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Association between obesity and lung function changes by sex and age in adults with asthma

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ABSTRACT

Objective: The lung function changes presenting before and after asthma treatment in obese people remain largely unknown. This study aimed to investigate the association between obesity and lung function changes before and after treatment in adults with asthma.

Methods: We enrolled 937 newly diagnosed asthma patients from Cohort for Reality and Evolution of Adult Asthma in Korea cohort in 2015–2017, who performed follow-up spirometry after three months of asthma treatment. The percentage changes (Δ) between the spirometry results before and after treatment were calculated. Patients were categorized into four body mass index (BMI) groups; underweight (<18.5), normal (18.5 – 22.9), overweight (23.0 – 24.9), and obese (≥ 25.0). Association between percent change of pulmonary function and BMI was analyzed according to sex and/or age (<45 yrs, 45 – 65 yrs, ≥ 65 yrs), which were statistically corrected for age, sex, smoking status, and medication history.

Results: There was no consistent correlation between BMI and each lung function parameter. However, there were significant differences between BMI and $\Delta FEV_1/FVC$ before and after 3 months of controller treatment. The obese asthmatics showed significantly lower $\Delta FEV_1/FVC$ ($6.0 \pm 13.5\%$) than the underweight ($12.6 \pm 21.4\%$, $P = 0.044$) or normal weight ($9.1 \pm 14.6\%$, $P = 0.031$). Middle-aged women had higher BMI (24.11 ± 3.60 vs. 22.39 ± 3.52) and lower $\Delta FEV_1/FVC$ ($5.7 \pm 11.9\%$ vs. $8.9 \pm 14.3\%$, $P = 0.012$) than young women.

Conclusions: Obesity is negatively correlated with the $\Delta FEV_1/FVC$ before and after controller treatment. Sex and age differentially contribute to lung function changes in response to asthma medications in adult asthmatics, showing a significant decrease in the $\Delta FEV_1/FVC$ in middle-aged women.

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Introduction

Worldwide, the incidence of obesity is growing, and the prevalence of overweight and obesity had risen by 27.5% among adults, between 1980 and 2013, in the United States (1). In Korea too, obesity-related trends

have been on an upward swing (2). Based on World Health Organization (WHO) criteria (body mass index [BMI] ≥ 25 kg/m²), 32.8% of Korean adults are obese, including 36.1% of men and 29.7% of women (2,3). Obesity is a social problem that poses a threat

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to public health, as it is associated with an increased incidence of several chronic diseases such as hypertension, diabetes, dyslipidemia, cardiovascular diseases and certain malignancies (4).

Asthma is among the most commonly observed chronic respiratory diseases, and is characterized by chronic airway inflammation, reversible airway obstruction, and airway hyper-responsiveness. The prevalence of asthma had increased by 12.6% to 358.2 million people from 1990 to 2015 (1). Several epidemiological studies have shown parallels in the increasing prevalence of obesity and asthma simultaneously, suggesting a relationship between the two diseases (5,6). Obesity is a risk factor for asthma development, increased asthma severity, poorer asthma control, poorer response to asthma therapy, and increased degree of asthma exacerbation (7–10). However, some researchers have reported that obesity and asthma exacerbation are not related (11). Moreover, higher body fat composition has been reported to have negative impact on lung function even in non-obese healthy children and adolescent (12).

A meta-analysis recently reported that those who were obese or overweight showed significant associations with decreased force expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC (%) values compared to normal weight adults with asthma (13). Moreover, the associations between obesity and asthma vary by sex, with the association shown to be stronger in women than men due to physiological and hormone-related influences (14). However, the results on the association between obesity and asthma control, by sex and pathophysiology, are conflicting and not clearly elucidated (15,16).

Most previous studies focusing on the association between asthma and obesity had a cross-sectional design. Few studies have investigated the lung function changes after 3 months of controller therapy, which may be a surrogate marker of asthma control. Therefore, we aimed to investigate the association of obesity and lung function after 3 months of controller therapy compared to baseline in adults newly diagnosed with asthma. We also analyzed the effects of sex and age on the relationship between obesity and lung function changes in such settings.

Materials and methods

Study participants

Study subjects were enrolled from the Cohort for Reality and Evolution of Adult Asthma in Korea

(COREA). The COREA was established in 2005 and included 21 university hospitals in Korea (17). All patients were ethnic Koreans aged ≥ 18 years and the COREA cohort is a prospective and observational multicenter cohort that reflects the real-world situation without artificial interventions during enrollment and follow-up. A total of 937 patients with asthma were enrolled in this study among 2,498 newly diagnosed asthma patients from 2015 to 2017 after the exclusion of those with missing data on BMI ($n = 9$) or follow-up pulmonary function values after 3 months of controller treatment ($n = 1,552$).

All patients had at least one chronic persistent respiratory symptom (cough, sputum, dyspnea, or wheezing) for more than 3 months, and asthma was diagnosed based on 1) a positive methacholine bronchial provocation test, defined as a concentration of methacholine ≤ 25 mg/mL that caused a 20% decrease in the FEV_1 (PC_{20}) or 2) a positive bronchodilator response ($\geq 12\%$ and 200-ml improvement in the FEV_1 after the inhalation of 200–400 μ g of albuterol) (18). The exclusion criteria included the patients who had been taking asthma controller medication regularly at the enrollment, poor adherence to treatment (visual analogue scale ≤ 7), the presence of respiratory infection, bronchiectasis, interstitial lung disease, chronic obstruction pulmonary disease, vocal cord dysfunction, obstructive sleep apnea, Churg-Strauss syndrome, cardiac dysfunction and allergic bronchopulmonary aspergillosis.

Patients attended consultations at their hospitals regularly every 3 months and were managed uniformly according to Global Initiative for Asthma (GINA) guidelines (19). At every 3-month visit, patients underwent spirometry and their asthma control test (ACT) scores were reported; the investigator reviewed and recorded the medications taken in the previous three months; compliance of the inhaled and oral medication was measured using self-reported visual analogue scale (0: none – 10: complete). Demographic information on smoking status, atopy tendency, serum total immunoglobulin E (IgE) and blood eosinophil counts was collected. The study protocol was approved by the institutional review boards of all participating hospitals. (Dongtan Sacred Heart Hospital, Hallym University; Seoul National University Hospital; Chung-Ang University Hospital; Seoul National University Bundang Hospital; Pusan National University Hospital; Soonchunhyang University Bucheon Hospital; Yeungnam University Hospital; Ajou University Hospital; Ewha Womans University Hospital; Yonsei University Hospital; Kangwon National University

Hospital; Ulsan University Hospital Hospital; Asan Medical Center).

Study variables

BMI was calculated as the weight (kg)/height² (m²). East Asians generally have higher body fat percentages than non-Asians at the same BMI. Therefore, patients were classified into four BMI categories, according to the WHO classification for the Asia-Pacific population (20): underweight (<18.5 kg/m²), normal weight (18.5–22.9 kg/m²), overweight (23.0–24.9 kg/m²), and obese (≥25.0 kg/m²). Patients were also categorized into three age groups: a young (< 45yrs), a middle-aged (45–65yr), an elderly group (≥ 65 yrs).

The asthma symptom control status was evaluated every 3 months based on the ACT score; well controlled for ACT 20–25, partly controlled for ACT 15–19, and uncontrolled for ACT 5–14 (21). The percentage change (Δ) in ACT scores before and after controller treatment was defined as $\{[(\text{value after treatment} - \text{value before treatment}) / \text{value before treatment}] \times 100\}$.

We collected medication history data pertaining to the use of any asthma controller medication such as ICS with or without long-acting beta₂-agonist, leukotriene receptor antagonists, oral theophylline, and oral corticosteroids in the past 4 weeks.

Asthma exacerbation was defined by any one of the following criteria: 1) use of systemic corticosteroids or an increase from a stable maintenance dose for at least 3 days, or 2) asthma-specific unscheduled visits and emergency department visits or hospitalization. The number of asthma exacerbation events was assessed by a careful review of medical records from the one year prior to enrollment.

Atopy was defined by the presence of one or more positive reactions (allergen/histamine ratio ≥1 and mean wheal diameter ≥ 3 mm) to skin prick tests with 11 common inhalant allergens (Bencard, UK; or Allergopharma, Germany), including *Dermatophagoides pteronyssinus*, *D. farinae*, tree pollen mixture, grass pollen mixture, ragweed, mugwort, cockroach, *Alternaria*, *Aspergillus*, cat, and dog (22).

Lung function

During the baseline visit, spirometry was performed before and after the use of a bronchodilator according to the American Thoracic Society guidelines (23). Baseline FVC and FEV₁ measurements were obtained in the absence of recent bronchodilator use (within 8 h). The basal and post-bronchodilator FEV₁, FVC,

and forced expiratory flow between 25 and 75% FVC were measured. We used Vmax Series 2130 Autobox Spirometry (Sensor Medics, Yorba Linda, CA, USA), and applied a calibration check every morning at 8:00 am. Follow-up spirometry was performed after 3 months of asthma treatment with controller medication. The percentage change (Δ) in the spirometry values before and after controller treatment was defined as $\{[(\text{value after treatment} - \text{value before treatment}) / \text{value before treatment}] \times 100\}$.

Statistical analysis

The patients' baseline characteristics were presented as mean ± standard deviations for continuous variables, and frequencies for categorical variables. One-way analysis of variance or a Kruskal-Wallis test was used for the continuous variables among the BMI groups, and a chi-square test or Fisher's exact test was used for the categorical variables. Pulmonary function test result comparisons were evaluated according to the four BMI groups using analysis of covariance (ANCOVA) adjusted for age, sex, smoking status, and medication history. As the use of separate ANCOVA leads to an inflated type 1 error, the Bonferroni correction was applied to each subgroup analysis. Statistical analysis was performed using IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA). A *p* values <0.05 was considered statistically significant.

Results

Baseline characteristics of the study participants

The characteristics of the study population are presented in Table 1. There were significant differences among the BMI groups in terms of age, sex, and onset age of asthma (*P* < 0.001, respectively). Underweight asthma patients were younger (43.5 ± 16.4yrs) and had a younger age at disease onset (39.2 ± 18.7yrs) than those in the normal, overweight, and obese groups (*P* < 0.05, respectively). The normal weight participants were younger (48.3 ± 15.3yrs) and had a younger age at disease onset (45.3 ± 16.2yrs) than those in the overweight (53.0 ± 14.3yrs, 49.6 ± 15.6yrs) and obese groups (55.0 ± 15.3yrs, 52.1 ± 16.6yrs) (*P* < 0.05, respectively). There were no differences in terms of smoking status, atopy tendency, serum total IgE level, blood eosinophil count, PC₂₀, asthma exacerbation frequency, and medication history across the BMI groups. In the lung function tests, there was no consistent correlation between BMI and each lung function parameter after adjustment for age, sex, smoking

Table 1. Clinical characteristics of study population.

	Underweight (BMI < 18.5)	Normal (BMI, 18.5–22.9)	Overweight (BMI, 23.0–24.9)	Obese (BMI ≥ 25.0)	P value
Number of subjects	31	317	244	345	
Mean age, yr	43.5 ± 16.4	48.3 ± 15.3 [¶]	53.0 ± 14.3 ^{¶, †}	55.0 ± 15.3 ^{¶, †}	<0.001
Female (%)	24 (77.4)	207 (65.3)	137 (56.1)	177 (56.1)	<0.001
Smoking status					0.079
Never	22 (71.0)	180 (57.1)	126 (52.1)	184 (54.1)	
Former	3 (9.7)	98 (31.1)	84 (34.7)	118 (34.7)	
Current	6 (19.4)	37 (11.7)	32 (13.2)	38 (11.2)	
Onset age, yr	39.2 ± 18.7	45.3 ± 16.2 [¶]	49.6 ± 15.6 ^{¶, †}	52.1 ± 16.6 ^{¶, †}	<0.001
Atopy (%)	32.3	32.9	27.9	24.2	0.096
Serum total IgE (IU/mL)	227.7 ± 187.1	244.3 ± 238.8	177.9 ± 196.1	212.0 ± 218.7	0.290
Blood eosinophil count (/mm ³)	346.0 ± 310.0	339.0 ± 263.3	348.8 ± 326.1	298.6 ± 232.5	0.495
PC ₂₀ (mg/mL)	5.1 ± 4.7	4.9 ± 4.6	4.9 ± 4.8	5.5 ± 4.8	0.329
Asthma control status (initial)					
Well controlled, n (%)	3 (27.3)	24 (32.9)	18 (35.3)	41 (43.6)	0.538
Partly controlled, n (%)	6 (54.5)	25 (34.2)	17 (33.3)	32 (34.0)	
Uncontrolled, n (%)	2 (18.2)	24 (32.9)	16 (31.4)	21 (22.3)	
Asthma control status (f/u)					
Well controlled, n (%)	26 (89.7)	222 (83.8)	169 (85.4)	226 (79.6)	0.623
Partly controlled, n (%)	3 (10.3)	41 (15.5)	27 (13.6)	53 (18.7)	
Uncontrolled, n (%)	0 (0.0)	2 (0.8)	2 (1.0)	5 (1.8)	
ΔACT (%)	28.2 ± 22.1	24.8 ± 28.4	29.2 ± 30.8	18.3 ± 26.1 [‡]	0.152
Asthma exacerbation	0.10 ± 0.40	0.32 ± 1.10	0.42 ± 1.51	0.29 ± 0.94	0.316
Medication					
Low dose ICS	1 (3.2)	5 (1.6)	3 (1.2)	4 (1.2)	0.597
Low dose ICS + LABA	8 (25.8)	76 (24.0)	42 (17.2)	70 (20.3)	0.227
Medium high dose ICS + LABA	13 (41.9)	133 (42.0)	110 (45.1)	155 (44.9)	0.844
LTRA	15 (48.4)	162 (51.1)	123 (50.4)	189 (54.8)	0.667
Oral theophylline	5 (16.1)	31 (9.8)	23 (9.4)	50 (14.5)	0.128
FEV ₁ , liter *	2.1 ± 0.7	2.2 ± 0.8	2.2 ± 0.9	2.2 ± 0.9 ^{¶, †}	0.005
FEV ₁ , % pred *	72.8 ± 21.0	76.5 ± 21.4	78.0 ± 21.5	77.6 ± 19.6	0.016
FVC, liter *	2.8 ± 0.7	3.1 ± 1.0	3.1 ± 1.0 [¶]	3.0 ± 1.1	0.032
FVC, % pred *	81.3 ± 16.7	88.5 ± 18.7 [¶]	88.5 ± 18.4 [¶]	84.4 ± 18.1	0.008
FEV ₁ /FVC, % *	73.4 ± 16.2	70.1 ± 12.4	70.8 ± 17.0	71.3 ± 10.6 [‡]	0.008

Values are presented as mean ± standard deviation or number (%).

One-way ANOVA or Kruskal-Wallis Test among four BMI groups for continuous variables and Chi-squared test or Fisher exact test for categorical variables. Asthma control status was evaluated base on ACT score; well controlled for ACT 20–25, partially controlled for ACT 15–19, and uncontrolled for ACT 5–14. F/U meant values after three month of asthma controller therapy. The percentage change (Δ) in ACT scores before and after controller treatment was defined as [(value after treatment–value before treatment)/value before treatment] × 100].

*Significance were derived using ANCOVA among the four BMI groups adjusted for age, sex, smoking status, and medication history.

BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

[¶], significantly different compared to underweight by post-hoc analysis; [†], significantly different compared to normal weight by post-hoc analysis; [‡], significantly different compared to overweight by post-hoc analysis.

status, and medication history. In general, the asthma control status was improved after controller treatment. The prevalences of the partly and uncontrolled statuses in the obese group tended to be higher than those in other BMI groups ($P > 0.05$). The obese group had a significantly lower ΔACT (%) value than the overweight group ($P < 0.05$). The FEV₁ and FVC tended to be lower in the underweight patients than the normal weight, overweight, and obese patients; however, the FEV₁/FVC tended to be higher in the underweight patients than those in the other three groups.

Association between obesity and lung function changes before and after asthma treatment

After 3 months of asthma controller treatment, patients showed FEV₁, FVC and FEV₁/FVC improvements. In general, the ΔFEV₁, ΔFVC and ΔFEV₁/FVC

values showed the most improvements in the underweight group (Table 2). Although the ΔFEV₁ and ΔFVC values did not show any significant differences across the BMI groups, there was a significant negative correlation between BMI and ΔFEV₁/FVC ($P = 0.013$). In the *post hoc* analysis, the obese group showed lower ΔFEV₁/FVC ($6.0 \pm 13.5\%$) values than the underweight ($12.6 \pm 21.4\%$, $P = 0.044$) and normal weight ($9.1 \pm 14.6\%$, $P = 0.031$) groups, after adjustment for age, sex, smoking status, and medication history (Table 2 and Figure 1).

Association between BMI and asthma before and after asthma treatment by sex

Table 3 presents the association between BMI and percentage changes in pulmonary function test after controller treatment for 3 months according to sex. Female asthma patients showed significant positive

Table 2. Percent change of pulmonary function test after controller treatment for 3 months.

Characteristic	Underweight (BMI < 18.5)	Normal (BMI, 18.5–22.9)	Overweight (BMI, 23.0–24.9)	Obese (BMI ≥ 25.0)	P value
FEV ₁ , % pred	72.8 ± 21.0	76.5 ± 21.4	78.0 ± 21.5	77.6 ± 19.6	0.016
FVC, % pred	81.3 ± 16.7	88.5 ± 18.7 [¶]	88.5 ± 18.4 [¶]	84.4 ± 18.1	0.008
FEV ₁ /FVC (%)	73.4 ± 16.2	70.1 ± 12.4	70.8 ± 17.0	71.3 ± 10.6 [†]	0.008
F/U_FEV ₁ , % pred	83.2 ± 18.7	85.5 ± 18.2	86.4 ± 18.3	84.3 ± 17.4	0.154
F/U_FVC, % pred	85.3 ± 14.9	91.9 ± 16.0 [¶]	92.0 ± 15.7 [¶]	98.3 ± 15.9 [‡]	0.001
F/U_FEV ₁ /FVC, %	80.5 ± 12.7	76.2 ± 12.3	74.1 ± 10.0	74.8 ± 9.8	0.089
Δ FEV ₁ , % pred	22.4 ± 46.2	17.8 ± 36.5	16.9 ± 38.4	13.3 ± 31.3	0.106
Δ FVC, % pred	7.4 ± 20.6	6.8 ± 22.9	7.0 ± 27.1	6.1 ± 22.5	0.624
Δ FEV ₁ /FVC, %	12.6 ± 21.4	9.1 ± 14.6	7.2 ± 17.3	6.0 ± 13.5 ^{¶, †}	0.013

Values are presented as mean ± standard deviation. F/U pulmonary function meant values after three month of asthma controller therapy. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Significance were derived using ANCOVA among the four BMI groups adjusted for age, sex, smoking status, and medication history.

¶, significantly different compared to underweight by post-hoc analysis; †, significantly different compared to normal weight by post-hoc analysis; ‡, significantly different compared to overweight by post-hoc analysis.

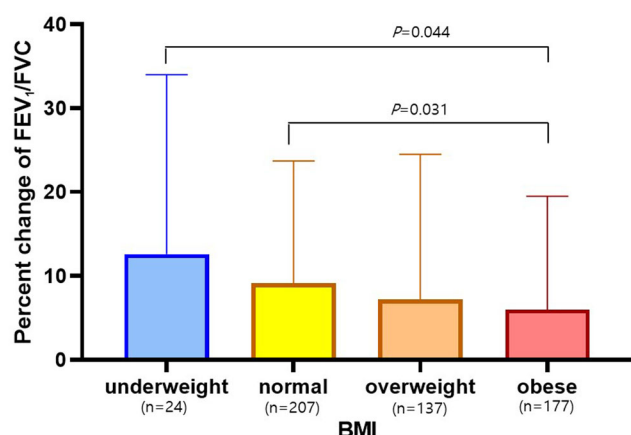


Figure 1. Percentage changes (Δ) of FEV₁/FVC according to body mass index (BMI) after three months of asthma controller medication use. ΔFEV₁/FVC was calculated as 100 × [(value after treatment–value before treatment)/value before treatment].

correlations between mean age and BMI ($P < 0.001$), and between asthma onset age and BMI ($P < 0.001$), while male asthma patients did not show any such significant correlations. The prevalences of the initial and F/U asthma control statuses were not significantly different among BMI groups in both sexes. Obese female group tended to have a lower ΔACT (%) value than the overweight female group with borderline significance ($P = 0.057$). In the women, the ΔFEV₁ and ΔFEV₁/FVC significantly decreased with increasing BMI ($P = 0.024$ and $P = 0.002$, respectively), after adjustment for age, smoking status, and medication history. Obese women with asthma showed lower ΔFEV₁/FVC ($4.1 \pm 11.2\%$) values than their underweight ($14.0 \pm 23.7\%$, $P = 0.005$) and normal weight ($8.4 \pm 12.0\%$, $P = 0.022$) counterparts, after adjustment for age, smoking status, and medication history. However, the men did not show significantly different associations between BMI and pulmonary function changes after treatment.

Association between BMI and asthma before and after asthma treatment by sex and age

The association between BMI and asthma according to sex and age is presented in Table 4. In the women, the BMI and asthma onset age significantly increased according to age ($P < 0.001$, respectively). The frequency of atopic patients ($P < 0.001$), serum total IgE level ($P = 0.033$), and blood eosinophil count ($P = 0.002$) significantly decreased according to age ($P < 0.05$, respectively). There were no significant differences in the asthma exacerbation frequency, PC₂₀ value, asthma control status (initial and follow-up), ΔACT (%) value, and medication history across the age groups.

In the men, there were no significant differences in the BMI across the age groups ($P > 0.05$). The asthma onset age significantly increased according to age ($P < 0.001$). The prevalence of atopy ($P < 0.001$) and blood eosinophil count ($P < 0.001$) significantly decreased according to age ($P < 0.001$). There were significant differences in the prevalence of smokers ($P < 0.001$), asthma control status (follow-up, $P = 0.023$), and number of asthma exacerbation events ($P = 0.018$). However, there were no significant differences in the PC₂₀ value, and medication history across the age groups.

Elderly asthma patients (aged ≥ 65 yrs) showed a lower ΔACT (%) value than the young group (aged < 45 yrs) in females with borderline significance ($P = 0.055$), and significantly lower prevalence of ‘well controlled’ status than the middle-aged group (aged 45 to 65 yrs) after 3-month asthma treatment in males ($P = 0.015$). In addition, Elderly asthma patients showed significantly weaker lung function both before and after asthma treatment than those in the middle-aged and younger groups, in both sexes. The ΔFEV₁/FVC in the middle-aged (5.7 ± 11.9) and elderly (6.7 ± 14.6) female groups was significantly lower than

Table 3. Association between BMI and percent change of pulmonary function test after controller treatment for 3 months according to sex.

	Female				P value	Male				P value
	Underweight (BMI < 18.5)	Normal (BMI, 18.5–22.9)	Overweight (BMI, 23.0–24.9)	Obese (BMI ≥ 25.0)		Underweight (BMI < 18.5)	Normal (BMI, 18.5–22.9)	Overweight (BMI, 23.0–24.9)	Obese (BMI ≥ 25.0)	
No. of subjects	24	207	137	177		7	110	107	168	
Mean age (yr)	41.4 ± 15.6	47.0 ± 14.1	52.8 ± 13.3 ^{§,†}	59.0 ± 13.2 ^{§,†,‡}	<0.001	51.0 ± 17.9	50.9 ± 17.0	53.3 ± 15.5	50.9 ± 16.3	0.716
Onset age (yr)	36.2 ± 18.4	44.1 ± 15.0	49.3 ± 14.8 ^{§,†}	56.1 ± 14.2 ^{§,†,‡}	<0.001	49.4 ± 16.9	47.5 ± 18.1	50.1 ± 16.5	47.9 ± 17.9	0.779
Smoke					0.671					0.083
Never	21 (87.5)	161 (78.5)	107 (78.7)	143 (82.2)		1 (14.3)	19 (17.3)	19 (17.9)	41 (24.7)	
Former	2 (8.3)	34 (16.6)	21 (15.4)	27 (15.5)		1 (14.3)	64 (58.2)	63 (59.4)	91 (54.8)	
Current	1 (4.2)	10 (4.9)	8 (5.9)	4 (2.3)		5 (71.4)	27 (24.5)	24 (22.6)	34 (20.5)	
Atopy (%)	7 (29.2)	62 (30.5)	35 (26.1)	29 (16.6)	0.016	3 (42.9)	41 (37.3)	32 (30.2)	53 (32.3)	0.638
Serum total IgE (IU/mL)	196.5 ± 189.8	204.0 ± 224.7	140.1 ± 166.1	180.4 ± 210.7	0.535	305.9 ± 220.8	309.1 ± 249.0	250.2 ± 229.2	249.4 ± 223.6	0.530
Blood eosinophil count (/mm ³)	356.0 ± 350.6	332.8 ± 267.0	357.2 ± 369.6	285.1 ± 242.3	0.445	315.9 ± 150.1	350.0 ± 257.7	337.0 ± 254.0	312.7 ± 221.8	0.858
PC ₂₀ (mg/mL)	5.8 ± 5.2	5.4 ± 5.0	4.8 ± 4.5	5.4 ± 4.4	0.775	3.5 ± 3.6	4.1 ± 3.8	4.9 ± 5.4	5.5 ± 5.3	0.624
Asthma control status (initial)										
Well controlled, n (%)	2 (25.0)	19 (38.0)	9 (30.0)	20 (43.5)	0.634	1 (33.3)	6 (26.1)	9 (42.9)	21 (43.8)	0.76
Partly controlled, n (%)	5 (62.5)	17 (34.0)	11 (36.7)	17 (37.0)		1 (33.3)	7 (30.4)	6 (28.6)	15 (31.3)	
Uncontrolled, n (%)	1 (12.5)	14 (28.0)	10 (33.3)	9 (19.6)		1 (33.3)	10 (43.5)	6 (28.6)	12 (25.0)	
Asthma control status (F/U)										
Well controlled, n (%)	20 (87.0)	149 (83.2)	89 (83.2)	106 (74.6)	0.384	6 (100.0)	73 (91.3)	80 (92.0)	120 (90.2)	0.981
Partly controlled, n (%)	3 (13.0)	28 (15.6)	18 (16.8)	33 (23.2)		0 (0.0)	7 (8.8)	7 (8.0)	13 (9.8)	
Uncontrolled, n (%)	0 (0.0)	2 (1.1)	0 (0.0)	3 (2.1)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
ΔACT (%)	21.7 ± 13.7	20.1 ± 27.5	32.7 ± 28.9	19.1 ± 25.8	0.199	43.3 ± 33.9	34.2 ± 30.2	28.5 ± 30.0	19.5 ± 26.3	0.179
Asthma exacerbation	0.1 ± 0.4	0.3 ± 1.2	0.5 ± 1.9	0.4 ± 1.2	0.686	0.0 ± 0.0	0.4 ± 0.9	0.3 ± 0.8	0.2 ± 0.5	0.113
Medication										
Low dose ICS	1 (4.2)	4 (1.9)	2 (1.5)	2 (1.1)	0.524	0 (0.0)	1 (0.01)	1 (0.01)	2 (0.01)	1.000
Low dose ICS + LABA	5 (20.8)	55 (26.6)	21 (15.3)	36 (20.3)	0.094	3 (42.9)	21 (19.1)	21 (19.6)	34 (20.2)	0.493
Medium high dose ICS + LABA	12 (50.0)	81 (39.1)	60 (43.8)	78 (44.1)	0.618	1 (14.3)	52 (47.3)	50 (46.7)	77 (45.8)	0.433
LTRA	12 (50.0)	108 (52.2)	71 (51.8)	96 (54.2)	0.960	3 (42.9)	54 (49.1)	52 (48.6)	93 (55.4)	0.598
FEV ₁ , % pred	74.1 ± 22.0	78.7 ± 20.5	80.9 ± 20.7	79.7 ± 18.5	0.138	68.5 ± 18.2	72.5 ± 22.5	74.2 ± 22.1	75.2 ± 20.6	0.660
FVC, % pred	81.9 ± 17.6	88.9 ± 17.8	91.4 ± 17.6 [§]	85.2 ± 17.9	0.006	79.3 ± 14.3	87.7 ± 20.4	84.8 ± 18.8	83.5 ± 18.4	0.176
FEV ₁ /FVC, %	74.4 ± 15.4	73.4 ± 10.9	72.0 ± 11.4	73.0 ± 9.1	0.045	69.6 ± 19.5	65.4 ± 13.3	69.3 ± 22.2	69.5 ± 11.8	0.090
F/U FEV ₁ , % pred	86.8 ± 15.8	87.4 ± 17.6	88.8 ± 18.1	85.2 ± 16.9	0.625	70.9 ± 23.6	81.9 ± 19.0	83.3 ± 18.3	83.3 ± 17.9	0.285
F/U FVC, % pred	88.4 ± 14.1	92.5 ± 15.2	93.7 ± 15.3	87.7 ± 16.4 [‡]	0.028	74.9 ± 13.3	90.8 ± 17.4	89.8 ± 16.0 [§]	86.9 ± 15.4 [§]	0.005
F/U FEV ₁ /FVC, %	82.2 ± 9.9	78.9 ± 10.2	75.9 ± 9.4	75.5 ± 8.9	0.268	74.6 ± 19.4	71.1 ± 14.3	71.8 ± 10.2	74.0 ± 10.7	0.192
Δ FEV ₁ , % pred	27.6 ± 50.1	15.9 ± 32.3	14.0 ± 29.2	9.7 ± 22.8 [§]	0.024	4.2 ± 23.8	21.4 ± 43.2	20.7 ± 47.5	17.0 ± 38.0	0.738
Δ FVC, % pred	10.5 ± 19.6	6.4 ± 20.5	4.3 ± 17.0	4.8 ± 19.6	0.224	−3.1 ± 21.8	7.6 ± 26.8	10.5 ± 36.0	7.4 ± 25.2	0.736
Δ FEV ₁ /FVC, %	14.0 ± 23.7	8.4 ± 12.0	6.9 ± 14.8	4.1 ± 11.2 [†]	0.002	7.7 ± 9.9	10.5 ± 18.5	7.6 ± 20.1	8.0 ± 15.4	0.663

Values are presented as mean ± standard deviation. Asthma control status was evaluated base on ACT score; well controlled for ACT 20–25, partially controlled for ACT 15–19, and uncontrolled for ACT 5–14. The percentage change (Δ) in ACT scores before and after controller treatment was defined as [(value after treatment) − (value before treatment)] / (value before treatment) × 100. F/U pulmonary function mean values after three month of asthma controller therapy. BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Significance were derived using ANCOVA among the four BMI groups adjusted for age, smoking status, and medication history.

[†], significantly different compared to underweight by post-hoc analysis; [‡], significantly different compared to normal weight by post-hoc analysis; [§], significantly different compared to overweight by post-hoc analysis.

Table 4. Association between BMI and percent change of pulmonary function test after controller treatment for 3 months according to sex and age.

	Female				Male			
	< 45yrs	45 – 65 yrs	≥ 65yrs	P-value	< 45yrs	45 – 65 yrs	≥ 65yrs	P-value
No. of subjects	161	256	128		120	170	102	
BMI	22.4 ± 3.5	24.1 ± 3.6 [¶]	25.4 ± 3.3 ^{¶,†}	<0.001	24.8 ± 3.8	24.6 ± 2.8	24.5 ± 3.1	0.867
Onset age (yr)	30.8 ± 9.2	50.8 ± 8.1 [¶]	68.0 ± 7.4 ^{¶,†}	<0.001	27.6 ± 10.6	51.5 ± 8.5 [¶]	67.7 ± 6.1 ^{¶,†}	<0.001
Smoke				0.019				<0.001
Never	122 (76.3)	207 (82.1)	103 (81.1)		41 (34.2)	22 (13.1)	17 (16.8)	
Former	24 (15.00)	38 (15.1)	22 (17.3)		42 (35.0)	110 (65.5)	67 (66.3)	
Current	14 (8.8)	7 (2.8)	2 (1.6)		37 (30.8)	36 (21.4)	17 (16.8)	
Atopy (%)	73 (46.5)	53 (20.87)	9 (5.6)	<0.001	68 (58.1)	55 (32.7)	6 (5.9)	<0.001
Serum total IgE (IU/mL)	200.5 ± 186.8	175.5 ± 205.7	152.1 ± 212.2	0.033	265.6 ± 247.3	300.6 ± 223.1	215.4 ± 223.1	0.061
Blood eosinophil count (/mm ³)	389.8 ± 348.7	314.0 ± 257.4 [¶]	269.9 ± 284.1 [¶]	0.002	407.5 ± 260.1	310.8 ± 228.5 [¶]	266.8 ± 208.1 [¶]	<0.001
PC ₂₀ (mg/mL)	4.7 ± 4.6	5.3 ± 4.8	6.2 ± 4.6	0.058	4.6 ± 4.4	5.0 ± 4.8	5.0 ± 5.7	0.855
Asthma control status (Initial)								
Well controlled, n (%)	13 (27.7)	22 (36.1)	15 (57.7)	0.18	12 (32.4)	14 (40)	11 (47.8)	0.54
Partly controlled, n (%)	20 (42.6)	23 (37.7)	7 (26.9)		15 (40.5)	9 (25.7)	5 (21.7)	
Uncontrolled, n (%)	14 (29.8)	16 (26.2)	4 (15.4)		10 (27)	12 (34.3)	7 (30.4)	
Asthma control status (F/U)								
Well controlled, n (%)	112 (81.8)	173 (83.6)	79 (73.8)	0.247	80 (88.9)	134 (95.7)	65 (85.5) [†]	0.023
Partly controlled, n (%)	23 (16.8)	32 (15.5)	27 (25.2)		10 (11.1)	6 (4.3)	11 (14.5)	
Uncontrolled, n (%)	2 (1.5)	2 (1.0)	1 (0.9)		0 (0.0)	0 (0.0)	0 (0.0)	
ΔACT (%)	24.5 ± 21.1	24.7 ± 29.5	14.2 ± 29.8	0.149	29.8 ± 25.0	23.4 ± 28.7	23.5 ± 33.9	0.404
Asthma exacerbation Medication	0.5 ± 1.6	0.3 ± 1.2	0.3 ± 1.4	0.055	0.4 ± 1.0	0.2 ± 0.5	0.2 ± 0.7	0.018
Low dose ICS	5 (3.1)	3 (1.2)	1 (0.8)	0.284	2 (1.7)	1 (0.6)	1 (1.0)	0.819
Low dose ICS + LABA	37 (23.0)	50 (19.5)	30 (23.4)	0.582	26 (21.7)	36 (21.2)	17 (16.7)	0.591
Medium high dose ICS + LABA	64 (39.8)	112 (43.8)	55 (43.0)	0.715	46 (38.3)	81 (47.7)	53 (52.0)	0.106
LTRA	75 (46.6)	148 (57.8)	64 (50.0)	0.065	63 (52.5)	79 (46.5)	60 (58.8)	0.138
FEV ₁ , % pred	81.4 ± 17.3	78.7 ± 20.3	78.2 ± 22.5	0.351	83.2 ± 16.2	72.7 ± 21.4 [¶]	65.7 ± 23.2 ^{¶,†}	<0.001
FVC, % pred	91.0 ± 15.5	88.5 ± 18.1	83.4 ± 19.5 ^{¶,†}	0.001	93.9 ± 16.1	84.8 ± 18.3 [¶]	74.7 ± 18.5 ^{¶,†}	<0.001
FEV ₁ /FVC, %	77.3 ± 10.7	72.3 ± 9.9 [¶]	68.9 ± 10.4 ^{¶,†}	<0.001	75.2 ± 9.5	67.3 ± 18.7 [¶]	61.6 ± 13.4 ^{¶,†}	<0.001
F/U_FEV ₁ , % pred	90.3 ± 13.7	86.1 ± 18.5	84.6 ± 18.9 [¶]	0.023	90.41 ± 13.76	82.8 ± 17.2 [¶]	73.4 ± 21.0 ^{¶,†}	<0.001
F/U_FVC, % pred	93.1 ± 12.2	92.1 ± 16.5	86.5 ± 17.3 ^{¶,†}	0.001	95.47 ± 15.00	88.6 ± 15.7 [¶]	80.5 ± 15.0 ^{¶,†}	<0.001
F/U_FEV ₁ /FVC, %	83.3 ± 9.3	75.7 ± 8.7 [¶]	72.5 ± 8.5 ^{¶,†}	<0.001	80.2 ± 8.5	72.4 ± 10.8 [¶]	64.0 ± 11.3 ^{¶,†}	<0.001
Δ FEV ₁ , % pred	15.6 ± 34.6	13.2 ± 27.1	13.1 ± 29.4	0.265	13.09 ± 33.94	22.6 ± 44.5	20.1 ± 45.9	0.286
Δ FVC, % pred	4.5 ± 19.6	5.8 ± 18.1	6.2 ± 21.5	0.358	2.97 ± 15.50	8.3 ± 26.8	13.8 ± 41.1	0.063
Δ FEV ₁ /FVC, %	8.9 ± 14.3	5.7 ± 11.9 [¶]	6.7 ± 14.6 [¶]	0.025	7.80 ± 15.39	10.8 ± 19.7	5.8 ± 15.8	0.143

Values are presented as mean ± standard deviation or number (%). Asthma control status was evaluated base on ACT score; well controlled for ACT 20–25, partially controlled for ACT 15–19, and uncontrolled for ACT 5–14. The percentage change (Δ) in ACT scores before and after controller treatment was defined as [(value after treatment – value before treatment)/value before treatment] × 100. F/U meant values after three month of asthma controller therapy.

Significance were derived using ANCOVA among the four BMI groups adjusted for smoking status, and medication history.

[¶]Significantly different compared to younger than 45 years by post-hoc analysis; [†], significantly different compared to 45–60 years by post-hoc analysis.

that in the younger female group (8.9 ± 14.3, $P < 0.025$), while the ΔFEV₁/FVC did not significantly differ across the male age groups.

Discussion

In the present study, there was no consistently significant association between BMI and each lung function parameter. However, we found significant negative correlations between BMI and percentage changes in the FEV₁, FVC, and FEV₁/FVC before and after 3 months of controller treatment. Interestingly, only female asthma patients showed significant negative associations between BMI and lung function changes before and after asthma treatment. This association was more prominent among female patients aged over 45 years. The men did not show any significant relationship between BMI and lung function changes after controller treatment.

A recent meta-analysis reported that all the measures of lung function (FEV₁, FVC, total lung capacity, and residual volume) are reduced in obese adults (13). Several studies have reported that obese patients have reduced FEV₁ and FVC values, due to interference of the increased abdominal and thoracic adipose tissue with the ideal expansion of the lungs (24,25). However, other studies have presented conflicting results, with some demonstrating that the effect of obesity on lung function was insignificant and even undetectable (26,27). The present study also found no significant association between BMI and lung function parameters: the FEV₁ and FVC were higher in the normal weight and overweight groups; the FEV₁/FVC was higher in the underweight group. Reports stating that airway hyper-reactivity (AHR) is associated with obesity are also controversial (28). One prospective study including more than 7,000 adults reported a positive association between obesity and AHR (29).

However, another study of 1,900 white adults found that while obesity and AHR were not correlated, the AHR was higher in the underweight group (30). In the present study, the AHR, as measured using PC₂₀ values from the methacholine challenge test, did not show any significant correlation with BMI.

Resistance to asthma therapy has been reported in obese asthma patients (31–33). In previous studies, weakened therapeutic response was assessed by monitoring the use of rescue medication in asthma exacerbation events or analyzing the characteristics of the severe refractory asthma phenotype (31,33). In addition, several studies have reported that bariatric (weight loss) surgery had a significant effect on asthma exacerbation events, by analyzing the frequency of emergency room visits following asthma deterioration (34,35). In the present study, the effect of obesity on response to asthma treatment was investigated using percentage changes in lung function before and after controller therapy. As a result, statistically significant reductions in the lung function changes were noted in obese or overweight asthma patients, which was partly consistent with the lowest Δ ACT (%) value in obese asthma patients.

There are several mechanisms behind the diminished response to asthma treatment in obese patients. Obesity is thought to render a pro-inflammatory state through an increase in the adipose tissue immune function degree via immune mediators, including tumor necrosis factor- α , interleukin-6, leptin, and adiponectin, which may activate the upregulation of pulmonary inflammatory processes (36,37). Leptin can also promote angiogenesis and airway remodeling via the vascular endothelial growth factor (38). Obesity may also be associated with changes in airway geometry, leading to a lower peripheral lung distribution and reduced responsiveness to ICS (39). Furthermore, commonly observed comorbidities such as sleep apnea or gastroesophageal reflux are associated with reduced asthma control in obese patients (25). Obesity is also one of the common comorbidities of asthma (40). Asthma patients with high BMI had poorer quality of life, which have an impact on poor asthma control.

Several studies have reported that only women show a significant association between asthma and obesity (14,41,42). One cluster analysis in Indian asthmatics have reported contradictory results in that obese male asthmatics tended to have poor attainment of maximum lung functions after at least 6-months treatment, while obese female asthmatics achieved normal lung function (43). However, the study population was only 100 patients. The 2012 National

Health Interview Survey in the USA revealed a higher incidence of asthma in people with obesity than those without, and the asthma incidence in women with extremely high BMI values was also more prominent than in men (14). Several reports have stated that asthma is more difficult to control in women than men, although the therapeutic strategies used do not differ (44,45). Our study showed a statistically significant association between obesity and decreased lung function changes before and after asthma treatment, but only in the women, not in the men. There is no clear explanation for this, but one hypothesis is that women have a higher percentage of body fat than men at any BMI range (46). Furthermore, the levels of leptin, an important factor associated with obesity and asthma, are higher in women than men with an equivalent BMI (47,48). Premenopausal women synthesize estrogens chiefly from the ovaries, while postmenopausal women synthesize them from adipose tissue (49). Postmenopausal women also have significantly increased levels of estrone, estradiol and free estradiol, which are all associated with increased BMI values (50,51). In the present study, we found that middle-aged menopausal female asthma patients had a higher BMI than those aged under 45 years and showed the least lung function changes following asthma controller therapy. Obesity lowers progesterone levels, while progesterone upregulates the number of β_2 -receptors (52). Therefore, decreased progesterone levels reduce the degree of β_2 -receptor function, leading to decreased bronchial smooth muscle relaxation reactivity (53). However, it is difficult to establish the phenotype of asthma because it contains a diverse population of patients. Further investigation is needed to determine the effects of menopause-related sex hormones and weight changes on asthma in women.

The present study has several limitations. First, while it is a prospective multicenter cohort study with voluntarily participating hospitals, the possibility of selection bias cannot be excluded. The study population enrolled newly diagnosed asthma patients from the COREA cohort without artificial interventions during enrollment and follow-up. The resulting significant loss of patients during follow-up and the female preponderance of study participants can indicate a selection bias. Second, the tri-monthly period for the assessment of pulmonary function changes may be insufficient for the evaluation of long-term asthma control. Third, we adopted the WHO classification for the Asia-Pacific population as definition of BMI categories, where cutoff of BMI for obesity is lower than western countries. In this reason, our

study results might have limitation for generalization worldwide. Forth, the BMI may not be a good indicator of body fat composition in comparison to the waist-hip ratio. In the present study, the lung function changes according to BMI were significantly lower in women, suggesting that women have a higher body fat composition compared to men in the same BMI group, resulting in increased obesity-related inflammation and poor asthma control. Further studies will be needed to elucidate the association between lung function changes and waist-hip ratio in asthmatics.

Despite these limitations, the present study was a nation-wide cohort study based on accurate asthma diagnoses. In addition, previous studies analyzed asthma control as an indirect method of analyzing emergency room visits or systemic steroid prescription frequency. However, this study analyzed asthma control through its evaluation as an objective indicator of lung function change.

Conclusion

The study results revealed that higher BMI values were associated with decreased percentage changes in lung function after 3 months of asthma treatment, especially in female asthmatics. Middle-aged female asthma patients had higher BMI values, which are important risk factors associated with decreased percentage changes in lung function. These findings suggest that higher BMI values are associated with a decreased therapeutic response to asthma medications in women, indicating a differential contribution of sex and age. Accordingly, physicians should consider this in the treatment of obese or overweight asthma patients.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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