use or ED visits, attacks with unconsciousness, mechanical ventilation and AIA attacks experienced in the 2008 and 2010 surveys. There were no significant differences in these rates between the normal and underweight groups in either survey.

MULTIPLE REGRESSION ANALYSIS FOR THE ACT SCORE

The multiple regression analysis for the ACT score 2008 using age (≥ mean or not), gender (male or female), disease duration (≥ mean or not), smoking status (non-, ex- or current smoker), use of peak flow

Table 6A Satisfaction with daily life in 2008 survey

	Very satisfied/Fairly satisfied/Mediocre/Slightly dissatisfied/Dissatisfied (%)
Normal group (*N* = 1464)	289/866/175/105/23 (19.6/59.2/12.9/7.2/1.6)
Underweight group (*N* = 174)	25/99/30/15/4 (14.4/59.6/17.2/8.6/2.3)

Table 6B Satisfaction with daily life in 2010 survey

	Very satisfied/Fairly satisfied/Mediocre/Slightly dissatisfied/Dissatisfied (%)
Normal group (*N* = 1260)	365/649/123/80/19 (29.0/51.5/9.8/6.3/1.5)
Underweight group (*N* = 155)	41/80/19/10/1 (26.5/51.8/12.3/6.5/0.6)

Table 7A Hospitalization, ambulance use or ED visits, attacks with unconsciousness, mechanical ventilation and AIA attacks in 2008 survey

	Normal group (*N* = 1464)	Underweight group (*N* = 174)
Hospitalization rate (%)	34.8	42.0
Ambulance use or ED visits rate (%)	32.0	37.4
Attacks with unconsciousness rate (%)	6.6	6.9
Mechanical ventilation rate (%)	5.7	5.2
AIA attacks rate (%)	7.1	3.4

ED, emergency department; AIA, aspirin intolerant asthma.

Table 7B Hospitalization, ambulance use or ED visits, attacks with unconsciousness, mechanical ventilation and AIA attacks in 2010 survey

	Normal group (*N* = 1260)	Underweight group (*N* = 155)
Hospitalization rate (%)	33.4	35.5
Ambulance use or ED visits rate (%)	31.0	32.3
Attacks with unconsciousness rate (%)	4.9	1.9
Mechanical ventilation rate (%)	5.0	3.2
AIA attacks rate (%)	6.7	9.7

ED, emergency department; AIA, aspirin intolerant asthma.

meter (use or not) and BMI (underweight or normal) as independent variables from the data 2008 were performed. The standard coefficient of regression of age, gender, disease duration, smoking status, use of PEFM and BMI in 2008 data were 0.088 ($p = 0.001$), 0.017 ($p = 0.562$), 0.065 ($p = 0.013$), 0.086 ($p = 0.004$), 0.087 ($p = 0.001$) and 0.069 ($p = 0.008$), respectively, and those in 2010 data were 0.057 ($p = 0.053$), 0.088 ($p = 0.007$), 0.092 ($p = 0.002$), 0.214 ($p < 0.001$), 0.067 ($p = 0.022$) and 0.085 ($p = 0.004$), respectively.

DISCUSSION

The aim of this study was to investigate the influence of underweight on asthma control in a clinical setting. Using the JASSO definitions, an underweight group of asthmatic patients (BMI < 18.5 kg/m^2) was compared to a normal weight group of asthmatics (18.5 kg/m^2 ≤ BMI < 25 kg/m^2). The results from the 2008 survey showed that compared to those of normal weight, there were adverse effects on asthma control from both obesity and underweight. We have previously reported the relationship between obesity and asthma control,[13] however, based on the 2008 findings, we wanted to re-confirm the apparent effect of underweight on asthma control because of the paucity of published studies to support this result. Therefore, we decided to repeat the same study using 2010 survey data.

The results clearly indicate that there is an association between underweight and asthma. The ACT scores (Table 3A, B), a reliable indicator for asthma control, clearly show that asthma control in the underweight group was worse than that in the normal weight group. Results regarding the frequency of asthma symptoms and attacks (Table 3, 4), also suggest that asthma control in the underweight group was worse than in the normal weight group, although this difference was not statistically significant. In 2010, the rate of asthma-related work absences during the year prior to the survey revealed the same findings as the ACT score. With regard to other factors such as personal characteristics or medication, which could potentially influence asthma control, there were no differences between the normal and

underweight groups. Taking all of this into account, we consider that this study confirms that underweight does adversely affect asthma control. However, the multiple regression analysis indicated that there were other known factors such as the peak flow meter use, which influenced the ACT score in this study. An important point was that the underweight was a new effector on asthma control.

As mentioned before, the association between underweight and asthma incidence has been well studied.[14-20] These studies showed a U-shape relationship between the incidence of asthma and BMI, meaning there is an adverse effect not only of overweight but also of underweight in relation to the incidence of asthma in children and adults. In contrast, there have been very few published reports about the effects of underweight on asthma control. Although Schachter *et al*. found that underweight was associated with a decreased forced expiratory volume in 1 second and enhanced airway responsiveness,[16] the patients studied were not asthmatics but normal subjects. Therefore, our results appear to be the first evidence of a relationship between underweight and asthma control in adult asthmatics. Combining our present study with our previous paper on asthma and overweight,[13] it would appear that the influence of BMI on asthma control is similar to its influence on asthma incidence.

There were some differences between the 2008 and 2010 survey data. In the 2010 survey data, females were more common in the underweight group than in the normal group, which was not the case in the 2008 survey. However, the multiple regression analysis using 2010 data indicated that this gender difference is unlikely to influence the results of our study. We found no significant differences between the underweight and normal weight groups in relation to satisfaction with daily life, hospitalizations, ambulance use or ED presentation, attacks with unconsciousness, mechanical ventilation or AIA attacks (Table 6, 7). The reason for this might be that the difference in asthma control between the normal and the underweight group was not so large as to affect these less common outcomes.

The mechanism for the adverse effect of underweight on asthma control remains unknown. Enhanced airway responsiveness and narrowing of the bronchi might play a role.[16] However, these mechanisms themselves are also not well understood. In COPD, physical capacity, systemic inflammation and nutritional status have been reported to play important roles in the reduction of respiratory function,[34] and nutritional status may similarly contribute to the underweight effect found in our study. In underweight subjects with anorexia nervosa or with gastrointestinal impairment from abdominal surgery for malignancy, respiratory muscle impairment has also been reported.[35,36] Although it is still unclear, these findings suggest that respiratory muscle weakness might be a potential mechanism to explain the association between underweight and asthma control.

In summary, we have attempted to elucidate the influence of underweight on asthma control by comparing indicators for asthma control in underweight asthmatic patients with asthmatic patients of normal BMI, using data obtained from questionnaire surveys. Using the Japanese definition of obesity, we found lower ACT scores in the underweight patients. We conclude that there is an association between underweight and asthma control in the clinical setting in Japan. A mechanism of interaction between asthma and underweight was completely unknown, and further investigation will be required.

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