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Body Mass Index and Phenotype in Mild-to-Moderate Persistent Asthma

E. Rand Sutherland, MD, MPH, Erik B. Lehman, MS, Mihaela Teodorescu, MD, MS, and Michael E. Wechsler, MD, MSc the NHLBI Asthma Clinical Research Network

Abstract

Background—While obesity has been hypothesized to worsen asthma, data from studies of well-characterized asthmatics are lacking.

Objective—Evaluate the relationship between body mass index (BMI), asthma impairment and response to therapy.

Methods—BMI (kg/m²) and asthma phenotypic and treatment response data were extracted from Asthma Clinical Research Network (ACRN) 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—1,265 subjects with mild-to-moderate persistent asthma were evaluated. Analyses of lean vs. overweight/obese asthmatics demonstrated small differences in FEV₁ (3.05 vs. 2.91 L, p=0.001), FEV₁/FVC (mean 83.5% vs. 82.4%, p=0.01), rescue albuterol use (1.1 vs. 1.2 puffs/day, p=0.03) and asthma-related quality of life (5.77 vs. 5.59, p=0.0004). Overweight/obese asthmatics demonstrated a smaller improvement in exhaled nitric oxide with inhaled corticosteroid (ICS) treatment than did lean asthmatics (3.6 vs. 6.5ppb, p=0.04). With ICS/long-acting beta agonist treatment, overweight/obese asthmatics demonstrated smaller improvements in lung function than lean asthmatics, with an 80mL (p=0.04) and 1.7% (p=0.02) lesser improvement in FEV₁ and FEV₁/FVC ratio, respectively. Significant differences in therapeutic response to leukotriene modifiers between BMI categories were not observed.

Conclusions—Elevated BMI is not associated with clinically-significant worsening of impairment in patients with mild-to-moderate persistent asthma. There is a modest association between elevated BMI and reduced therapeutic effect of ICS-containing regimens in this patient population. Prospective studies evaluating the impact of overweight and obesity on treatment response in asthma are warranted.

Clinical Implications—In individuals with mild to moderate persistent asthma, being overweight or obese does not appear to modify indices of asthma-related impairment. Elevated body mass index may reduce response to inhaled corticosteroid-containing treatment regimens.

Keywords

Asthma; obesity; treatment; severity

Correspondence: E. Rand Sutherland, MD, MPH, National Jewish Health, 1400 Jackson Street, J-201, Denver, CO 80206, Phone: 303-398-1081, Fax: 303-398-1780, sutherland@njc.org.

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Introduction

Obesity and asthma are prevalent diseases, each with a significant public health impact. Concurrent increases in prevalence of these disorders, along with emerging data on potential overlapping pathobiologic mechanisms, have suggested a link between the two.¹ Although the exact nature of this association remains unclear, a number of relevant observations have recently emerged: first, that being overweight (defined as a body mass index (BMI (kg/m²) between 25 and 29.9) or obese (BMI ≥ 30) increase the risk of incident asthma,^{2–6} second, that overweight and obesity predispose to a more severe or difficult-to-control asthma phenotype,⁷ third, that overweight and obesity alter response to asthma controller therapy,^{8–10} and fourth, that weight loss in obese asthmatics can result in clinical and physiologic improvement.^{11,12} Notwithstanding, the precise mechanisms by which overweight and obesity interact with asthma remain unclear.¹³ Although it is possible that overweight and obesity might modify risk for or severity of asthma by increasing airway or systemic inflammation^{14,15} or by leading directly to physiologic impairment (*e.g.* airway hyperresponsiveness) by reducing airway caliber,^{16,17} emerging data suggest that the effects of obesity on individuals with asthma might not be mediated solely by alterations in 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 While these epidemiologic approaches facilitate the assessment of 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 asthmatics enrolled in prospective clinical trials provide an opportunity for more robust cross-sectional and longitudinal assessment of the 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-funded Asthma Clinical Research Network (ACRN),²¹ we evaluated the association between elevated BMI and phenotypic characteristics of asthma,²² hypothesizing that 1) indices of asthma-related impairment (*e.g.* symptoms, quality of life, airway inflammation and physiologic limitation) would be unfavorably impacted 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): BAGS,²³ BARGE,²⁴ DICE,²⁵ IMPACT,²⁶ MICE,²⁷ PRICE,²⁸ SLIC,²⁹ SLIMSIT,³⁰ SMOG³¹ and SOCS.³² Aspects of the design and results of these studies have been reviewed previously.²¹ All studies were IRB approved at participating ACRN centers, and all subjects provided written informed consent.

All analyses were performed in SAS 9.1.3. If subjects participated in more than one study, only the most recent study data were used. Descriptive statistics were utilized to summarize baseline characteristics (*e.g.* forced expiratory volume in one second (FEV₁), methacholine PC₂₀, exhaled nitric oxide) of randomized study subjects, with baseline values defined at the visit closest to randomization. For outcomes measured with a daily diary (*e.g.* peak flow rate, rescue beta-agonist use), baseline was defined as the average value over the two weeks prior to randomization.

Baseline phenotypic data (adjusted for age, gender and race) were analyzed with BMI treated as both a categorical (lean (BMI <25) vs. overweight/obese (BMI ≥25)) and continuous variable. To evaluate the possibility that inclusion of overweight subjects (BMI 25 – 29.9) might dilute important differences between lean and obese (BMI ≥30) subjects, categorical comparisons of lean vs. obese subjects were also performed with baseline data; these comparisons were not performed with treatment-response data due to 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 non-normally-distributed continuous variables. To assess the association between phenotypic variables and incremental increases in continuous BMI, linear regression was used to determine the fold-change (beta) in the variable per unit increase in 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 monotherapy regimens, 3) inhaled corticosteroid/long-acting beta-agonist combination regimens and 4) leukotriene modifier monotherapy regimens. A linear mixed model was used to test change in outcome variables from baseline to end of treatment between the BMI categories. Additionally, the relationship between BMI category and the risk of an asthma exacerbation was assessed 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 inhaled corticosteroids 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 (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.

To account for between-study differences in treatment and evaluation, all analyses were adjusted for study; analyses were also adjusted for age, gender and race/ethnicity. To determine if associations with BMI were greater in subjects with more severe baseline impairment, sensitivity analyses in subjects with baseline FEV₁ <80% were performed.

Results

Baseline characteristics

A total of 1,265 unique subjects were included in the analysis. Demographic, clinical and physiologic characteristics are reported in Table 1. 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 mild and moderate persistent asthmatics, with a mean (± standard deviation) prebronchodilator FEV₁ of 82.9 ± 13.5% and a mean rescue use of as-needed albuterol of 1.2 ± 1.8 puffs/day.

Relationship between body mass index and asthma impairment

The incremental fold-change in markers of asthma impairment per one-unit increase in continuous BMI (beta) is reported in Table 2. No significant effect of increasing BMI on spirometry (FEV₁, FVC, FEV₁/FVC) 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 decline in asthma-related quality of life. Small statistically-significant inverse associations

between BMI and the log-transformed variables PC₂₀ methacholine and exhaled nitric oxide were observed, and there was a small positive association between BMI and rescue albuterol use (Table 2).

To quantify differences between BMI categories, BMI category was dichotomized (lean vs. overweight/obese, Table 3). Adjusted analyses demonstrate an association between elevated BMI and FEV₁ (mean and [95% confidence interval]) expressed in liters (3.05 [2.98, 3.11] vs 2.91 [2.85, 2.97], adjusted $p = 0.001$), but not as percent predicted. As compared to lean asthmatics, a slight reduction in FEV₁/FVC was observed in overweight/obese asthmatics (72.6% [71.8, 73.4] vs. 71.3% [70.6, 72.1], adjusted $p = 0.01$), but no differences were observed in morning peak expiratory flow rate, airway hyperresponsiveness to methacholine, exhaled nitric oxide, total number of positive allergen skin tests 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 [5.69, 5.85] in lean subjects and 5.59 [5.52, 5.67] in overweight/obese subjects (adjusted $p = 0.004$), and mean number of puffs of rescue albuterol of 1.08 [0.98, 1.18] in lean subjects and 1.2 [1.1, 1.3] in overweight/obese subjects (adjusted $p = 0.03$).

The differences observed with regard to FEV₁ persisted and increased slightly when only lean and obese subjects were compared (i.e. when overweight participants were excluded). These analyses (Table 4) indicated a slight increase in the between-group differences in FEV₁ (L), which translated into a statistically-significant difference in FEV₁ (%) of 83.5% [82.4, 84.5] in lean vs 81.4% [80.0, 82.8] in overweight/obese participants (adjusted $p = 0.01$). FEV₁/FVC ratio no longer differed significantly between the two 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 [0.83, 1.15] vs. 1.23 mg/mL [1.01, 1.5] (adjusted $p = 0.03$) in lean vs. obese subjects. Additionally, exhaled nitric oxide was slightly higher in lean vs. obese subjects (16.3 [14.7, 18.2] vs 13.8 ppb [12.2, 15.7], adjusted $p = 0.02$).

Relationship between body mass index and short-term clinical course of asthma

To evaluate whether elevated BMI was associated with an altered natural history of asthma over the period covered by the individual studies (range 8 – 48 weeks), 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 BAGS,²³ BARGE,²⁴ DICE,²⁵ IMPACT,²⁶ PRICE,²⁸ SLIC²⁹ and SOCS³² studies (Table 5). No difference in the course of participants treated with placebo intervention (adjusted for study) between the two BMI categories (lean vs. overweight/obese) were observed with regard to lung function (FEV₁, FEV₁/FVC), airway hyperresponsiveness (PC₂₀), airway inflammation (FeNO), or clinical status (quality of life, symptoms, rescue beta-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 two BMI categories in the likelihood of subjects allocated to placebo experiencing an asthma exacerbation, with an adjusted hazard ratio of 1.47 ([0.86, 2.49], $p = 0.2$).

Overweight/obesity and response to inhaled corticosteroids

Overweight and obesity were associated with a reduced effect of ICS on FeNO, with a -3.6ppb reduction in FeNO in overweight/obese subjects vs. a -6.5ppb reduction in lean subjects allocated to inhaled corticosteroid (ICS)-only regimens as part of participation in the DICE,²⁵ IMPACT,²⁶ MICE,²⁷ PRICE,²⁸ SLIC,²⁹ SLIMSIT,³⁰ SMOG³¹ and SOCS³² studies ($p=0.04$, Table 6). 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 exacerbation in ICS-treated subjects with elevated BMI, with an adjusted hazard ratio of 0.70 ([0.29, 1.68], $p = 0.4$), with no differential effect of BMI in subjects with baseline FEV₁ values <80% of predicted (data not shown).

Overweight/obesity and response to inhaled glucocorticoid/long-acting beta-agonist regimens

When subjects allocated to inhaled glucocorticoid/long-acting beta-agonist combinations (ICS/LABA) as part of participation in the SLIC²⁹ and SLIMSIT³⁰ studies were examined, there was an association between overweight/obesity and reduced response to ICS/LABA with regard to both FEV₁ (L) and FEV₁/FVC ratio, with a mean 80mL smaller improvement in FEV₁ and a 1.77% smaller improvement in FEV₁/FVC in subjects with BMI ≥ 25 vs. those with BMI <25 (Table 7). The likelihood of experiencing an asthma exacerbation was similar in overweight/obese vs. lean subjects treated with ICS/LABA, with an adjusted hazard ratio of 1.08 ([0.52, 2.26], $p = 0.8$). As was seen with ICS-only regimens, differential effects of BMI were not observed when an analysis restricted to subjects with baseline FEV₁ values <80% of predicted was performed (data not shown).

Overweight/obesity and response to leukotriene modifier treatment regimens

In a smaller subset of participants, comparative differences between participants in the two BMI categories and clinical, physiologic and inflammatory outcomes were not observed in subjects allocated to leukotriene modifiers as part of participation in the IMPACT²⁶ and SMOG³¹ studies (Table 8). As with other treatment regimens, a differential likelihood of experiencing an asthma exacerbation was not observed in subjects with elevated BMI allocated to leukotriene modifiers, with an adjusted hazard ratio of 0.84 ([0.19, 3.74], $p = 0.8$), and differential between-BMI category differences were not observed in the analysis of subjects with baseline FEV₁ values <80% of predicted (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 patients with asthma, our findings do not support the conclusion that there is a clinically-meaningful effect of elevated body mass on markers of impairment in mild-to-moderate persistent asthmatics. 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 elevated BMI and response to controller therapy regimens, our analyses did demonstrate an approximately 55% reduction in the effectiveness of ICS monotherapy in lowering exhaled nitric oxide 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, as there has been a substantial amount of discussion in the literature about if and how obesity might modify asthma. First, although a statistically-significant and dose-response effect of elevated 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 impact 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 impact of overweight and obesity on asthma risk, they suggest that, at least in adults with mild and moderate persistent asthma, elevated BMI does not substantially increase

asthma-related impairment or airway inflammation. These findings are consistent with findings in different populations (*e.g.* both in pediatric subjects and in adults subjects 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. While there was a weak inverse relationship between BMI and bronchodilator reversibility ($\beta = -0.003$, $p = 0.02$), there was no impact of BMI on airway hyperresponsiveness.³⁴ In adults, a recent report from the NHLBI-funded Severe Asthma Research Program³⁵ indicated that in approximately 250 subjects with severe asthma, ³⁶ obesity was not more prevalent in severe versus moderate asthma.

Our findings do suggest, however, that the small observed effect of elevated body mass in impairment-related domains may have a biological 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 inhaled corticosteroids, either alone or in combination with long-acting beta-agonists. While this finding may be an *in vivo* manifestation of recent data suggesting that overweight and obesity are associated with reduced response to glucocorticoids *in vitro* in subjects with asthma,¹⁰ prospective validation of this finding is warranted to determine if glucocorticoid insensitivity underlies the reduced effect of ICS 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 impact 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 mild-to-moderate asthmatics and may not be generalizable to individuals with more severe asthma. However, the finding of a minimal impact of BMI in mild and moderate persistent asthma is important and has potential bearing on the large proportion of the asthma population that falls into these two 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 a obese, nonasthmatic comparator group limits our ability to determine the extent to which obesity alone impacted the outcomes evaluated; it is possible that the observed differences are attributable not to the interaction of overweight/obesity and asthma, but rather to body weight itself. Finally, overweight and obesity may reflect dietary, environmental, or other important factors that might play a role in modifying biological 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 which 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 which 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 elevated BMI and asthma in the absence of these potential confounding comorbidities.

In sum, elevated BMI is not a clinically-significant modifier of impairment in patients 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 impacts response to therapy in asthma.

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Abbreviations

ACRN	Asthma Clinical Research Network
IRB	Institutional Review Board
FEV₁	forced expiratory volume in one second
FVC	forced vital capacity
BMI	body mass index
ICS	inhaled corticosteroid
LABA	long-acting beta agonist

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Table 1

Demographic, clinical and physiologic characteristics of study population.

	n (%)	Mean ± Standard Deviation
Age (years)	1265	31.7 ± 10.1 years
Female	721 (57)	-
White	835 (66)	-
African-American	246 (20)	-
Hispanic/Latino	102 (8)	-
Body Mass Index (kg/m ²)	-	26.7 ± 6.1 kg/m ²
BMI < 18.5 (underweight)	28 (2)	-
BMI 18.5 – 24.9 (normal)	565 (45)	-
BMI 25 – 29.9 (overweight)	393 (31)	-
BMI ≥ 30 (obese)	279 (22)	-
FEV ₁ (L (%), prebronchodilator)	1264	3.0 ± 0.7 L (82.9 ± 13.5%)
Morning peak expiratory flow (L/min)	1263	434.1 ± 112.5 L/min
Daily rescue albuterol use (puffs)	1259	1.2 ± 1.8 puffs
PC ₂₀ methacholine (mg/mL)	1122	1.1 ± 1.3 [*] mg/mL
Exhaled nitric oxide (ppb)	671	15.3 ppb [9.7 – 27.3] [†]

^{*} geometric mean ± coefficient of variation,

[†] median [25% – 75% interquartile range].

BMI: body mass index.

Table 2
Continuous BMI and physiologic and clinical characteristics of asthma.

Variable	Change per unit increase in BMI (beta, [95% CI])	p
FEV ₁ (L, prebronchodilator) (n=1264)	0.001 [-0.004, 0.005]	0.8
FEV ₁ (% , prebronchodilator) (n=1264)	-0.05 [-0.16, 0.61]	0.4
FEV ₁ /FVC (n=1264)	0.04 [-0.04, 0.13]	0.3
Morning peak expiratory flow (L/min) (n=1263)	1.09 [0.23, 1.96]	0.01
Daily rescue albuterol use (puffs) (n=1259)	1.01 *	0.001
Log PC ₂₀ methacholine (mg/mL) (n= 1122)	1.02 *	0.02
Exhaled nitric oxide (ppb) (n=671)	1.0 *	0.02
Total number of positive skin tests (n=1127)	0.02 [-0.01, 0.05]	0.2
Asthma-related quality of life (n=1059)	-0.02 [-0.03, -0.01]	<0.0001
Mini-ACQ score (n=475)	0.005 [-0.004, 0.014]	0.3

Beta adjusted for study, age, gender and race.
* Relative change reported for log-transformed variables. CI = confidence interval, ACQ = Asthma Control Questionnaire.

Table 3
BMI category and physiologic and clinical characteristics of asthma.

Variable	BMI < 25*	BMI ≥ 25*	Crude p	Adjusted p*
FEV ₁ (L, prebronchodilator) (n=593/671)	3.05 [2.98, 3.11]	2.91 [2.85, 2.97]	0.0001	0.001
FEV ₁ (% , prebronchodilator) (n=593/671)	83.5 [82.5, 84.5]	82.4 [81.5, 83.4]	0.03	0.1
FEV ₁ /FVC (%)(n=593/671)	72.6 [71.8, 73.4]	71.3 [70.6, 72.1]	0.01	0.01
Morning peak expiratory flow (L/min) (n=592/671)	437.4 [427.6, 447.2]	443.7 [434.4, 453.0]	0.5	0.3
Daily rescue albuterol use (puffs) (n=590/669)	1.08 [0.98, 1.18]	1.2 [1.1, 1.3]	0.05	0.03
PC ₂₀ methacholine (mg/mL) (n=531/591)	1.0 [0.86, 1.16]	1.07 [0.93, 1.24]	0.1	0.4
Exhaled nitric oxide (ppb) (n=300/371)	16.0 [14.5, 17.6]	14.9 [13.6, 16.3]	0.1	0.2
Total number of positive skin tests (n=523/604)	5.23 [4.94, 5.51]	5.28 [5.01, 5.55]	0.7	0.8
Asthma-related quality of life (n=492/567)	5.77 [5.69, 5.85]	5.59 [5.52, 5.67]	0.001	0.0004
Mini-ACQ score (n=206/269)	1.09 [1.0, 1.19]	1.09 [1.0, 1.18]	0.7	1.0

n reported for BMI <25/BMI ≥ 25.

* Means and p values after adjustment for study, age, gender and race. ACQ = Asthma Control Questionnaire. Data presented as mean and [95% CI].

Table 4
BMI category and physiologic and clinical characteristics of asthma.

Variable	BMI < 25*	BMI ≥ 30*	Crude p	Adjusted p*
FEV ₁ (L, prebronchodilator) (n=593/279)	3.05 [2.98, 3.11]	2.78 [2.69, 2.86]	<0.0001	<0.0001
FEV ₁ (% prebronchodilator) (n=593/279)	83.5 [82.4, 84.5]	81.4 [80.0, 82.8]	0.0003	0.01
FEV ₁ /FVC (%)(n=593/279)	72.7 [71.8, 73.5]	72.2 [71.0, 73.4]	0.3	0.5
Morning peak expiratory flow (L/min) (n=592/278)	436.6 [426.6, 446.5]	432.0 [418.4, 445.6]	0.2	0.6
Daily rescue albuterol use (puffs) (n=590/277)	1.08 [0.98, 1.19]	1.27 [1.13, 1.43]	0.06	0.01
PC ₂₀ methacholine (mg/mL) (n=531/251)	0.98 [0.83, 1.15]	1.23 [1.01, 1.5]	0.01	0.03
Exhaled nitric oxide (ppb) (n=300/163)	16.3 [14.7, 18.2]	13.8 [12.2, 15.7]	0.02	0.02
Total number of positive skin tests (n=523/258)	5.23 [4.94, 5.52]	5.48 [5.09, 5.86]	0.2	0.3
Asthma-related quality of life (n=492/234)	5.75 [5.67, 5.84]	5.46 [5.35, 5.57]	<0.0001	<0.0001
Mini-ACQ score (n=206/125)	1.11 [1.01, 1.22]	1.12 [0.99, 1.25]	0.5	0.9

n reported for BMI<25/BMI≥30.

* Means and p values after adjustment for study, age, gender and race.

ACQ = Asthma Control Questionnaire.

Table 5

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

Variable	BMI < 25	BMI ≥ 25	p for difference
FEV ₁ (L) (n=188/190)	-0.07 [-0.12, -0.02]	-0.08 [-0.14, -0.03]	0.7
FEV ₁ (% predicted) (n=188/190)	-2.62 [-4.18, -1.06]	-2.81 [-4.38, -1.24]	0.8
FEV ₁ /FVC (n=182/184)	-1.36 [-2.21, -0.50]	-1.62 [-2.49, -0.75]	0.6
Morning peak expiratory flow (n=194/195)	-13.32 [-19.14, -7.50]	-9.68 [-15.53, -3.83]	0.3
Quality of Life (n=124/137)	-0.04 [-0.17, 0.08]	-0.07 [-0.20, 0.05]	0.7
PC ₂₀ FEV ₁ (n=88/95)	-0.60 [-1.09, -0.11]	-0.14 [-0.63, 0.35]	0.1
FeNO (n=89/84)	5.77 [2.64, 8.9]	3.32 [0.04, 6.6]	0.2
Average Daily Symptoms (n=194/195)	0.05 [0.02, 0.08]	0.05 [0.03, 0.08]	0.8
Average Daily Rescue Use (n=194/195)	0.19 [0.07, 0.31]	0.14 [0.02, 0.26]	0.5

Data presented as mean change and [95% CI].

Table 6
BMI category and change in outcomes in inhaled glucocorticoid treated subjects.

Variable	BMI < 25	BMI ≥ 25	p for difference
FEV ₁ (L) (n=183/200)	0.1 [0.05, 0.16]	0.1 [0.05, 0.15]	0.8/1.0
FEV ₁ (% predicted) (n=183/200)	2.50 [1.15, 3.85]	2.94 [1.65, 4.22]	0.8/0.6
FEV ₁ /FVC (n=119/141)	1.68 [0.81, 2.56]	1.11 [0.28, 1.93]	0.2/0.3
Morning peak expiratory flow (n=192/206)	3.21 [-1.58, 7.99]	2.48 [-2.11, 7.06]	0.5/0.8
Quality of Life (n=73/85)	0.31 [0.15, 0.48]	0.24 [0.08, 0.40]	0.4/0.5
PC ₂₀ FEV ₁ (n=54/68)	0.19 [-1.01, 1.39]	0.36 [-0.72, 1.44]	0.7/0.8
FeNO (n=56/64)	-6.54 [-8.88, -4.20]	-3.57 [-5.77, -1.38]	0.04/0.06
Average Daily Symptoms (n=192/206)	-0.03 [-0.05, 0.00]	-0.04 [-0.06, -0.02]	0.6/0.5
Average Daily Rescue Use (n=191/206)	-0.24 [-0.33, -0.15]	-0.20 [-0.29, -0.12]	0.4/0.5

Data presented as mean change and [95% CI]. Reported p values adjusted for baseline and baseline + study, with 1 p value reported if both identical.

Table 7
BMI category and change in outcomes in inhaled glucocorticoid/long-acting beta-agonist treated subjects.

Variable	BMI < 25	BMI ≥ 25	p for difference
FEV ₁ (L) (n=115/182)	0.13 [0.07, 0.19]	0.05 [0.00, 0.10]	0.04
FEV ₁ (% predicted) (n=115/182)	3.93 [2.22, 5.64]	2.16 [0.80, 3.52]	0.1
FEV ₁ /FVC (n=115/182)	2.20 [1.17, 3.22]	0.52 [-0.30, 1.33]	0.02/0.01
Quality of Life (n=115/182)	0.31 [0.19, 0.44]	0.32 [0.23, 0.42]	0.9
PC ₂₀ FEV ₁ (n=92/151)	-1.93 [-3.22, -0.64]	-0.46 [-1.45, 0.53]	0.04/0.08
FeNO (n=84/158)	0.78 [-3.22, 4.77]	2.82 [-0.24, 5.88]	0.5/0.4
Average Daily Symptoms (n=114/187)	-0.06 [-0.08, -0.03]	-0.04 [-0.05, -0.02]	0.2
Average Daily Rescue Use (n=115/187)	-0.38 [-0.50, -0.26]	-0.28 [-0.37, -0.18]	0.1/0.2

Data presented as mean change and [95% CI]. Reported p values adjusted for baseline and baseline + study, with 1 p value reported if both identical.

Table 8
BMI category and change in outcomes in leukotriene-modifier treated subjects.

Variable	BMI < 25	BMI ≥ 25	p for difference
FEV ₁ (L) (n=66/76)	-0.04 [-0.10, 0.02]	0.03 [-0.03, 0.08]	0.1
FEV ₁ (% predicted) (n=66/76)	-0.90 [-2.47, 0.68]	0.73 [-0.74, 2.19]	0.2/0.1
FEV ₁ /FVC (n=66/76)	0.11 [-0.84, 1.06]	0.84 [-0.04, 1.73]	0.3
Quality of Life (n=34/40)	0.16 [-0.05, 0.36]	0.16 [-0.03, 0.35]	1.0
PC ₂₀ FEV ₁ (n=32/39)	-0.35 [-2.55, 1.86]	1.64 [-0.36, 3.64]	0.2
FeNO (n=30/32)	-2.53 [-7.73, 2.67]	1.84 [-3.47, 7.15]	0.2 *
Average Daily Symptoms (n=69/82)	0.01 [-0.02, 0.04]	0.02 [0.00, 0.05]	0.5
Average Daily Rescue Use (n=67/81)	0.10 [-0.02, 0.23]	0.15 [0.04, 0.27]	0.7/0.6

Data presented as mean change and [95% CI]. Reported p values adjusted for baseline and baseline + study, with 1 p value reported if both identical.
* data from IMPACT ²⁶ only, single-study p adjusted for baseline, age, gender, race and study center.