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Overweight improves long-term survival in Japanese patients with asthma

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Abbreviations:
ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD-10 Version, International Statistical Classification of Diseases and Related Health Problems 10th Revision; SD, standard deviation; UMIN, University Hospital Medical Information Network; WHO, World Health Organization; 95% CI, 95% confidence interval

ABSTRACT

Background: Obesity is a risk factor for severe and difficult-to-treat asthma. However, the impact of different physiques on long-term outcomes is poorly understood. We aimed to investigate the correlation between obesity and asthma-associated long-term mortality in Japanese adults.
Methods: From the data on 3146 individuals with air pollution-related respiratory diseases in the Omuta City Air Pollution-Related Health Damage Cohort Program, 697 adult patients with asthma were analyzed. Hazard ratios for long-term all-cause and respiratory disease -related mortality were compared in patients with different physiques using the Cox proportional hazard models. The classification of physiques was based on the WHO obesity criteria.
Results: Of the 697 patients, 439 died during the median observation period of 26.3 years. The number (% of total) of underweight, normal-weight, pre-obese, and obese class I–III individuals were 75 (10.8%), 459 (65.9%), 140 (20.1%), and 23 (3.3%), respectively. The Cox proportional hazard model (adjusted hazard ratio [95% confidence interval], *P* value) showed that pre-obese group had a significantly reduced risk for all-cause (0.65 [0.51 to 0.83], $P < 0.05$) and respiratory disease (0.55 [0.37 to 0.81], $P < 0.05$)-related mortality related to normal-weight group.
Conclusions: Our cohort program demonstrated that being slightly overweight may reduce the risk of long-term mortality in patients with asthma. However, the influence of obesity on long-term outcomes remains unclear in asthma, because of the small number of obese patients included in our study. Our findings suggest that interventions, including nutrition and exercises, should be provided to Japanese patients with asthma.

Introduction

Between 2001 and 2010, the age-standardized asthma mortality rate was 9.34 per million for all ages.[1,2] However, a Japanese updated survey report has indicated that the number of deaths due to asthma has been decreasing in the last few decades from 5926 in 1996 to 1511 in 2015.[3,4]

Severe diseases and their poor control affect asthma-related mortality.[5,6] Previous cluster analyses have demonstrated that obesity is associated with severe and difficult-to-treat asthma.[7–10] Obesity is also associated with asthma exacerbations and hospitalization.[11–13] However, no significant correlation has been reported between physiques and the long-term mortality rates in patients with asthma, including those from Japanese.[14–16]

In accordance with the Pollution-related Health Damage Compensation Act since 1973, the Omuta City Air Pollution-Related

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Health Damage Cohort Program prospectively monitors residents who have been certified as having air pollution-related chronic respiratory diseases such as asthma, chronic bronchitis and pulmonary emphysema.[3] In general, obesity is diagnosed based on the Global World Health Organization (WHO) obesity criteria.[17] Using data from the cohort program, this study primarily aimed to investigate the correlation between obesity and asthma-associated long-term mortality in Japanese adults. The secondary aim was to investigate the same correlation in patients diagnosed with obesity according to the Asian WHO obesity criteria.[18]

Methods

Cohort program and study design

The Omuta City Air Pollution-Related Health Damage Cohort Program (Omuta, Fukuoka, Japan) established by the Pollution-related Health Damage Compensation Act was conducted between 1974 and 1988 (Supplementary Method 1). During this period, 3146 victims with air pollution-related respiratory diseases were registered. All information on adult Japanese patients (certified age ≥20 years) with asthma were obtained from the Department of Health and Welfare, Omuta City. Baseline characteristics including age, gender, height, weight, smoking status, diagnosis of chronic respiratory diseases, and spirometry data were collected at the certification. However, the study did not assess data from blood tests and medicines for the management of asthma. The Act did not collect any information regarding comorbid disease. The date and cause of death were obtained from the death certificate. The main cause and classification of mortality were selected based on the code for the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 Version 2016) (Supplementary Method 2).[19] To investigate the correlation between obesity and prognosis, long-term all-cause and respiratory disease-related mortality were compared between individuals of different physiques according to the Global and Asian WHO obesity criteria.[17,18]

Ethical considerations

The study was conducted in accordance with the Good Clinical Practice guidelines and was approved by the local ethics board of the Kurume University (No. 15–135, September 11, 2015). The study protocol was registered in the University Hospital Medical Information Network (UMIN) Center (UMIN No. 000031509) on February 28, 2018. The participation of patients with asthma was by an opt-out methodology between the date of certification and August 31, 2015. The investigators signed a contract with the Omuta City for permission to use the data on August 27, 2015 (updated on August 19, 2016).

Quality control of spirometry data

To obtain adequate data on forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) for quality control of spirometry, the shape of the maximal expiratory flow–volume curve was re-evaluated according to the recommendations for standardization of lung function testing (Supplementary Method 3).[20] The % FEV_1 and %FVC predicted were calculated according to the Japanese Respiratory Society recommendations.[21]

Diagnosis of asthma and chronic obstructive pulmonary disease

Diagnosis of asthma was based on the criteria stipulated in the Pollution-related Health Damage Compensation Act, which included symptoms such as occasional spasmodic, repeated, and fluctuating wheezing and dyspnea. Other respiratory diseases were excluded on the basis of chest roentgenograms by each physician. However, the diagnosis of asthmatic bronchitis was considered as asthma. Chronic obstructive pulmonary disease (COPD) was defined as a comorbid disease according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports 2019[22] based on the following criteria: baseline age ≥40 years, history of smoking, and a post-bronchodilation FEV_1/FVC ratio of <0.7. However, based on the Pollution-related Health Damage Compensation Act, post-bronchodilation spirometry data is not needed. Consequently, the term COPD-like features, not COPD, was used in accordance with age ≥40 years, history of smoking, and a pre-bronchodilation FEV_1/FVC ratio of <0.7 in this study.

Classification of BMI by WHO obesity criteria

Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Patients with asthma were classified into six different physique groups by BMI, according to the Global WHO obesity criteria for adults.[17] Underweight, normal-weight, pre-obese, and obese class I, class II, and class III individuals had a BMI of <18.50, 18.50–24.99, 25.00–29.99, and 30.00–34.99, 35.00–39.99, and ≥40.00 kg/m^2, respectively (Supplementary Table 1). For sub-analyses, the participants were also classified according to the Asian obesity criteria,[18] which defined underweight, normal-weight, pre-obese, and obese class I, class II, and class III individuals as those with a BMI of <18.50, 18.50–22.99, 23.00–27.49, and 27.50–32.49, 32.50–37.49, and ≥37.50 kg/m^2, respectively (Supplementary Table 1). The effect of BMI on the long-term mortality should be considered a time-dependent cofounder. However, our study only included BMI at certification. Consequently, no repeated measurements were available in this study. However, the effect of this might be marginal as the analysis of the effects of obesity stratified by age at entry (<50 or ≥50 years) did not lead to significant improvement in model fitting.

Statistical analyses

Baseline characteristics were expressed as mean ± standard deviation (SD) and number (%) of patients. Using the Global and Asian WHO obesity criteria,[17,18] the characteristics were compared among different physique groups using analysis of variance (ANOVA) and Pearson's chi-squared tests. Supplementary Table 2 shows the comparative analyses between survivors and non-survivors. The Cox proportional hazard models were used to estimate the hazard ratios (95% confidence interval [CI]) for all-cause and respiratory disease-related mortality in the underweight, pre-obese, and obese class I, class II, and class III groups relative to the normal-weight group (see full analyses according to Global and Asian WHO obesity criteria in Supplementary Table 3A, B, 4A-C, and 5A-C). To evaluate the hazard ratio, we considered the following two models. Model 1 estimated hazard ratios adjusted for age, gender (men or women), smoking status (non-, ex-, or current), and %FEV_1 predicted, which were selected as potential confounders based on previous studies.[15,23] In model 2, %FVC predicted, although was available, was not considered a potential confounder to avoid multicollinearity due to its strong correlation with %FEV_1 predicted. The model 1, but not model 2, was accepted, because the %FEV_1 predicted appeared to be a better indicator of the outcomes than %FVC predicted in the study. In addition to the analysis for respiratory disease-related mortality, mortality from subtypes such as asthma attacks or exacerbations (asthma), and respiratory tract infections, were separately analyzed (see the correlations among

confounders in Supplementary Fig. 1, 2). *P*-values less than 0.05 were considered as statistically significant. Statistical analyses were performed using JMP version 14.2.0 software package (SAS Institute Japan Inc., Tokyo, Japan).

Results

Study population

From 3146 victims with chronic respiratory diseases, a total of 697 adult patients with asthma were analyzed (Fig. 1) (see classification based on the Asian WHO obesity criteria in Supplementary Fig. 3). The median (25th and 75th percentile [range]) observation period was 26.3 years (17.4 and 30.2 years [0.9 and 40.9 years], respectively). Among these 697 patients with asthma, 439 died during the observation period (Supplementary Table 2). The most common cause of mortality (number of deaths; % of 439 deaths) was respiratory diseases (n = 191; 43.5%) including asthma and respiratory tract infections, followed by neoplasms (n = 90; 20.5%), cardiovascular diseases (n = 53; 12.1%), accidents (n = 22; 5.0%), and central nervous system diseases (n = 22; 5.0%) (Supplementary Fig. 4). The mean (±SD) BMI was 22.7 ± 3.6 (range 14.2–36.2) kg/m^2 for the total study population. The mean BMI of women (23.0 ± 3.9 kg/m^2) was significantly higher than that of men (22.3 ± 2.9 kg/m^2) ($P = 0.0171$) (Supplementary Fig. 1a). Using the Global WHO obesity criteria,[17] the number (% of total) of underweight, normal-weight, pre-obese, and obese class I, class II, and class III individuals were 75 (10.8%), 459 (65.9%), 140 (20.1%), and 20 (2.9%), 3 (0.4%), and 0 (0%), respectively. In this study, the risk of long-term mortality was compared between underweight, normal-weight, pre-obese, and obese class I/II groups. The complete data comparing underweight, normal-weight, pre-obese, obese class I, and obese class II (i.e., obese class I and II separately) patients are shown in Supplementary Table 3A, 4A, and 5A.

Baseline characteristics of patients

Table 1 shows significant differences in the proportion of men ($P = 0.0009$), mean of %FVC predicted ($P = 0.0067$) and FEV_1/FVC ratio ($P = 0.0127$), events of respiratory disease-related deaths ($P = 0.0087$) and mean ages at death ($P = 0.0037$) among the different physique groups (see full data according to the Global and Asian WHO obesity criteria in Supplementary Table 3A,B).

Adjusted hazard risks associated with different physiques for long-term mortality

As shown in Table 2, based on the Global WHO criteria, while pre-obese individuals were at a significantly reduced risk of all-cause (0.65 [0.51 to 0.83], $P = 0.0005$) and respiratory disease-related (0.55 [0.37 to 0.81], $P = 0.0027$) mortality (see full data in Supplementary Table 4A, C, and each result under other cause-related mortality in Supplementary Table 6, and the Kaplan–Meier curves in Supplementary Fig. 5A,B). Pre-obese individuals were at a significantly reduced risk of asthma- (0.32 [0.17 to 0.63], $P = 0.0009$), but not respiratory tract infection-related (0.73 [0.44 to 1.24], $P > 0.05$), mortality. Underweight, and obese class I/II individuals did not have a significantly higher risk of any long-term outcome than normal-weight individuals (both $P > 0.05$). Based on the Asian WHO obesity criteria[18] (Supplementary Table 4B), pre-obese individuals had a significantly lower adjusted hazard ratio for all-cause mortality (0.80 [0.65 to 0.99], $P = 0.0420$), whereas underweight individuals had a significantly higher adjusted hazard ratio (1.55 [1.01 to 2.37]) for respiratory-related mortality ($P = 0.0459$) compared to the normal-weight individuals. When obese class I and class II are analyzed separately (Supplementary Table 4C), obese class I individuals had significantly lower adjusted hazard ratios for respiratory disease (0.37 [0.16 to 0.86], $P = 0.0209$)-, and asthma (0.23 [0.06 to 0.97], $P = 0.0449$)-related mortality.

Gender differences

Regarding gender differences, men had a significantly and independently higher risk of all-cause and respiratory disease-related-mortality than women; the adjusted hazard ratios (95% CI) for men were 1.32 (1.06–1.66) ($P = 0.0142$) for all-cause, 1.57 (1.12–2.20) ($P = 0.0093$) for respiratory disease-related, 1.13 (0.71–1.80) ($P = 0.5983$) for asthma-related, and 2.23 (1.33–3.72) ($P = 0.023$) for respiratory tract infection-related mortality

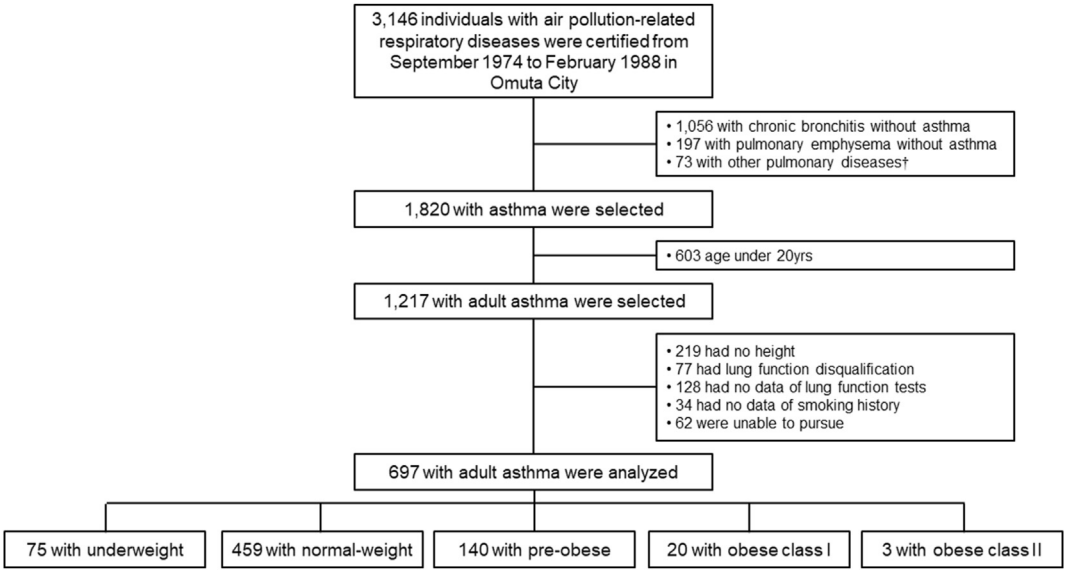

Fig. 1. Study design. Different physiques were classified according to the Global WHO obesity criteria. † The 73 patients with other pulmonary diseases including old pulmonary tuberculosis (n = 39), pneumoconiosis (n = 19), bronchiectasis (n = 11), and interstitial pneumonitis (n = 4) were excluded on the basis of chest radiograms at certification.

Table 1
Baseline characteristics of patients with different physiques classified based on the Global WHO obesity criteria.

Characteristics	Underweight	Normal-weight	Pre-obese	Obese class I/II	*P* value
Number (% of total)	75 (10.8)	459 (65.8)	140 (20.1)	23 (3.3)	
Age, years, mean ± SD	53.0 ± 15.4	52.9 ± 13.3	55.7 ± 11.9	51.1 ± 11.4	0.1
Men, n (%)	49 (65.3)	258 (56.2)	45 (32.1)	2 (8.7)	0.0009*
Body mass index, kg/m^2, mean ± SD	17.2 ± 1.0	21.9 ± 1.8	26.8 ± 1.3	32.1 ± 1.9	<0.0001*
Smoking status, n (%)					
Non-	32 (42.7)	234 (51.0)	79 (56.4)	17 (74.0)	
Ex-	21 (28.0)	109 (23.8)	28 (20.0)	3 (13.0)	
Current	22 (29.3)	116 (25.3)	33 (23.6)	3 (13.0)	0.2
Lung function, mean ± SD					
FVC, L	2.20 ± 0.89	2.43 ± 0.89	2.16 ± 0.74	2.29 ± 0.83	0.0034*
%FVC predicted, %	73.1 ± 18.5	79.2 ± 18.5	75.8 ± 15.4	82.9 ± 17.4	0.0067*
FEV_1, L	1.70 ± 0.82	1.82 ± 0.72	1.70 ± 0.60	1.82 ± 0.76	0.2
%FEV_1 predicted, %	67.3 ± 21.6	71.1 ± 21.3	72.0 ± 17.9	78.4 ± 23.1	0.1
FEV_1/FVC ratio	0.76 ± 0.13	0.75 ± 0.14	0.79 ± 0.12	0.79 ± 0.13	0.0127*
COPD-like feature as comorbidity, n (%)	16 (21.3)	72 (15.7)	15 (10.7)	1 (4.4)	0.1
Events of deaths, n (%)					
All-cause	49 (65.3)	293 (63.8)	83 (59.3)	14 (60.9)	0.8
Respiratory disease-related	31 (41.3)	126 (27.5)	31 (22.1)	3 (13.0)	0.0087*
Age at death, years, mean ± SD	79.2 ± 10.2	78.1 ± 9.7	82.6 ± 9.7	79.2 ± 8.3	0.0037*

No obese class III patients were enrolled in the study. Data are expressed as number (% of each group) of patients and mean ± standard deviation (SD). According to the Global WHO obesity criteria, underweight, normal-weight, pre-obese, and obese class I/II individuals had BMIs of <18.50, 18.50–24.99, 25.00–29.99, and ≥30.00 kg/m^2, respectively.
*$P < 0.05$ among groups.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SD, standard deviation; WHO, World Health Organization.

compared to women with cofounders, including age, BMI, %FEV_1 predicted, and smoking status. Table 3 shows the hazard ratios for long-term mortality among different physiques based on the Global WHO obesity criteria for each gender (see full data in Supplementary Table 5A). Both pre-obese men and women were at significantly reduced risk of all-cause, respiratory disease-related, and asthma-related mortality. However, pre-obese men, but not women, were at a significantly reduced risk of respiratory tract infection-related mortality. Based on the Asian WHO obesity criteria (Supplementary Table 5B, Supplementary Fig. 5B), there was no difference in the risk of long-term mortality among different physiques for men and women, whereas only obese class I women were at a significantly reduced risk of respiratory disease-related mortality when obese class I and obese class II are analyzed separately (Supplementary Table 5C, Supplementary Fig. 5B).

Discussion

Only a few previous studies have examined the long-term outcomes in patients with asthma.[15,24–26] Our long-term cohort study shows that some physiques affect all-cause and respiratory disease-related mortality in Japanese adult patients with asthma, based on data from the Omuta City Air Pollution-Related Health Damage Cohort Program. The Cox proportional hazard models found that being pre-obese [25.00–29.99 and 23.00–27.49 kg/m^2, respectively], based on the Global and Asian WHO obesity criteria,[17,18] was an independent factor for all-cause survival in patients with asthma, even after adjustment for age, gender, smoking status, and lung functions. Besides, pre-obese [25.00–29.99 kg/m^2] and obese class I [27.50–32.49 kg/m^2] individuals based on the Global and Asian WHO obesity criteria,[17,18] respectively, showed at a significantly reduced risk of respiratory disease-related mortality

Table 2
Adjusted hazard ratios for all-cause and respiratory disease-related, and asthma- and respiratory tract infection-related, mortality in different physique groups based on the Global WHO obesity criteria.

Classification	All-cause mortality			Respiratory disease-related mortality		
	Events/Total	Adjusted hazard ratio (95% CI)	*P* value	Events/Total	Adjusted hazard ratio (95% CI)	*P* value
Underweight	49/75	1.06 (0.78–1.44)	0.7	31/75	1.46 (0.97–2.20)	0.1
Normal-weight	293/459	1.00		125/459	1.00	
Pre-obese	83/140	0.65 (0.51–0.83)	0.0005*	32/140	0.55 (0.37–0.81)	0.0027*
Obese class I/II	14/23	1.17 (0.68–2.01)	0.6	3/23	0.68 (0.21–2.13)	0.5
Classification	Asthma-related mortality			Respiratory tract infection-related mortality		
	Events/Total	Adjusted hazard ratio (95% CI)	*P* value	Events/Total	Adjusted hazard ratio (95% CI)	*P* value
Underweight	18/75	1.41 (0.83–2.40)	0.2	13/75	1.57 (0.83–2.97)	0.2
Normal-weight	71/459	1.00		54/459	1.00	
Pre-obese	10/140	0.32 (0.17–0.63)	0.0009*	20/140	0.73 (0.44–1.24)	0.2
Obese class I/II	2/23	0.65 (0.16–2.69)	0.6	1/23	0.72 (0.10–5.35)	0.8

Each hazard ratio (95%CI) was adjusted for confounding factors such as age, gender, smoking status, and %FEV_1 predicted. Among the 191 dead, two patients died due to acute exacerbations of interstitial pneumonia except for asthma attack and respiratory tract infections. According to the Global WHO obesity criteria, underweight, normal-weight, pre-obese, and obese class I/II individuals had BMIs of <18.50, 18.50–24.99, 25.00–29.99, and ≥30.00 kg/m^2, respectively.
*$P < 0.05$ when compared with the normal-weight group as reference.
BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; n/a, not available; WHO, World Health Organization.

Table 3
Adjusted hazard ratios for all-cause and respiratory disease-related mortality in men and women with different physiques based on the Global WHO obesity criteria.

Classification	All-cause mortality			Respiratory-disease related mortality		
	Events/Total	Adjusted hazard ratio (95% CI)	*P* value	Events/Total	Adjusted hazard ratio (95% CI)	*P* value
Men						
Underweight	18/26	1.19 (0.72–1.96)	0.5	10/26	1.23 (0.62–2.47)	0.6
Normal-weight	143/201	1.00		69/201	1.00	
Pre-obese	30/45	0.58 (0.39–0.87)	0.0081*	15/45	0.51 (0.29–0.90)	0.0208*
Obese class I/II	1/2	1.41 (0.19–10.34)	0.7	1/2	6.03 (0.78–46.67)	0.1
Women						
Underweight	31/49	0.98 (0.66–1.46)	0.9	21/49	1.53 (0.91–2.58)	0.1
Normal-weight	150/258	1.00		57/258	1.00	
Pre-obese	53/95	0.67 (0.49–0.91)	0.0119*	16/95	0.54 (0.31–0.93)	0.0258*
Obese class I/II	13/21	1.21 (0.68–2.14)	0.5	2/21	0.50 (0.12–2.07)	0.3

Classification	Asthma-related mortality			Respiratory tract infection-related mortality		
	Events/Total	Adjusted hazard ratio (95% CI)	*P* value	Events/Total	Adjusted hazard ratio (95% CI)	*P* value
Men						
Underweight	6/26	1.38 (0.55–3.41)	0.5	4/26	1.23 (0.62–2.47)	0.6
Normal-weight	34/201	1.00		35/201	1.00	
Pre-obese	5/45	0.37 (0.14–0.96)	0.0417*	9/45	0.51 (0.29–0.90)	0.0208*
Obese class I/II	1/2	11.82 (1.43–97.46)	0.0218*	0/2	6.03 (0.78–46.67)	0.1
Women						
Underweight	12/49	1.39 (0.71–2.72)	0.3	9/49	1.93 (0.83–4.50)	0.1
Normal-weight	37/258	1.00		19/258	1.00	
Pre-obese	5/95	0.26 (0.10–0.68)	0.0054*	11/95	0.85 (0.40–1.83)	0.1
Obese class I/II	1/21	0.35 (0.05–2.54)	0.3	1/21	0.98 (0.13–7.46)	1.0

Each hazard ratio (95%CI) was adjusted for confounding factors such as age, smoking status and %FEV_1 predicted. According to the Global WHO obesity criteria, underweight, normal-weight, pre-obese, and obese class I/II individuals had BMIs of <18.50, 18.50–24.99, 25.00–29.99, and ≥30.00kg/m2, respectively.
*P < 0.05 when compared with the normal–weight group as reference.
BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in 1 s; n/a, not available; WHO, World Health Organization.

compared to normal-weight individuals. Taken together, our study demonstrates that being slightly overweight, but not underweight, was predictive of significantly better long-term survival compared to being normal-weight. A previous Japanese cohort study on the healthy general population demonstrated that lowest risk of mortality for BMI 21–27 kg/m^2 in the middle-aged and elderly population.[27] The discrepancy in the results of the study including the Japanese cohort and our study might be attributed to the differences in the sample size, endpoints (e.g., causes of mortality), and subject population (i.e., healthy people or patients with asthma). A 15-year follow-up cohort study[14] demonstrated that obesity significantly reduced the risk of all-cause mortality among asthmatics. Being underweight may increase the risk of mortality in patients with asthma, but not in healthy subjects.[14,27]

An “obesity paradox” that obese or overweight patients have better clinical outcomes than normal-weight or underweight patients is well-known for several diseases such as COPD,[28–30] chronic kidney disease,[31] and acute myocardial infarction after a percutaneous coronary intervention.[32,33] However, obesity is strongly associated with increased overall morbidity and mortality and with cardiovascular risk factors, including diabetes mellitus, hypertension, and dyslipidemia.[34–37] The reasons for this paradox remain unclear. In our study based on the Asian WHO obese criteria,[18] underweight individuals had at a higher risk of respiratory disease-related mortality than normal-weight individuals (Supplementary Table 4A, C). Underweight patients are likely to have latent cardiac cachexia and those with severe or advanced diseases may even be malnourished, with inadequate calorie and protein intake.[38,39] Being underweight negatively impacts some capacities for emergencies such as during an asthma attacks and acute exacerbations compared to being of normal-weight or overweight.

In previous studies on severe asthma,[10,40] the obese population with BMI ≥30.00 kg/m^2 in Japan was smaller (5%–7%) than that reported in the United States (37%). There were few obese patients based on the global WHO obese criteria.[17] Our study could not confirm the risk of long-term mortality in patients with asthma, although obesity may be a significant risk factor for mortality among the Japanese healthy adult population.[27] When using the Asian WHO obesity criteria,[18] which have a lower BMI range for obesity than the Global criteria,[17] obese class I individuals had significantly lower respiratory disease-related and asthma-related mortality (Supplementary Table 4B), and obese class I/II individuals did not have any increased risk of long-term mortality (Supplementary Table 4C). The risk of long-term mortality remains unclear in obese patients with asthma.

To investigate the correlation between physique and mortality in asthma, we studied several confounders, including age, gender, smoking status, and lung functions. Gender has been shown to affect the severity and mortality in asthma, with the incidence of difficult-to-treat asthma higher among obese women compared to obese men.[10–14,40,41] Gender affects the BMI in Japanese patients with asthma (Supplementary Fig. 1a). Our Cox proportional hazard models found that the risk of long-term mortality was 25–40% less among women when compared to men. However, the adjusted hazard ratios for all-cause and respiratory disease-related mortality for the different physiques were similar between men and women. There was no correlation between BMI and age in men and women (Supplementary Fig. 1b). No significant difference was seen in the proportion of non-, ex- and current smokers in both men and women, although smoking may reduce body weight and therefore affect BMI (Supplementary Fig. 1a). Our Cox proportional hazard models found that the risk of long-term mortality is increased by 1.3–1.5 folds in current smokers compared to non- and ex-smokers. However, there was no significant difference in the risks between non- and ex-smokers (data not shown). With regards to BMI and lung functions, %FEV_1 predicted showed a very weak association with BMI (Supplementary Fig. 2). Considering the complicated relationships among BMI, age, gender, smoking status, and lung functions, we set the presence or absence of COPD-like feature as comorbidity (Supplementary Fig. 1). Patients with COPD-like feature had a significantly lower BMI than non-COPD-like feature patients (Supplementary Fig. 1c). The proportion of underweight

patients with COPD-like feature was higher, but not statistically significance, compared to other physique groups (Table 1 and Supplementary Table 3A,B). Underweight patients with COPD should, therefore, be diagnosed and provided the necessary support and nutritional education early on.

Our study has several limitations. First, we classified different physiques by only BMI. The severity of asthma may be associated with not only body physiques but also body shapes such as waist size and body composition such as fat mass.[41,42] To understand the "obesity paradox," these parameters should be evaluated in the future. Previous studies have demonstrated a correlation between visceral or abdominal fat mass and pathogenesis of difficult-to-treat asthma.[43–46] Changes in the airway and gastrointestinal microbiota composition[47] and altered pro-inflammatory macrophages in adipose tissue[48] due to systemic inflammation were associated with disease severity in obese patients with asthma. Second, we only used data on baseline patient characteristics. BMI can change during the median 26 years of observation, as in this study. Japanese long-term cohort studies[49–51] have demonstrated that BMI showed a stable or decreasing trend among women, whereas, in overweight and obese men, it increased from 1951 to 2014. The changes in BMI were not assessed in the study. Third, adult patients were enrolled between 1974 and 1988. The physiques 30–40 years ago were different from those in the present day. In the past, mean BMI was lower than what it is now, and obese patients with a BMI of $\geq$30.00 kg/m^2 were few. The correlation between the higher degree of obesity and long-term mortality is still unclear. Fourth, the symptoms,[52,53] disease control levels,[54] history of exacerbation,[55] duration of disease,[56] and comorbid diseases, including other allergic diseases,[57] are important risk factors that affect prognosis. Fifth, pharmacological treatments may contribute to the mortality of asthma. However, this study did not assess medications, such as inhaled corticosteroids and long-acting bronchodilators.[58] Our cohort study showed that the age at death seemed to increase year by year (see in Supplementary Figs. 6(a)–6(c)). The relationship between mortality and medication regimen remains unclear; however, the development of treatment may improve mortality in patients with asthma. Further studies are required to evaluate these important risk factors affecting the prognosis, development, and severity of airflow obstruction.

In conclusion, our study evaluates the long-term all-cause and respiratory disease-related mortality in Japanese patients of different physiques with asthma. Slightly overweight patients were significantly associated with low long-term all-cause and respiratory disease-related mortality compared to normal-weight and underweight patients. Appropriate nutrition and exercise may help reduce all-cause and respiratory disease-related mortality among Japanese patients with asthma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.09.009

Conflict of interest

TKa received grants from Novartis, and lecture fees from AstraZeneca, GlaxoSmithKline (GSK), Boehringer Ingelheim, Novartis, Teijin Home Healthcare, Sanofi, and Kyorin, MeijiSaika Pharma. TKi received grants from GSK, AstraZeneca, and a lecture fee from AstraZeneca. TH received a grant from GSK, Novartis, and Chugai Pharmaceutical. The rest of the authors have no conflict of interest.

Authors' contributions

All authors contributed to the data analysis, drafting, and critical revision of the paper, and agreed to be accountable for all aspects of the work. Each author mainly contributed as follows: CY contributed to the protocol design, analysis, and writing of the manuscript; TKa contributed to the protocol design and editing of the manuscript; TKi, YT and KF contributed to the analysis; JS, YS, MM, HI, MN and KM contributed to the data collection and editing of the manuscript; TH supervised the protocol design and edited the manuscript.

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