

Airway Hyperresponsiveness Is Negatively Associated with Obesity or Overweight Status in Patients with Asthma

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Key Words

Obesity · Asthma · Bronchial hyperreactivity

Abstract

Background: Obesity is a risk factor for asthma in the general population, but the effect of obesity on airway hyperresponsiveness (AFHR) or airway inflammation in asthma is not clear. This study evaluated the relationship between obesity and asthma, assessing aspects of symptoms, AHR, and severity. **Methods:** In total, 852 patients with asthma diagnosed by asthma specialists based on AHR as confirmed by a methacholine bronchial provocation test, were enrolled from the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) adult asthma cohort. The intensity of AHR was assessed by the concentration of methacholine needed to cause a 20% decrease in FEV₁ (PC₂₀). Patients were classi-

fied into four categories based on body mass index (BMI): underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30). **Results:** BMI was negatively correlated with FEV₁ (l), FVC (l), and FEV₁/FVC (%) in lung function tests. The prevalence of wheezing increased with higher BMI after adjustment for age, sex, smoking, medication history, and PC₂₀ ($p < 0.0001$). logPC₂₀ was lower in the normal weight group compared with the overweight group ($p = 0.003$). The risk of moderate or severe AHR (PC₂₀ ≤ 4 mg/ml) decreased with increased BMI after adjustment for age, sex, smoking, and medication history ($p = 0.035$). **Conclusions:** Obesity is a risk factor for asthma in the general population, but obesity in asthmatic patients is negatively correlated with the intensity of AHR and is not related to asthma severity. Obesity is positively related with the prevalence of wheezing but negatively related to AHR in asthmatic patients.

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Introduction

Obesity and asthma are important public health problems. The prevalence of both has increased in the last 30 years, and a causal relationship between obesity and asthma has been evaluated. In many studies, obesity appears to be a risk factor for asthma and to be associated with an increased prevalence of asthma [1–5]. Asthma is an airway disease characterized by chronic airway inflammation and airway hyperresponsiveness (AHR), but the evidence regarding a relationship between obesity and AHR has been inconsistent [5]. Some studies have reported that obesity increased AHR and that weight gain was positively related to the prevalence of AHR in general populations [4–7]; in contrast, other studies have shown no relationship, or even a negative association, between obesity and the presence of AHR in asthma patients [2, 8–11]. Furthermore, there is evidence indicating that the chronic inflammation associated with obesity lessens Th2 inflammation [12–14], which is closely related to AHR in asthma.

The effects of obesity on the clinical features of asthma must be determined in asthmatic patients in order to provide improved management of the growing number of obese or overweight individuals with asthma. This study evaluated the relationship between obesity and asthma in asthmatic patients by assessing asthma symptoms, AHR, and asthma severity.

Methods

Study Subjects

In total, 852 adult asthmatics were enrolled from the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA), which was established in 2005 and involved 11 university hospitals [15]. Inclusion criteria were a diagnosis of asthma made by an asthma specialist based on clinical symptoms and AHR as confirmed by a positive methacholine bronchial provocation test (MBPT) result, which was defined as a concentration of methacholine that caused a 20% decrease in FEV_1 (PC_{20}) $\leq$ 25 mg/ml. MBPT was performed as previously described using the five-breath dosimeter method [16]. All COREA patients had been enrolled during medical office visits, and thus their height and weight were measured by technicians at enrollment. All patients had been suffering from at least one chronic persistent respiratory symptom (dyspnea, cough, sputum production, or wheezing) for more than 3 months, and the frequency of each symptom was accessed for the previous 3 months (the case report form for the assessment of asthma symptoms is presented in online suppl. table 1, www.karger.com/doi/10.1159/000335926). Exclusion criteria were asthma exacerbation or infection within the previous 8 weeks and lack of MBPT data. Demographic characteristics,

smoking status, asthma severity, asthma medication history during the previous 4 weeks, skin-prick tests for 13 common inhalant allergens, serum total IgE, and blood eosinophil counts were collected. The study protocol was approved by the institutional review board of each participating hospital, and informed consent was obtained from all patients.

Definitions

Body mass index (BMI) was calculated as weight (kg)/height² (m²). Patients were classified into four categories based on BMI, according to the WHO classification: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese ($\geq$ 30) [17]. The intensity of AHR was assessed by PC_{20} . AHR intensity was arbitrarily divided into four levels based on PC_{20} : severe AHR ($PC_{20} \leq 1$ mg/ml), moderate AHR ($1 < PC_{20} \leq 4$ mg/ml); mild AHR ($4 < PC_{20} \leq 16$ mg/ml), and borderline AHR ($16 < PC_{20} \leq 25$ mg/ml). Asthma severity was evaluated during the first visit based on the Global Initiative for Asthma (GINA) guidelines. However, for patients with a history of inhaled corticosteroid (ICS) use, an asthma specialist assessed asthma severity by taking into account current treatments and asthma control; severity was classified as mild intermittent, mild persistent, moderate persistent, or severe persistent asthma [18, 19]. The number of asthma exacerbations was defined by the summative number of unscheduled outpatient clinic visits, emergency room visits, and admissions due to asthma exacerbation during the past year. The number of severe asthma exacerbations was defined as the number of asthma exacerbations requiring an emergency room visit or admission. Skin-prick tests were performed for 13 common inhalant allergens, and a mean wheal diameter $\geq$ 3 mm was regarded as a positive reaction. Atopy was defined as a positive skin-prick test result for one or more of the inhalant allergens. Medication history was defined as the use of any asthma-controller medications, including ICS, ICS combined with long-acting β_2 -agonists, leukotriene modifiers, oral theophylline, and oral corticosteroids, during the previous 4 weeks.

Statistical Analysis

Baseline characteristics, presented as means and standard deviations (SD) for continuous variables and relative frequencies for categorical variables, were compared using one-way ANOVA or the χ^2 test. Lung function test results were evaluated according to the four BMI groups using general linear model univariate analysis of variance adjusted for age, sex, smoking status, and medication history. Spearman correlations were calculated for variables of interest that did not follow a normal distribution.

Differences in AHR among the four BMI groups were assessed using log transformations of PC_{20} values. Relationships between BMI and AHR or wheezing were assessed by multiple regression analysis for BMI as the continuous variable and using multiple logistic regression models for the four BMI groups. Odds ratios (ORs) and 95% confidence intervals (CIs) for severe AHR or the presence of wheezing were calculated with the risk for the normal BMI group as the reference. Estimates for the relationship between BMI and AHR were adjusted for age, sex, smoking status, and medication history. Age and sex were significantly different among the four BMI groups, and smoking status and medication history could be important confounding factors for AHR. Estimates for the relationship between BMI and the presence of wheezing were adjusted for the same covari-

Table 1. Clinical characteristics of study population

Characteristics	Underweight BMI <18.5	Normal BMI 18.5–24.9	Overweight BMI 25–29.9	Obese BMI ≥30	p value*
Subjects, n	31	546	233	42	
Sex, % female	77.4	56.4	45.9	73.8	<0.0001
Mean age ± SD, years	29.3 ± 10.9	45.5 ± 15.5	49.5 ± 15.9	53.4 ± 14.3	<0.0001
Smoking status					0.184
Never	15	248	110	27	
Former	8	204	86	12	
Current	8	94	37	3	
FEV ₁ , liter	2.72 ± 0.72	2.48 ± 0.85	2.47 ± 0.87	1.99 ± 0.87	0.097**
FEV ₁ , %	83.3 ± 16.9	85.3 ± 19.0	87.0 ± 17.7	81.5 ± 19.1	0.037**
FVC, liter	3.22 ± 0.77	3.27 ± 0.98	3.34 ± 1.68	2.57 ± 1.00	0.028**
FVC, %	83.3 ± 15.7	91.9 ± 16.6	91.2 ± 16.1	84.6 ± 15.9	0.001**
FEV ₁ /FVC, %	84.0 ± 6.6	79.8 ± 5.9	78.1 ± 5.9	79.2 ± 4.7	0.207**
PC ₂₀	4.37 ± 4.91	4.81 ± 5.63	6.30 ± 6.43	5.63 ± 6.53	0.010
Atopy, %	51.6	46.2	41.6	28.6	0.097
Blood eosinophil count	277 ± 289	347 ± 311	324 ± 292	316 ± 361	0.557
Serum total IgE	202 ± 233	381 ± 635	379 ± 555	188 ± 359	0.192
Severity, % mild	40.0	43.7	43.6	30.0	0.397
Asthma exacerbation	0.13 ± 0.43	0.29 ± 1.28	0.14 ± 0.54	0.29 ± 0.98	0.326
Severe asthma exacerbation	0.13 ± 0.43	0.13 ± 0.65	0.07 ± 0.31	0.20 ± 0.78	0.530
Allergic rhinitis, %	84.6	76.6	73.5	75.0	0.618
Medication history, %	61.3	51.1	48.9	52.4	0.627
Low-dose ICS, %	6.5	3.1	4.3	4.8	0.668
Low-dose ICS + LABA, %	29.0	16.7	12.9	11.9	0.096
Medium high-dose ICS + LABA, %	25.8	28.4	30.0	33.3	0.859

SD = Standard deviation; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist.

* Significance was derived using one-way ANOVA among the four BMI groups for continuous variables, or the χ^2 test for proportions.

** Significance was derived using general linear model univariate analysis of variance among the four BMI groups adjusted for age, sex, smoking status, and medication history.

ates and PC₂₀ as a marker of AHR, which is an important factor for wheezing in asthmatics. Statistical significance was accepted for p values <0.05. All statistical analyses were performed using PASW Statistics 18.0 for Windows (SPSS Inc., Chicago, Ill., USA).

Results

Baseline Characteristics

The characteristics of the study population are presented in table 1. There were more females than males in the underweight and obese groups and more younger patients than older patients in the underweight group. For the lung function tests, FEV₁ (%), FVC (l), and FVC (%) differed significantly among the four groups (p = 0.037, p = 0.028, and p = 0.001, respectively) after adjustment for age, sex, smoking status, and medication his-

tory. BMI was negatively correlated with FEV₁ (l), FVC (l), and FEV₁/FVC (%) ($r = -0.122$, $p < 0.0001$; $r = -0.098$, $p = 0.005$; $r = -0.134$, $p < 0.0001$, respectively; fig. 1). There were no differences in asthma severity, asthma exacerbation, and severe exacerbation among the four BMI groups, and no significant relationship between BMI and asthma severity or asthma exacerbation was observed.

BMI and AHR

Differences in logPC₂₀ were observed among the four BMI groups (p = 0.025), with higher logPC₂₀ values in the overweight and obese groups compared with the normal weight group (p = 0.003; fig. 2). Correlation analysis revealed a positive correlation between PC₂₀ and BMI as a continuous variable ($r = 0.076$, $p = 0.027$). In moderate to severe AHR (PC₂₀ ≤ 4 mg/ml), multiple logistic regres-

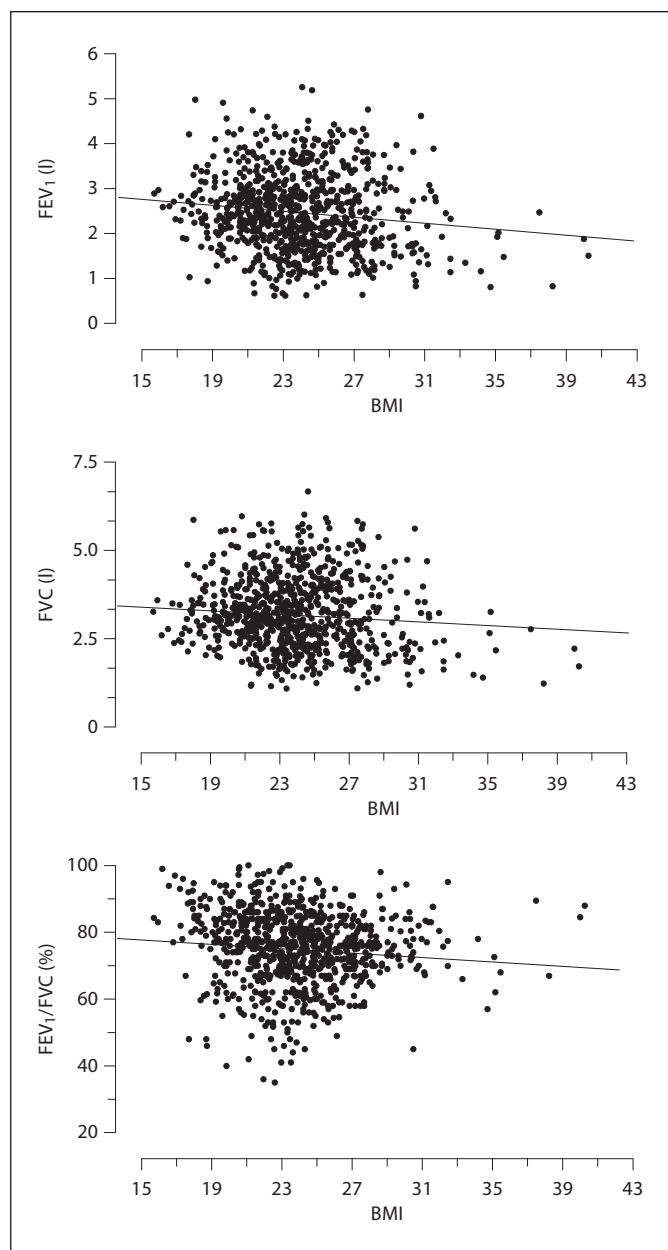


Fig. 1. Correlation between the BMI and lung function test results. BMI was negatively correlated with FEV₁, FVC, and FEV₁/FVC ($r = -0.122$, $p < 0.0001$; $r = -0.098$, $p = 0.005$; $r = -0.134$, $p < 0.0001$, respectively).

sion showed a 4.5% decrease in the likelihood of moderate to severe AHR for every 1 kg/m² increase in BMI, after adjusting for age, sex, smoking status, and medication history ($p = 0.035$). Among the four BMI groups, the prevalence of moderate to severe AHR was significantly lower in the overweight group than in the normal weight

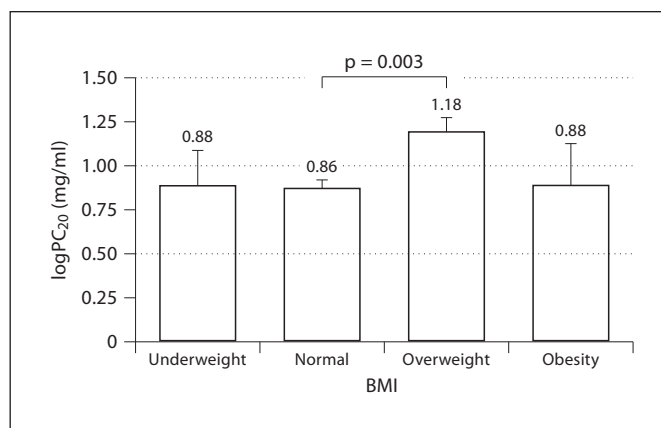


Fig. 2. Comparison of logPC₂₀ values among the four groups based on BMI. logPC₂₀ values were significantly different between the normal weight and overweight groups ($p = 0.003$). logPC₂₀ values were significantly different among the four groups ($p = 0.025$).

group, after adjusting for age, sex, smoking status, and medication history (OR 0.659, 95% CI 0.481–0.903, $p = 0.01$; fig. 3a).

BMI and Wheezing

More patients in the obese group than in the other groups had experienced wheezing during the previous 3 months ($p = 0.002$). After adjusting for age, sex, smoking status, PC₂₀, and medication, the prevalence of wheezing was higher in the obese group than in the normal weight group (OR 3.169, 95% CI 1.561–6.434, $p = 0.002$; fig. 3b). Multiple regression analysis, adjusted by age, sex, smoking status, PC₂₀, and medication history, demonstrated an 8.8% increase in the prevalence of wheezing for every 1 kg/m² increase in BMI ($p < 0.0001$). Cough and dyspnea during the previous 3 months and the presence of atopy were not related to BMI.

Discussion

In the present study, increased BMI was negatively correlated with the intensity of AHR in asthmatic patients, but BMI was associated with increased prevalence of wheezing after adjustment for age, sex, smoking status, medication history, and AHR. Wheezing was more prevalent in the obese group than in the normal weight group, although the degree of AHR was lower in the groups with higher BMI.

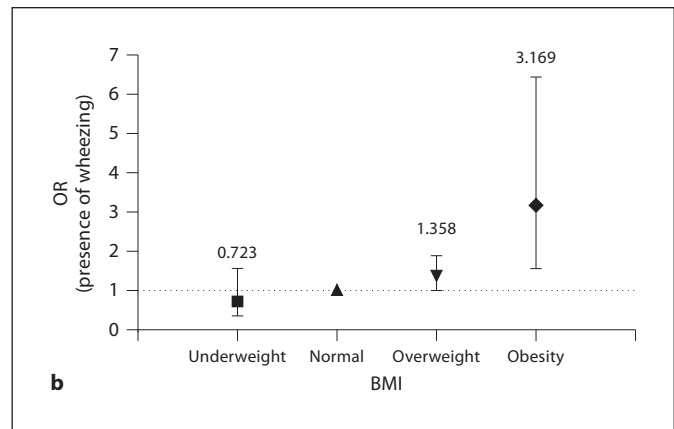
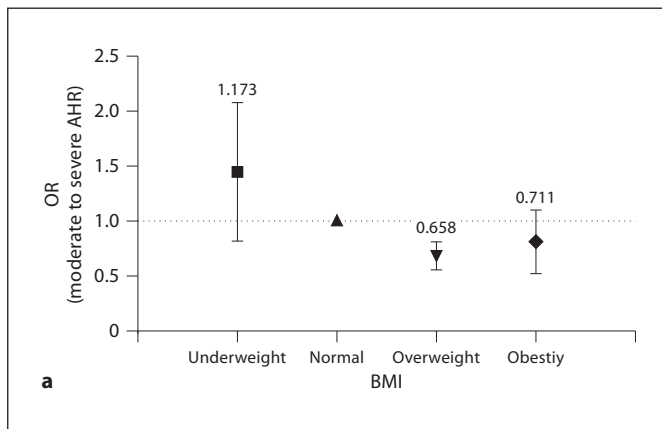


Fig. 3. Association between BMI and moderate to severe AHR or wheezing after adjustment for age, sex, smoking status, PC₂₀, and medication history. **a** ORs for the association between BMI and moderate to severe AHR, according to a conditional logistic regression model. **b** Association between the presence of wheez-

ing and BMI in asthmatic patients by BMI group. The presence of wheezing symptoms was significantly associated with BMI. The prevalence of wheezing was higher in the overweight and obese groups compared with the normal weight group ($p = 0.002$).

In an earlier report, BMI was negatively correlated with the presence of AHR confirmed by MBPT [11], and others have reported that obesity is a risk factor for asthma and wheezing, but not for AHR [2, 8–11, 20, 21]. However, many studies have shown a link between obesity and increases in both AHR and the prevalence of asthma in the general population [4–7]. In several animal studies, obese mice showed increased AHR [22, 23], whereas in human studies, obesity suppressed AHR [2, 20]. These inconsistent results may be attributable to the heterogeneity of the study populations, possibly including differences in the ratio of asthmatics to non-asthmatics, the sex distribution, the proportion of underweight subjects, the regional origins of subjects, and the definition of asthma, including whether diagnosis was based on questionnaires or on bronchial provocation tests [5]. In studies assessing obesity and asthma, the definition of asthma is critical because obesity can mimic asthma by causing wheezing [10, 24, 25]. Studies in asthmatic patients have consistently shown no relationship, or even a negative association, between obesity and AHR [2, 8–11]. It is inferred that obesity has different effects on AHR in asthmatic individuals compared with non-asthmatic individuals. Although AHR may be observed in the general non-asthmatic population, AHR appears to be more severe and to be related to Th2 inflammation in asthmatic patients [26, 27]. Given the differences in airway environments with respect to inflammation and lung physiology between asthmatic and non-asthmatic indi-

viduals, the effects of obesity on the airways would also be expected to differ.

Our finding that obesity increases the prevalence of wheezing is concordant with many previous studies [1–5]. However, wheezing related to obesity was independent of AHR among the asthmatic individuals in the present study, indicating that wheezing related to obesity has a mechanism different from AHR. The mechanism in the relation between obesity and asthma remains unclear, but two possible mechanisms have been suggested: mechanical changes in the lung and chronic systemic inflammation [28]. Changes in lung mechanics include decreased functional residual capacity, reduced loading of the airway smooth muscle, and low tidal volume. These mechanical factors can cause airway obstruction and reduce the bronchodilatory effect of a deep breath. Obesity can also cause chronic systemic inflammation attributable to increased expression of inflammatory molecules and adipokines such as leptin. Increases in TNF- α and other inflammatory molecules in obesity may aggravate AHR in the general population [28], but the chronic inflammation in obesity is not eosinophilic or Th2-type inflammation. Furthermore, obesity was associated with reduced eosinophilic inflammation in a mouse model of asthma [14, 29], and BMI was inversely related with sputum eosinophils and FE_{NO} [12]. As AHR in asthma has been shown to be correlated with markers of airway eosinophilic inflammation, obesity could decrease AHR in asthmatic individuals. Therefore, wheezing related to

obesity in asthmatic patients seems more likely to be caused by changes in lung mechanics. This study, along with others [2, 7], reported decreased lung function, including FEV₁, FVC, and FEV₁/FVC, with obesity.

It could be that the increase in wheezing in obese and overweight individuals may increase the number of visits to doctors, increase the diagnosis of asthma, and be regarded as severe asthma with frequent symptoms. Thus, it is important to consider weight reduction in obese asthmatic patients who show poor response to asthma medication, rather than to increase anti-inflammatory medication such as inhaled or oral corticosteroids, which may hinder weight loss. It is also suggested that obese and overweight asthmatic patients should be evaluated for AHR to facilitate the correct differential diagnosis of wheezing.

The present study has limitations. First, the correlations between BMI and lung function or PC₂₀ were very small, indicating a minimal effect. Weak negative correlations between BMI and lung function have also been observed in other studies, and these observations were also too weak to have clinical meaning [2, 7]. This may suggest that other factors affect lung function and AHR. Nevertheless, such consistent results support the theory that obesity affects AHR via a mechanical mechanism. In addition, although the negative correlations between BMI and PC₂₀ were too small to have clinical implica-

tions, multiple logistic analysis showed a clear relationship between BMI and moderate to severe AHR in asthmatics. Second, the assessment of asthma symptoms over the previous 3 months could be a limitation in the evaluation of the long-term presence of wheezing. However, the inclusion criteria for the COREA include the presence of at least one chronic persistent respiratory symptom, i.e. dyspnea, cough, sputum production, or wheezing, for more than 3 months. Therefore, the asthma symptoms during the previous 3 months may reflect the symptoms of patients with stable asthma and may be related to BMI at the time of enrollment.

Obesity is a risk factor for asthma in the general population, but in patients with obesity and asthma, it is negatively correlated with the intensity of AHR and is not related to asthma severity. Although obesity does not increase AHR, it increases the prevalence of wheezing in asthmatic individuals. Clinicians should be aware that wheezing may develop in obese individuals with asthma, regardless of the presence of AHR.

Acknowledgement

This study was supported by a grant from the Ministry for Health, Welfare, and Family Affairs, ROK (A102065).

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Supplementary Table 1

Case report form for the assessment of asthma symptoms.

How often have you experienced the following symptoms in the previous 3 months?

	Cough		Dyspnea		Wheezing	
	☐ Yes	☐ No	☐ Yes	☐ No	☐ Yes	☐ No
	Night time	Day time	Night time	Day time	Night time	Day time
1	☐ 1 night/week	☐ 1–2 days/month	☐ 1 night/week	☐ 1–2 days/month	☐ 1 night/week	☐ 1–2 days/month
2	☐ 2–6 nights/week	☐ >3 days/month	☐ 2–6 nights/week	☐ >3 days/month	☐ 2–6 nights/week	☐ >3 days/month
3	☐ Almost every night	☐ >1 day/week	☐ Almost every night	☐ >1 day/week	☐ Almost every night	☐ >1 day/week
4	☐ Continuous	☐ Almost everyday	☐ Continuous	☐ Almost everyday	☐ Continuous	☐ Almost everyday