

Body mass index and phenotype in subjects with mild-to-moderate persistent asthma

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Background: Although obesity has been hypothesized to worsen asthma, data from studies of subjects with well-characterized asthma are lacking.

Objective: We sought to evaluate the relationship between body mass index (BMI), asthma impairment, and response to therapy. **Methods:** BMI (in kilograms per meter squared) and asthma phenotypic and treatment response data were extracted from Asthma Clinical Research Network studies. The cross-sectional relationship between BMI and asthma impairment was analyzed, as was the longitudinal relationship between BMI and response to asthma controller therapies.

Results: One thousand two hundred sixty-five subjects with mild-to-moderate persistent asthma were evaluated. Analyses of lean versus overweight/obese asthmatic subjects demonstrated small differences in FEV₁ (3.05 vs 2.91 L, $P = .001$), FEV₁/forced vital capacity ratio (mean, 83.5% vs 82.4%; $P = .01$), rescue albuterol use (1.1 vs 1.2 puffs per day, $P = .03$), and asthma-related quality of life (5.77 vs 5.59, $P = .0004$).

Overweight/obese asthmatic subjects demonstrated a smaller improvement in exhaled nitric oxide levels with inhaled corticosteroid (ICS) treatment than did lean asthmatic subjects (3.6 vs 6.5 ppb, $P = .04$). With ICS/long-acting β -agonist treatment, overweight/obese asthmatic subjects demonstrated smaller improvements in lung function than lean asthmatic subjects, with an 80 mL ($P = .04$) and 1.7% ($P = .02$) lesser

improvement in FEV₁ and FEV₁/forced vital capacity ratio, respectively. Significant differences in therapeutic response to leukotriene modifiers between BMI categories were not observed.

Conclusions: Increased BMI is not associated with clinically significant worsening of impairment in subjects with mild-to-moderate persistent asthma. There is a modest association between increased BMI and reduced therapeutic effect of ICS-containing regimens in this patient population. Prospective studies evaluating the effect of being overweight or obese on treatment response in asthma are warranted. (J Allergy Clin Immunol 2009;123:1328-34.)

Key words: Asthma, obesity, treatment, severity

Obesity and asthma are prevalent diseases, each with a significant public health effect. Concurrent increases in the prevalence of these disorders, along with emerging data on potential overlapping pathobiologic mechanisms, have suggested a link between them.¹ Although the exact nature of this association remains unclear, a number of relevant observations have recently emerged: (1) that being overweight (defined as a body mass index [BMI; in kilograms per meter squared] of between 25 and 29.9) or obese (BMI ≥ 30) increases the risk of incident asthma,²⁻⁶ (2) that being overweight or obese predisposes to a more severe or difficult-to-control asthma phenotype,⁷ (3) that being overweight or obese alters response to asthma controller therapy,⁸⁻¹⁰ and (4) that weight loss in obese asthmatic subjects can result in clinical and physiologic improvement.^{11,12}

Notwithstanding these observations, the precise mechanisms by which overweight and obesity interact with asthma remain unclear.¹³ Although it is possible that being overweight and obese might modify the risk for or severity of asthma by increasing airway or systemic inflammation^{14,15} or by leading directly to physiologic impairment (eg, airway hyperresponsiveness) through reduction of airway caliber,^{16,17} emerging data suggest that the effects of obesity on individuals with asthma might not be mediated solely by alterations in the inflammatory¹⁸ or physiologic phenotype but also by modification of pathways governing response to controller therapies.⁸⁻¹⁰ Much of the research evaluating the relationship between obesity and asthma has been conducted at the population level, relying on self-reported diagnosis of the two disorders as the principal method of case ascertainment.¹⁹ Although these epidemiologic approaches facilitate the assessment of a large number of subjects and have led to important observations, such as those cited above, the ability of studies of this nature to carefully assess phenotype with regard to both obesity and asthma is limited. In contrast, particularly with regard to detailed phenotypic characterization of asthma, cohorts of asthmatic subjects enrolled in prospective clinical trials provide an opportunity for more robust cross-sectional and longitudinal assessment of the

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*A list of participating Asthma Clinical Research Network investigators is available in Appendix E1 in this article's Online Repository at www.jacionline.org.

Supported by National Institutes of Health grants (U10) HL51831, HL51845, HL51823, HL51843, HL56443, HL51834, HL51810, HL74227, HL74231, HL074204, HL74212, HL74073, HL074206, HL074208, HL74225, and HL74218.

Disclosure of potential conflict of interest: E. R. Sutherland is on advisory boards for GlaxoSmithKline, and Dey; is a Data and Safety Monitoring Board member for Schering-Plough; and received grant support from the National Institutes of Health, Novartis and Dey. M. Teodorescu received grant support from the University of Wisconsin School of Medicine and Public Health. M. E. Wechsler is a consultant for AstraZeneca, Schering-Plough, Novartis, GlaxoSmithKline, Merck, and Genentech; is on the advisory board for AstraZeneca, Schering-Plough, Novartis, GlaxoSmithKline, Merck, and Genentech; is on the speakers' bureau for AstraZeneca, Novartis, GlaxoSmithKline, Merck, and Genentech; and receives grant support from Astmatx, GlaxoSmithKline, and the National Institutes of Health. The rest of the authors have declared that they have no conflict of interest.

Received for publication February 9, 2009; revised March 19, 2009; accepted for publication April 1, 2009.

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doi:10.1016/j.jaci.2009.04.005

Abbreviations used

ACRN:	Asthma Clinical Research Network
BAGS:	The Addition of Regular-use to Intermittent Rescue β -Agonist for Patients with Mild Asthma
BARGE:	β -Agonist Response by Genotype
BMI:	Body mass index
DICE:	Dose of Inhaled Corticosteroids with Equisystemic Effects
FENO:	Fraction of exhaled nitric oxide
FEV ₁ :	Forced expiratory volume in one second
FVC:	Forced vital capacity
ICS:	Inhaled corticosteroid
IMPACT:	Improving Asthma Control Trial
LABA:	Long-acting β -agonist
MICE:	Measuring Inhaled Corticosteroid Efficacy
PRICE:	Predicting Responses for Inhaled Corticosteroid Efficacy
SLIC:	Salmeterol with and without Inhaled Corticosteroids
SLIMSIT:	Salmeterol and Leukotriene Modifiers Versus Salmeterol and ICS Treatment
SMOG:	Smoking Modulates Outcomes of Glucocorticoid Therapy in Asthma
SOCS:	Salmeterol off Corticosteroids

obesity-asthma relationship than can be conducted in epidemiologic studies.

Taking advantage of data from carefully phenotyped²⁰ subjects enrolled in prospective clinical trials of the National Heart, Lung, and Blood Institute–funded Asthma Clinical Research Network (ACRN),²¹ we evaluated the association between increased BMI and phenotypic characteristics of asthma,²² hypothesizing that (1) indices of asthma-related impairment (eg, symptoms, quality of life, airway inflammation, and physiologic limitation) would be unfavorably affected in individuals who were overweight or obese and (2) that being overweight or obese would be associated with a blunted response to asthma controller therapy, as defined by outcomes including change in lung function and asthma control.

METHODS

Data were derived from the following randomized, controlled trials of the ACRN (aggregated www.clinicaltrials.gov registration NCT00000577): The Addition of Regular-use to Intermittent Rescue β -Agonist for Patients with Mild Asthma (BAGS) trial,²³ the β -Agonist Response by Genotype (BARGE) trial,²⁴ the Dose of Inhaled Corticosteroids with Equisystemic Effects (DICE) trial,²⁵ the Improving Asthma Control Trial (IMPACT),²⁶ the Measuring Inhaled Corticosteroid Efficacy (MICE) trial,²⁷ the Predicting Responses for Inhaled Corticosteroid Efficacy (PRICE) trial,²⁸ the Salmeterol with and without Inhaled Corticosteroids (SLIC) trial,²⁹ the Salmeterol and Leukotriene Modifiers Versus Salmeterol and ICS Treatment (SLIMSIT) trial,³⁰ the Smoking Modulates Outcomes of Glucocorticoid Therapy in Asthma (SMOG) trial,³¹ and the Salmeterol off Corticosteroids (SOCS) trial.³² Aspects of the design and results of these studies have been reviewed previously.²¹ All studies were institutional review board approved at participating ACRN centers, and all subjects provided written informed consent.

All analyses were performed with SAS 9.1.3 software (SAS, Institute Inc, Cary, NC). If subjects participated in more than 1 study, only the most recent study data were used. Descriptive statistics were used to summarize baseline characteristics (eg, FEV₁, methacholine PC₂₀, and exhaled nitric oxide) of randomized study subjects, with baseline values defined at the visit closest to randomization. For outcomes measured with a daily diary (eg, peak flow rate and rescue β -agonist use), baseline was defined as the average value over the 2 weeks before randomization.

Baseline phenotypic data (adjusted for age, sex, and race) were analyzed, with BMI treated as both a categorical (lean [BMI <25] vs overweight/obese [BMI $\geq$ 25]) and a continuous variable. Categorical comparisons of lean versus obese subjects were also performed with baseline data to evaluate the possibility that inclusion of overweight subjects (BMI, 25–29.9) might dilute important differences between lean and obese (BMI $\geq$ 30) subjects; these comparisons were not performed with treatment-response data because of limitations of sample size. Categorical comparisons used a linear mixed model to test the relationship between BMI and normally distributed continuous variables or log-transformed nonnormally distributed continuous variables. Linear regression was used to determine the fold change (β) in the variable per unit increase in BMI to assess the association between phenotypic variables and incremental increases in continuous BMI.

The relationship between BMI category and response to therapy (defined as change in variable between baseline and end of treatment) was evaluated, with the following treatment allocations assessed: (1) placebo, (2) inhaled corticosteroid [ICS] monotherapy regimens, (3) ICS/long-acting β -agonist (LABA) combination regimens, and (4) leukotriene modifier monotherapy regimens. A linear mixed model was used to test change in outcome variables from baseline to the end of treatment between the BMI categories. Additionally, the relationship between BMI category and the risk of an asthma exacerbation was assessed by using Kaplan-Meier survival analysis adjusted for study. Significant asthma exacerbations or treatment failures were defined *a priori* in ACRN studies as either (1) the use of oral, parenteral, or increased ICSs for asthma; (2) the occurrence of a significant asthma exacerbation associated with decreased lung function or increased asthma rescue medication use; (3) emergency treatment or hospitalization for an acute asthma exacerbation; or (4) asthma exacerbation based on physician assessment. The time to exacerbation (in days) was calculated from the start date of randomized study treatment to the start of the treatment failure. If no exacerbation occurred, the time to censoring was calculated from the start to the end of treatment; when choosing between multiple exacerbations for a subject, the shortest time was used.

All analyses were adjusted for study to account for between-study differences in treatment and evaluation; analyses were also adjusted for age, sex, and race/ethnicity. Sensitivity analyses in subjects with a baseline FEV₁ of less than 80% were performed to determine whether associations with BMI were greater in subjects with more severe baseline impairment.

RESULTS

Baseline characteristics

A total of 1265 unique subjects were included in the analysis. Demographic, clinical, and physiologic characteristics are reported in Table I. Women constituted 57% of the study population, which was 66% white and of which 53% were overweight or obese. In general, the analysis population consisted of subjects with mild and moderate persistent asthma with a mean $\pm$ SD pre-bronchodilator FEV₁ of 82.9% $\pm$ 13.5% and a mean rescue use of as-needed albuterol of 1.2 $\pm$ 1.8 puffs per day.

Relationship between BMI and asthma impairment

The incremental fold change in markers of asthma impairment per 1-unit increase in continuous BMI (β) is reported in Table II. No significant effect of increasing BMI on spirometric results (FEV₁, forced vital capacity [FVC], and FEV₁/FVC ratio) was observed. Numerically small but statistically significant incremental change in multiple parameters was observed for each unit of BMI increase, including a 1.09 L/min increase in morning peak expiratory flow and a 0.02-unit decrease in asthma-related quality of life. Small, statistically significant inverse associations between BMI and the log-transformed variables PC₂₀ methacholine and exhaled nitric oxide level were observed, and there was a small positive association between BMI and rescue albuterol use (Table II).

TABLE I. Demographic, clinical, and physiologic characteristics of the study population

	No. (%)	Mean $\pm$ SD
Age (y)	1265	31.7 $\pm$ 10.1
Female sex	721 (57)	—
White	835 (66)	—
African American	246 (20)	—
Hispanic/Latino	102 (8)	—
BMI (kg/m ²)	—	26.7 $\pm$ 6.1
BMI <18.5 (underweight)	28 (2)	—
BMI 18.5–24.9 (normal)	565 (45)	—
BMI 25–29.9 (overweight)	393 (31)	—
BMI $\geq$ 30 (obese)	279 (22)	—
FEV ₁ (L), prebronchodilator	1264	3.0 $\pm$ 0.7 (82.9% $\pm$ 13.5%)
Morning peak expiratory flow (L/min)	1263	434.1 $\pm$ 112.5
Daily rescue albuterol use (puffs)	1259	1.2 $\pm$ 1.8
PC ₂₀ methacholine (mg/mL)	1122	1.1 $\pm$ 1.3*
Exhaled nitric oxide (ppb)	671	15.3 (9.7–27.3)†

*Geometric mean $\pm$ coefficient of variation.

†Median (25%–75% interquartile range).

BMI category was dichotomized (lean vs overweight/obese, Table III) to quantify differences between BMI categories. Adjusted analyses demonstrate an association between increased BMI and FEV₁ (mean, 3.05 L [95% CI, 2.98–3.11] vs 2.91 L [95% CI, 2.85–2.97]; adjusted P = .001) but not as percent predicted. Compared with lean asthmatic subjects, a slight reduction in FEV₁/FVC ratio was observed in overweight/obese asthmatic subjects (72.6% [95% CI, 71.8%–73.4%] vs 71.3% [95% CI, 70.6%–72.1%], adjusted P = .01), but no differences were observed in morning peak expiratory flow rate, airway hyperresponsiveness to methacholine, exhaled nitric oxide level, total number of positive allergen skin test responses, or score on the mini-Asthma Control Questionnaire.³³ Statistically significant but numerically small differences in mean asthma-specific quality of life and rescue albuterol use were observed, with a quality-of-life score of 5.77 (95% CI, 5.69–5.85) in lean subjects and 5.59 (95% CI, 5.52–5.67) in overweight/obese subjects (adjusted P = .004) and a mean number of puffs of rescue albuterol of 1.08 (95% CI, 0.98–1.18) in lean subjects and 1.2 (95% CI, 1.1–1.3) in overweight/obese subjects (adjusted P = .03).

The differences observed with regard to FEV₁ persisted and increased slightly when only lean and obese subjects were compared (ie, when overweight participants were excluded). These analyses (Table IV) indicated a slight increase in the between-group differences in FEV₁ in liters, which translated into a statistically significant difference in FEV₁ as a percentage of 83.5% (95% CI, 82.4%–84.5%) in lean versus 81.4% (95% CI, 80.0%–82.8%) in overweight/obese participants (adjusted P = .01). FEV₁/FVC ratio no longer differed significantly between the 2 groups, but the observed differences in rescue albuterol use and quality of life remained. An inverse association was observed between obesity and degree of airway hyperresponsiveness, with a PC₂₀ methacholine of 0.98 mg/mL (95% CI, 0.83–1.15) versus 1.23 mg/mL (95% CI, 1.01–1.5; adjusted P = .03) in lean versus obese subjects. Additionally, exhaled nitric oxide levels were slightly higher in lean versus obese subjects (16.3 [95% CI, 14.7–18.2] vs 13.8 ppb [95% CI, 12.2–15.7], adjusted P = .02).

TABLE II. Continuous BMI and physiologic and clinical characteristics of asthma

Variable	Change per unit increase in BMI (β , [95% CI])	P value
FEV ₁ (L), prebronchodilator (n = 1264)	0.001 (–0.004 to 0.005)	.8
FEV ₁ (%), prebronchodilator (n = 1264)	–0.05 (–0.16 to 0.61)	.4
FEV ₁ /FVC (n = 1264)	0.04 (–0.04 to 0.13)	.3
Morning peak expiratory flow (L/min) (n = 1263)	1.09 (0.23 to 1.96)	.01
Daily rescue albuterol use (puffs) (n = 1259)	1.01*	.001
Log PC ₂₀ methacholine (mg/mL) (n = 1122)	1.02*	.02
Exhaled nitric oxide (ppb) (n = 671)	1.0*	.02
Total no. of positive skin test responses (n = 1127)	0.02 (–0.01 to 0.05)	.2
Asthma-related quality of life (n = 1059)	–0.02 (–0.03 to –0.01)	<.0001
Mini-ACQ score (n = 475)	0.005 (–0.004 to 0.014)	.3

 β value if adjusted for study, age, sex, and race.

ACQ, Asthma Control Questionnaire.

*Relative change is reported for log-transformed variables.

Relationship between BMI and short-term clinical course of asthma

Changes in clinical, physiologic, and inflammatory outcomes (stratified by BMI category) between time of randomization and study completion were analyzed in subjects allocated to placebo as part of participation in the β -Agonist in Mild Asthma trial,²³ the Beta Agonist Response by Genotype study,²⁴ the DICE study,²⁵ IMPACT,²⁶ the PRICE trial,²⁸ the SLIC study,²⁹ and the SOCS study³² to evaluate whether increased BMI was associated with an altered natural history of asthma over the period covered by the individual studies (range, 8–48 weeks; Table V). No differences in the course of participants treated with placebo intervention (adjusted for study) between the 2 BMI categories (lean vs overweight/obese) were observed with regard to lung function (FEV₁ and FEV₁/FVC ratio), airway hyperresponsiveness (PC₂₀), airway inflammation (fraction of exhaled nitric oxide [FENO]), or clinical status (quality of life, symptoms, and rescue β -agonist use), and a similar lack of effect was observed when BMI was treated as a continuous variable (data not shown). Additionally, there was no significant difference between the 2 BMI categories in the likelihood of subjects allocated to placebo experiencing an asthma exacerbation, with an adjusted hazard ratio of 1.47 (95% CI, 0.86–2.49; P = .2).

Being overweight or obese and response to ICS

Being overweight or obese was associated with a reduced effect of ICSs on FENO, with a –3.6 ppb reduction in FENO levels in overweight/obese subjects versus a –6.5 ppb reduction in lean subjects allocated to ICS-only regimens as part of participation in the DICE trial,²⁵ IMPACT,²⁶ the MICE trial,²⁷ the PRICE trial,²⁸ the SLIC trial,²⁹ the SLIMSIT trial,³⁰ the SMOG trial,³¹ and the SOCS trial³² (P = .04, Table VI). No other significant associations between BMI category and clinical, physiologic, and inflammatory outcomes were observed. There was no significant difference in the likelihood of experiencing an asthma

TABLE III. BMI category and physiologic and clinical characteristics of asthma in lean vs overweight and obese subjects

Variable	BMI <25*	BMI ≥25*	Crude <i>P</i> value	Adjusted <i>P</i> value*
FEV ₁ (L), prebronchodilator (n = 593/671)	3.05 (2.98-3.11)	2.91 (2.85-2.97)	.0001	.001
FEV ₁ (%), prebronchodilator (n = 593/671)	83.5 (82.5-84.5)	82.4 (81.5-83.4)	.03	.1
FEV ₁ /FVC (%) (n = 593/671)	72.6 (71.8-73.4)	71.3 (70.6-72.1)	.01	.01
Morning peak expiratory flow (L/min) (n = 592/671)	437.4 (427.6-447.2)	443.7 (434.4-453.0)	.5	.3
Daily rescue albuterol use (puffs) (n = 590/669)	1.08 (0.98-1.18)	1.2 (1.1-1.3)	.05	.03
PC ₂₀ methacholine (mg/mL) (n = 531/591)	1.0 (0.86-1.16)	1.07 (0.93-1.24)	.1	.4
Exhaled nitric oxide (ppb) (n = 300/371)	16.0 (14.5-17.6)	14.9 (13.6-16.3)	.1	.2
Total no. of positive skin test responses (n = 523/604)	5.23 (4.94-5.51)	5.28 (5.01-5.55)	.7	.8
Asthma-related quality of life (n = 492/567)	5.77 (5.69-5.85)	5.59 (5.52-5.67)	.001	.0004
Mini-ACQ score (n = 206/269)	1.09 (1.0-1.19)	1.09 (1.0-1.18)	.7	1.0

Numbers (*n*) in parentheses are for BMI of <25/BMI of ≥30. Data are presented as means (95% CIs).

ACQ, Asthma Control Questionnaire.

*Means and *P* values are shown after adjustment for study, age, sex, and race.

TABLE IV. BMI category and physiologic and clinical characteristics of asthma in lean vs obese subjects

Variable	BMI <25*	BMI ≥30*	Crude <i>P</i> value	Adjusted <i>P</i> value*
FEV ₁ (L), prebronchodilator (n = 593/279)	3.05 (2.98-3.11)	2.78 (2.69-2.86)	<.0001	<.0001
FEV ₁ (%), prebronchodilator (n = 593/279)	83.5 (82.4-84.5)	81.4 (80.0-82.8)	.0003	.01
FEV ₁ /FVC (%) (n = 593/279)	72.6 (71.8-73.5)	72.2 (71.0-73.4)	.3	.5
Morning peak expiratory flow (L/min) (n = 592/278)	436.6 (426.6-446.5)	432.0 (418.4-445.6)	.2	.6
Daily rescue albuterol use (puffs) (n = 590/277)	1.08 (0.98-1.19)	1.27 (1.13-1.43)	.06	.01
PC ₂₀ methacholine (mg/mL) (n = 531/251)	0.98 (0.83-1.15)	1.23 (1.01-1.5)	.01	.03
Exhaled nitric oxide (ppb) (n = 300/163)	16.3 (14.7-18.2)	13.8 (12.2-15.7)	.02	.02
Total no. of positive skin test responses (n = 523/258)	5.23 (4.94-5.52)	5.48 (5.09-5.86)	.2	.3
Asthma-related quality of life (n = 492/234)	5.75 (5.67-5.84)	5.46 (5.35-5.57)	<.0001	<.0001
Mini-ACQ score (n = 206/125)	1.11 (1.01-1.22)	1.12 (0.99-1.25)	.5	.9

Numbers (*n*) in parentheses are for BMI of <25/BMI of ≥30. Data are presented as means (95% CIs).

ACQ, Asthma Control Questionnaire.

*Means and *P* values are shown after adjustment for study, age, sex, and race.

exacerbation in ICS-treated subjects with increased BMIs, with an adjusted hazard ratio of 0.70 (95% CI, 0.29-1.68; *P* = .4), and no differential effect of BMI in subjects with a baseline FEV₁ of less than 80% of predicted value (data not shown).

Being overweight or obese and response to inhaled glucocorticoid/LABA regimens

When subjects allocated to ICS/LABA regimens as part of participation in the SLIC²⁹ and SLIMSIT³⁰ studies were examined, there was an association between being overweight or obese and reduced response to ICS/LABA treatment with regard to both FEV₁ (in liters) and FEV₁/FVC ratio, with a mean 80 mL smaller improvement in FEV₁ and a 1.77% smaller improvement in FEV₁/FVC in subjects with a BMI of 25 or greater versus those with a BMI of less than 25 (Table VII). The likelihood of experiencing an asthma exacerbation was similar in overweight/obese versus lean subjects treated with ICS/LABA regimens, with an adjusted hazard ratio of 1.08 (95% CI, 0.52-2.26; *P* = .8). As was seen with ICS-only regimens, differential effects of BMI were not observed when an analysis restricted to subjects with baseline FEV₁ of less than 80% of predicted value was performed (data not shown).

Being overweight or obese and response to leukotriene modifier treatment regimens

In a smaller subset of participants, comparative differences between participants in the 2 BMI categories and clinical,

physiologic, and inflammatory outcomes were not observed in subjects allocated to leukotriene modifiers as part of participation in IMPACT²⁶ and the SMOG trial³¹ (Table VIII). As with other treatment regimens, a differential likelihood of experiencing an asthma exacerbation was not observed in subjects with increased BMI allocated to leukotriene modifiers, with an adjusted hazard ratio of 0.84 (95% CI, 0.19-3.74; *P* = .8), and differential between-BMI category differences were not observed in the analysis of subjects with a baseline FEV₁ of less than 80% of predicted value (data not shown).

DISCUSSION

Although it has been postulated that being overweight or obese is associated with a greater degree of clinical and physiologic impairment in subjects with asthma, our findings do not support the conclusion that there is a clinically meaningful effect of increased body mass on markers of impairment in subjects with mild-to-moderate persistent asthma. In the longitudinal analyses of clinical course in subjects allocated to the placebo arm of treatment trials ranging between 8 and 48 weeks in duration, there were not substantial differences between BMI categories with regard to change in physiologic, inflammatory, or clinical outcomes, suggesting that overweight and obese subjects with mild-to-moderate asthma do not necessarily fare worse over time than their lean counterparts. However, with regard to the relationship between increased BMI and response to controller

TABLE V. BMI category and change in outcomes in untreated subjects (placebo group)

Variable	BMI <25	BMI ≥25	P value for difference
FEV ₁ (L) (n = 188/190)	-0.07 (-0.12 to -0.02)	-0.08 (-0.14 to -0.03)	.7
FEV ₁ (% predicted) (n = 188/190)	-2.62 (-4.18 to -1.06)	-2.81 (-4.38 to -1.24)	.8
FEV ₁ /FVC (n = 182/184)	-1.36 (-2.21 to -0.50)	-1.62 (-2.49 to -0.75)	.6
Morning peak expiratory flow (n = 194/195)	-13.32 (-19.14 to -7.50)	-9.68 (-15.53 to -3.83)	.3
Quality of life (n = 124/137)	-0.04 (-0.17 to 0.08)	-0.07 (-0.20 to 0.05)	.7
PC ₂₀ FEV ₁ (n = 88/95)	-0.60 (-1.09 to -0.11)	-0.14 (-0.63 to 0.35)	.1
FENO (n = 89/84)	5.77 (2.64 to 8.9)	3.32 (0.04 to 6.6)	.2
Average daily symptoms (n = 194/195)	0.05 (0.02 to 0.08)	0.05 (0.03 to 0.08)	.8
Average daily rescue use (n = 194/195)	0.19 (0.07 to 0.31)	0.14 (0.02 to 0.26)	.5

Data are presented as mean changes (95% CIs). Numbers (n) in parentheses represent number of subjects with BMI <25/number of subjects with BMI ≥25.

TABLE VI. BMI category and change in outcomes in inhaled glucocorticoid treated-subjects

Variable	BMI <25	BMI ≥25	P value for difference
FEV ₁ (L) (n = 183/200)	0.1 (0.05 to 0.16)	0.1 (0.05 to 0.15)	.8/1.0
FEV ₁ (% predicted) (n = 183/200)	2.50 (1.15 to 3.85)	2.94 (1.65 to 4.22)	.8/.6
FEV ₁ /FVC (n = 119/141)	1.68 (0.81 to 2.56)	1.11 (0.28 to 1.93)	.2/.3
Morning peak expiratory flow (n = 192/206)	3.21 (-1.58 to 7.99)	2.48 (-2.11 to 7.06)	.5/.8
Quality of life (n = 73/85)	0.31 (0.15 to 0.48)	0.24 (0.08 to 0.40)	.4/.5
PC ₂₀ FEV ₁ (n = 54/68)	0.19 (-1.01 to 1.39)	0.36 (-0.72 to 1.44)	.7/.8
FENO (n = 56/64)	-6.54 (-8.88 to -4.20)	-3.57 (-5.77 to -1.38)	.04/.06
Average daily symptoms (n = 192/206)	-0.03 (-0.05 to 0.00)	-0.04 (-0.06 to -0.02)	.6/.5
Average daily rescue use (n = 191/206)	-0.24 (-0.33 to -0.15)	-0.20 (-0.29 to -0.12)	.4/.5

Data are presented as mean changes (95% CIs). Reported P values are adjusted for baseline and baseline plus study, with 1 P value reported if both are identical. Numbers (n) in parentheses represent number of subjects with BMI <25/number of subjects with BMI ≥25.

TABLE VII. BMI category and change in outcomes in inhaled glucocorticoid/LABA-treated subjects

Variable	BMI <25	BMI ≥25	P value for difference
FEV ₁ (L) (n = 115/182)	0.13 (0.07 to 0.19)	0.05 (0.00 to 0.10)	.04
FEV ₁ (% predicted) (n = 115/182)	3.93 (2.22 to 5.64)	2.16 (0.80 to 3.52)	.1
FEV ₁ /FVC (n = 115/182)	2.20 (1.17 to 3.22)	0.52 (-0.30 to 1.33)	.02/.01
Quality of life (n = 115/182)	0.31 (0.19 to 0.44)	0.32 (0.23 to 0.42)	.9
PC ₂₀ FEV ₁ (n = 92/151)	-1.93 (-3.22 to -0.64)	-0.46 (-1.45 to 0.53)	.04/.08
FENO (n = 84/158)	0.78 (-3.22 to 4.77)	2.82 (-0.24 to 5.88)	.5/.4
Average daily symptoms (n = 114/187)	-0.06 (-0.08 to -0.03)	-0.04 (-0.05 to -0.02)	.2
Average daily rescue use (n = 115/187)	-0.38 (-0.50 to -0.26)	-0.28 (-0.37 to -0.18)	.1/.2

Data are presented as mean changes (95% CIs). Reported P values are adjusted for baseline and baseline plus study, with 1 P value reported if both are identical. Numbers (n) in parentheses represent number of subjects with BMI <25/number of subjects with BMI ≥25.

therapy regimens, our analyses did demonstrate an approximately 55% reduction in the effectiveness of ICS monotherapy in decreasing exhaled nitric oxide levels in overweight/obese subjects, as well as a reduction of the beneficial effect of ICS/LABA combinations on FEV₁ and FEV₁/FVC ratio in overweight and obese subjects.

Our findings must be viewed in context, for there has been a substantial amount of discussion in the literature about whether and how obesity might modify asthma. First, although a statistically significant and dose-response effect of increased BMI on asthma risk was demonstrated in a recent meta-analysis,² there was heterogeneity of effect among included epidemiologic studies, with reported odds ratios for the effect of being overweight or obese on asthma risk ranging between 1.0 and 3.5, suggesting that prospective validation of this hypothesis in carefully phenotyped cohorts is warranted to confirm these findings. Although our data cannot shed light on the effect of

being overweight or obese on asthma risk, they suggest that, at least in adults with mild and moderate persistent asthma, increased BMI does not substantially increase asthma-related impairment or airway inflammation. These findings are consistent with findings in different populations (eg, both in pediatric subjects and in adults with severe asthma); for example, in the Childhood Asthma Management Program cohort, investigators did not find a correlation between BMI and markers of asthma control, and BMI did not modify eosinophil counts or IgE concentrations. Although there was a weak inverse relationship between BMI and bronchodilator reversibility ($\beta = -0.003$, $P = .02$), there was no effect of BMI on airway hyperresponsiveness.³⁴ A recent report from the National Heart, Lung, and Blood Institute-funded Severe Asthma Research Program³⁵ indicated that in approximately 250 adult subjects with severe asthma,³⁶ obesity was not more prevalent in subjects with severe versus moderate asthma.

TABLE VIII. BMI category and change in outcomes in leukotriene modifier–treated subjects

Variable	BMI <25	BMI ≥25	P value for difference
FEV ₁ (L) (n = 66/76)	−0.04 (−0.10 to 0.02)	0.03 (−0.03 to 0.08)	.1
FEV ₁ (% predicted) (n = 66/76)	−0.90 (−2.47 to 0.68)	0.73 (−0.74 to 2.19)	.2/0.1
FEV ₁ /FVC (n = 66/76)	0.11 (−0.84 to 1.06)	0.84 (−0.04 to 1.73)	.3
Quality of life (n = 34/40)	0.16 (−0.05 to 0.36)	0.16 (−0.03 to 0.35)	1.0
PC ₂₀ FEV ₁ (n = 32/39)	−0.35 (−2.55 to 1.86)	1.64 (−0.36 to 3.64)	.2
FENO (n = 30/32)	−2.53 (−7.73 to 2.67)	1.84 (−3.47 to 7.15)	.2*
Average daily symptoms (n = 69/82)	0.01 (−0.02 to 0.04)	0.02 (0.00 to 0.05)	.5
Average daily rescue use (n = 67/81)	0.10 (−0.02 to 0.23)	0.15 (0.04 to 0.27)	.7/.6

Data are presented as mean changes (95% CIs). Reported P values are adjusted for baseline and baseline plus study, with 1 P value reported if both are identical. Numbers (n) in parentheses represent number of subjects with BMI <25/number of subjects with BMI ≥25.

*Data are from IMPACT²⁶ only: single-study P value adjusted for baseline, age, sex, race, and study center.

Our findings do suggest, however, that the small observed effect of increased body mass in impairment-related domains might have a biologic basis, in that there was evidence of a dose-related increase (albeit small and of questionable clinical significance) in the inverse relationship between BMI and lung function, albuterol use, and quality of life, a relationship that has been demonstrated in other studies of the obesity-asthma relationship.^{2,10} Additionally, being overweight or obese might be associated with reduced efficacy of asthma controller therapies, particularly those regimens that contain ICSs, either alone or in combination with LABAs. Although this finding might be an *in vivo* manifestation of recent data suggesting that being overweight or obese is associated with a reduced response to glucocorticoids *in vitro* in subjects with asthma,¹⁰ prospective validation of this finding is warranted to determine whether glucocorticoid insensitivity underlies the reduced effect of ICSs observed in these analyses.

These data must be viewed in light of a number of potential limitations. First, these are *post-hoc* analyses of existing clinical trial data, and in none of the studies was BMI an *a priori* stratification variable. However, there was a relatively symmetric distribution of BMI across the study population, with slightly more than 50% of the study population being overweight or obese, suggesting that randomization resulted in relatively equal distribution of this variable.

Second, the effects observed are small, suggesting that despite the large number of subjects evaluated, adequate power might not have existed to detect small differences. However, the finding of small effects of uncertain clinical effect is, in this scenario, an important observation in that it calls into question the assertion that BMI is an important modifier of asthma severity and response to therapy.

Third, these observations were made in subjects with mild-to-moderate asthma and might not be generalizable to individuals with more severe asthma. However, the finding of a minimal effect of BMI in subjects with mild and moderate persistent asthma is important and has potential bearing on the large proportion of the asthmatic population, which falls into these 2 categories, suggesting that weight loss might not yield significant asthma-related clinical benefits in this population.

Fourth, BMI alone is a relatively crude technique for characterizing obesity, and we are unable in this dataset to assess other important obesity-related variables, such as body fat distribution or degree of systemic inflammation.

Fifth, the absence of an obese, nonasthmatic comparator group limits our ability to determine the extent to which obesity

alone affected the outcomes evaluated. It is possible that the observed differences are attributable not to the interaction of being overweight/obese and asthma but rather to body weight itself.

Finally, being overweight or obese might reflect dietary, environmental, or other important factors that might play a role in modifying biologic processes relevant to asthma impairment and response to therapy, and these factors cannot be evaluated in this type of study. Therefore it is important to recognize these findings as requiring prospective validation.

A major strength of these analyses, however, and one that distinguishes it from other contributions to the literature, is the extent to which clinical status, physiology, and airway inflammation have been rigorously characterized in a large sample size. One significant concern surrounding epidemiologic studies, on which many of the aforementioned conclusions have been based, is a limited ability to characterize relevant physiologic and inflammatory variables. This could lead to significant misclassification of obesity-related dyspnea, resulting in erroneous conclusions about the nature of the obesity-asthma relationship. Additionally, the analysis population is representative with regard to sex, age, and race and ethnicity, all features that enhance the generalizability of our findings to individuals with mild or moderate asthma. Finally, because comorbid illnesses, such as clinically significant obstructive sleep apnea and gastroesophageal reflux disease (both of which are clearly associated with obesity^{37,38} and which could also influence asthma control^{39–41}), are typically exclusionary conditions in these trials, our analysis has the benefit of being able to assess the relationship between increased BMI and asthma in the absence of these potential confounding comorbidities.

In summary, increased BMI is not a clinically significant modifier of impairment in subjects with mild-to-moderate asthma, but it is associated with a modest reduction of therapeutic effect of ICS-containing regimens with regard to indices of airway inflammation and lung function. Additional prospective studies are needed to further define relevant mechanisms by which obesity affects response to therapy in asthma.

Clinical implications: In individuals with mild-to-moderate persistent asthma, being overweight or obese does not appear to modify indices of asthma-related impairment. Increased BMI might reduce the response to ICS-containing treatment regimens.

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APPENDIX E1

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