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Obesity's Impact on Asthma Extends to Diagnostic Criteria

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Abstract

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Background—The use of inflammatory biomarkers to delineate the type of lung inflammation present in asthma is increasingly common. However, the impact of obesity on these markers is unknown.

Objectives—We aimed to determine the impact of obesity on conventional markers of inflammation in asthma.

Methods—We performed secondary analysis of data from 652 patients previously enrolled in two ACRN trials. We performed linear correlations between biomarkers and logistic regression analysis to determine the predictive value of IgE, blood eosinophils and FeNO in relationship to sputum eosinophils (>2%), as well as to determine if cut points existed that would maximize the sensitivity and specificity for predicting sputum eosinophilia in the three weight groups.

Results—Overall, statistically significant but relatively weak correlations were observed among all four markers of inflammation. Within obese subjects, the only significant correlation found was between IgE and blood eosinophils ($r=0.33$, $p<0.001$); furthermore, all other correlations between inflammatory markers were approximately 0, including correlations with sputum eosinophils. In addition, the predictive value of each biomarker alone or in combination was poor in obese subjects. In fact in obese subjects, none of the inflammation biomarkers significantly predicted the presence of high sputum eosinophils. Obese asthma subjects have lower cut points for IgE, (268IU), FeNO (14.5ppb) and blood eosinophils (96 cells/ul) than all other groups.

Conclusions—In obese asthma, conventional biomarkers of inflammation are poorly predictive of eosinophilic airway inflammation. As such, biomarkers currently used to delineate eosinophilic inflammation in asthma should be approached with caution in these patients.

Keywords

Asthma; Obesity; Eosinophils; Inflammatory Markers and FeNO

Introduction

An association exists between the development of asthma and increased BMI {Beuther, 2007 #221;Beuther, 2007 #221;Beuther, 2007 #221}. Obesity in asthma is associated with increased symptoms, increased disease severity, and a decreased response to conventional medications {Boulet, 2008 #425;Peters-Golden, 2006 #426;Peters-Golden, 2006 #426;Boulet, 2008 #425.;Peters-Golden, 2006 #426}. Additionally, it has been appreciated that obese patients with asthma demonstrate phenotypic heterogeneity similar to that seen in lean individuals {Sutherland, 2012 #1538}. The most commonly accepted and well-described phenotype of asthma is one encompassed by eosinophilic inflammation resulting from type 2 cells that include CD4 and innate lymphoid cells that produce the cytokines interleukin (IL)-4, IL-5 and IL-13, among others {Woodruff, 2009 #361;Lambrecht, 2015 #430}. Eosinophilic inflammation is also associated with the presence of atopy, increased FeNO, serum IgE, sputum eosinophils, and peripheral eosinophils {Bousquet, 1990 #398;Fahy, 2009 #399}. Obesity is known to affect immune responses and alter T cell function and eosinophil migration, and may affect type II responses in a subgroup of obese patients with asthma {Agrawal, 2011 #427;Michalek, 2011 #429;Calixto, 2010 #400}.

Inflammatory biomarkers such as sputum eosinophils, blood eosinophils, periostin, IgE, and fraction of exhaled nitric oxide (FeNO) are increasingly being used to identify eosinophilic asthma phenotypes and predict response to therapy {Ortega, 2014 #372;Michils, 2008 #132;Kharitonov, 1996 #128;Dweik, 2011 #98;Deykin, 2005 #122;Corren, 2011 #243}. The gold standard of eosinophilic inflammation is the identification of eosinophils in airway tissue via bronchoscopy and analysis of endobronchial biopsies. However, this test is invasive and costly, limiting its use as a phenotyping tool. Sputum eosinophils have been extensively utilized in clinical trials as a marker of tissue eosinophilia, but induced sputum is generally unavailable for use as a clinical tool. In clinical trials, sputum eosinophils have rapidly gained favor as being predictive of important asthma outcomes, although the correlation between sputum and tissue eosinophils is not always consistent with a proportion of patients who demonstrate discordance between sputum and tissue eosinophilia {Jia, 2012 #112;Lemiere, 2006 #431}. In this study, we considered sputum eosinophils to be the gold standard of eosinophilic inflammation.

The limited availability of sputum eosinophils in clinical settings has led to increased interest in surrogate markers of inflammation, however these markers are not always accurately predictive of the presence of eosinophilic or neutrophilic inflammation{Hastie, 2013 #1561}. In addition, the effect of obesity on the ability of biomarkers to accurately depict underlying eosinophilic inflammation is unknown. For instance, studies have shown that sputum eosinophils and FeNO predict response to inhaled corticosteroids (ICS) {Deykin, 2005 #122;Brightling, 2005 #408;Brightling, 2005 #408;McGrath, 2012 #289;Dweik, 2011 #98}, and treatment strategies aimed at reducing sputum eosinophils result in a reduction in asthma exacerbation rates {Baigelman, 1983 #377;Petsky, 2007 #404}. However, two recent publications report discordance between submucosal eosinophilia and both bronchoalveolar lavage and sputum eosinophilia in obese patients with asthma {Desai, 2013 #349} {van der Wiel, 2014 #423}. FeNO, a biomarker shown to correlate with eosinophilic inflammation {Lemiere, 2006 #431}, is low in obese asthma and therefore may not be predictive {Komakula, 2007 #279;Maniscalco, 2015 #401}, but data are conflicting {Ciprandi, 2014 #402}. Blood eosinophils have become gradually accepted as a useful biomarker of asthma severity and are significantly decreased in response to anti-IgE and anti-IL-5 therapies {Massanari, 2010 #118;Pavord, 2012 #113;Ortega, 2014 #372}. The data supporting the use of blood eosinophils to predict response to ICS are mixed and widespread utilization of blood eosinophils as a biomarker has yet to occur {Meijer, 2002 #405;Pascoe, 2015 #407}. IgE has been a target of asthma therapy, but it appears that clinical characteristics including a history of exacerbation, need for high dose ICS, and the presence of low lung function are better predictors of response to omalizumab than serum IgE levels {Bousquet, 2004 #409} {Visness, 2009 #411;Fitzpatrick, 2012 #412}. However, a recent report did suggest that peripheral eosinophils >260 /μl and FeNO >19.5 ppb, as well as serum periostin >50 mg/ml (a biomarker associated with interleukin-13) were associated with response to Xolair{Hanania, 2013 #1415}.

Given the possible discordance between peripheral biomarkers and pulmonary inflammation in obese asthmatic patients, we hypothesized that the presence of obesity in asthma would decrease the ability of FeNO, serum IgE and peripheral blood eosinophil counts to predict

sputum eosinophilia, which could subsequently decrease the ability to predict treatment responses.

Methods

Study Design

The Duke University IRB approved this study (Protocol number Pro00056566) and data were obtained from NHLBI BioLINCC. Secondary analyses of data from a common run-in period in two Asthma Clinical Research Network (ACRN) trials were performed (n=652), including 1) Best Adjustment Strategy for Asthma over Long Term (BASALT, ClinicalTrials.gov number: NCT00495157, n=363){Calhoun, 2012 #337} and 2) Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC, ClinicalTrials.gov number: NCT00565266, n=289){Peters, 2010 #179}.

The inclusion criteria included age ≥ 18 years; a physician diagnosis of asthma confirmed by positive methacholine, or the presence of reversibility of the forced expiratory volume in one second (FEV_1) by 12% and 200 ml after four puffs of inhaled albuterol; a baseline FEV_1 of more than 40% predicted; and a smoking history of less than ten pack years. Exclusion criteria included the presence of other lung disease, presence of respiratory tract infection, or a significant asthma exacerbation within four weeks of study entry. During the run-in period, lung function testing, including spirometry pre- and post-bronchodilator FEV_1 and methacholine testing, was performed. FeNO was measured and sputum induction was completed for differential cell counts. Additionally, all subjects had a serum IgE, peripheral eosinophil count and skin prick testing performed. Subjects completed the Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), Asthma Evaluation Questionnaire (AEQ) and Asthma Symptom Utility Index (ASUI) during the run-in period.

Statistical Analysis

Descriptive statistics were performed including the mean (standard deviation) or median (25^{th} percentile, 75^{th} percentile) to describe continuous variables dependent on variable distribution. The count (percentage) was used to describe categorical variables with non-missing values. Body mass index (BMI) was treated as both a continuous and categorical variable with three categories: lean (BMI≤24.9), overweight (BMI 25–29.9), and obese (BMI≥30). The Kolmogorov-Smirnov test was used to determine if continuous variables were normally distributed. The Kruskal-Wallis or F-test was used to make comparisons across BMI categories as appropriate followed by pairwise comparisons between weight categories, while the chi-square test was used to compare categorical variables. The prevalence of eosinophilic inflammation was defined as the presence of an elevated FeNO at two thresholds values [>50 and >25 parts per billion (ppb)], or sputum eosinophils >2%, or blood eosinophils >300 cells/μl {Bacci, 2012 #441;Pavord, 2012 #113;Dweik, 2011 #98}. Subjects were assigned to non-eosinophilic status as long as all three factors were non-missing and lower than the set threshold. Pearson's correlation coefficients with 95% confidence intervals (based on Fisher's Z transformation) were used to determine the relationship among FeNO, IgE, sputum eosinophils, and blood eosinophils overall and

within each weight category. Logistic regression analysis was then used to determine if FeNO, IgE and blood eosinophils were predictive of high sputum eosinophils (>2%) overall and within each weight category. Regression splines were used to determine if the relationship between each biomarker and high sputum level was linear, revealing that the natural log transformation provided an approximate linear relationship. Each regression model was adjusted for study (BASALT, TALC), gender, age, BMI, and race (Caucasian, non-Caucasian).

A logistic regression model was then used to determine the value (cut point) that best predicted high sputum eosinophils for each biomarker. The values were determined by maximizing the area under the receiver operating characteristic curve (AUC), the sensitivity and the specificity. The regression models were applied across all patients and by weight group.

We did not adjust for multiple comparisons as all analyses were exploratory, thus a p-value < 0.05 was considered statistically significant. All data analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Demographics and Baseline Characteristics

Six hundred and fifty-two subjects were included in the analyses. Significantly more female subjects were found in the obese (70.1%) and lean asthma groups (72.0%) compared to the overweight (59.5%) group (p=0.014) (Table 1). The median age for patients who were obese (40 years) or overweight (36 years) was higher compared to lean subjects (30 years) (p<0.001), furthermore, a larger proportion of obese patients (55.6%) were diagnosed with asthma at >12 years of age (p=0.002) compared to lean (39.3%) or overweight (50.5%) subjects. Lean (69.7%) and overweight (67.2%) asthmatics were more likely to be Caucasian compared to obese subjects (47.7%) (p<0.001). Smoking history, presence of atopy via skin prick testing, and use of inhaled corticosteroids at baseline did not differ significantly across BMI groups.

Lean (20.1 ppb) and overweight (22.9 ppb) subjects had significantly higher median FeNO levels in comparison to obese (16.5 ppb) asthma subjects (p<0.001). FeNO levels did not differ significantly between lean and overweight subjects (p=0.068). **L**ean (145 IU/ml) and overweight (125 IU/ml) subjects also had significantly higher median IgE levels compared to obese (96 IU/ml) subjects (p=0.042), while IgE levels did not differ significantly between lean and overweight subjects (p=0.611). In addition, blood (p=0.796) and sputum eosinophil (p=0.358) counts did not differ significantly across BMI groups (Table 2).

Baseline lung function measurements were found to be significantly lower in obese asthma subjects compared to lean and overweight asthma subjects, including pre-bronchodilator forced vital capacity (FVC), pre-bronchodilator FEV_1 (absolute and %predicted), post-albuterol FEV_1 (absolute and %predicted), post-ipratropium FEV_1 (absolute and %predicted) (all p<0.001) (Table 3). We also determined the prevalence of reversible airway obstruction and hyper-responsiveness as a function of BMI. Across all subjects, we found a

low prevalence of reversible airflow obstruction to both albuterol and ipratropium with only approximately 35% of patients demonstrating reversibility. The remaining 65% of subjects were enrolled in the studies on the basis of a positive methacholine challenge test with a PC_{20} <16 mg/ml, in the absence of reversibility. BMI group had no impact on the prevalence (p=0.750) or response to methacholine PC_{20} (p=0.967) nor on the reversibility to ipratropium (p=0.098), however, reversibility to albuterol (p=0.038) was more prevalent within the overweight (40.5%) and obese (42.8%) groups compared to the lean group (30.7%).

Obese asthma subjects had a higher symptom burden as indicated by higher asthma symptom scores including higher Asthma Evaluation Questionnaire (AEQ; p=0.010), Asthma Control Questionnaire (ACQ; p<0.001), and Asthma Symptom Utility Index (ASUI; p=0.005) scores compared to lean and overweight subjects. In addition, obese subjects had a significant concomitant decrease in the quality of life scores (AQLQ) (p<0.001). Although these symptom burden results are statistically significant, the differences were small and therefore may not be clinically meaningful (Table 4).

The prevalence of eosinophilic inflammation according to FeNO threshold (>25 ppb or >50 ppb), sputum eosinophils >2% or blood eosinophils >300 cells/μl was significantly lower in obese compared to lean and overweight asthma subjects (p=0.010) if the FeNO threshold was >25 ppb. If the FeNO threshold was increased to >50 ppb, then the eosinophilic inflammation was not significantly different (p=0.311) across BMI categories (Table 5).

Correlation between FeNO, IgE, blood eosinophils and sputum eosinophils overall and within BMI groups

Overall, statistically significant but relatively weak correlations were observed among all four markers of inflammation, ranging from r=0.17 (IgE and FeNO) to r=0.22 (sputum eosinophils and both blood eosinophils and FeNO) as demonstrated in Table 6. Pearson's correlations were then determined within each weight category. Lean asthma subjects were noted to have the strongest correlations between inflammation markers with significant correlations found between all biomarkers except sputum eosinophils and IgE. The strongest correlation within the lean group occurred between sputum eosinophils and FeNO (r=0.43; p<0.001). As BMI increased, the number of significant associations between biomarkers diminished. As such, overweight subjects only demonstrated significant but relatively weak correlations between sputum eosinophils and IgE (r=0.41; p<0.001) and blood eosinophils and both sputum eosinophils (r=0.33; p<0.001) and FeNO (r=0.016; p=0.039). Within obese subjects, the only significant correlation found was between IgE and blood eosinophils (r=0.33, p<0.001); furthermore, all other correlations between inflammatory markers were approximately 0, including correlations with sputum eosinophils.

Predicting high sputum eosinophils (>2%) overall and within BMI groups

Logistic regression models for FeNO, quantitative IgE and blood eosinophils adjusted for study, age, gender, race and BMI were used to predict high sputum eosinophils (>2%) across all subjects and within each weight category (Table 7). Overall blood eosinophils [OR=1.44; 95% CI: (1.06–1.96)], IgE [OR=1.25; 95% CI: (1.03–1.51)] and FeNO [OR=2.06; 95% CI:

(1.32–3.23)] significantly predicted high sputum eosinophils. When each weight category was modeled separately, IgE was poorly predictive of high sputum eosinophils regardless of weight, while FeNO was predictive of high sputum eosinophils but only in lean asthma subjects [OR 3.89; 95% CI: (1.56, 9.65)]. Lastly, blood eosinophils were most predictive of high sputum eosinophils in lean [OR 1.67; 95% CI: (0.98, 2.85)] and overweight [OR 3.01; 95% CI: (1.35, 6.73)] asthma subjects but not obese subjects [OR 0.96; 95% CI: (0.67, 1.38)]. In fact, none of the inflammation biomarkers significantly predicted the presence of high sputum eosinophils in asthmatic obese patients.

We then utilized a multivariable logistic regression model to determine the predictive value of using all three inflammatory biomarkers in the model while still adjusting for the same baseline descriptors as above. FeNO continued to be predictive of sputum eosinophilia but only in lean subjects [OR=6.02; 95% CI: (1.86, 19.51); p=0.003]. Blood eosinophils were no longer predictive in lean subjects when all three biomarkers were considered. In overweight subjects, blood eosinophils was most predictive of sputum eosinophilia [OR=3.33; 95% CI: (1.36, 7.78); p=0.008], indicating that blood eosinophils continue to be predictive of sputum eosinophils after accounting for the other markers. The combination of all three biomarkers did not result in any improvements in the ability to predict high sputum eosinophils in obese subjects.

Cut points for predicting high sputum eosinophils (>2%) overall and by weight group

We performed analyses to determine if cut points existed for each biomarker individually (FeNO, IgE and blood eosinophils) for predicting high sputum eosinophils across all subjects and by weight group (Table 8). The cut-points for IgE, FeNO and blood eosinophils that maximize sensitivity and specificity differ by weight category. Obese asthma subjects have lower cut points for IgE, (268IU), FeNO (14.5ppb) and blood eosinophils (96 cells/ul) than all other groups.

Discussion

The principal finding of this study was that conventional markers of eosinophilic inflammation were poorly predictive of sputum eosinophilia in obese asthma subjects. Consistent with other studies, we found that obesity is associated with a more significant respiratory symptom burden and poorer quality of life scores concomitant with lower lung function, even in this population of patients with mild to moderate asthma. Further, we demonstrated that obese asthma subjects are more likely to be female, older age and have adult onset asthma.

Our data revealed no differences in baseline sputum and blood eosinophil levels on the basis of obesity. However there were significant differences in IgE and FeNO. Similar to currently published literature, obesity appeared to result in lower FeNO levels but, contrary to our expectations based on available literature, IgE levels were lower in obese than lean subjects with asthma {Maniscalco, 2015 #401;Visness, 2009 #411}. Obese asthma subjects had significantly lower prevalence of eosinophilic inflammation defined as sputum eosinophils > 2% or blood eosinophils > 300 cells/ml or FeNO >25ppb (p=0.01). However, when a higher FeNO threshold is used (>50ppb) there are no significant differences in the prevalence of

eosinophilia (Table 5). There were no significant differences in the prevalence of eosinophilic inflammation on the basis of obesity and additionally, greater than 85% of subjects in the study demonstrated positive skin prick testing. Although age of onset has been reported as being a key factor in differentiating the eosinophilic and non-eosinophilic obesity phenotypes, our data did not reveal any differences in inflammatory markers on the basis of age of onset in obese subjects {Holguin, 2011 #351}.

Furthermore, our data revealed increasingly poor correlations between markers of inflammation as subjects become gradually more obese. Whereas lean asthma subjects demonstrated a high degree of correlation between FeNO, blood eosinophils, sputum eosinophils and IgE, these associations became increasingly poor as BMI increased. As a result, obese patients only had a significant correlation between IgE and blood eosinophils. One can postulate that this was secondary to alterations in surrogate markers that led to increased discordance between the actual inflammatory milieu in the compartments of the lung and the surrogate measurements that we obtained clinically. For instance, nitric oxide levels were reduced in obesity and this may have been related to the presence of underlying oxidative stress and subsequent changes in NOS signaling associated with increased asymmetric dimethyl arginine that could result in a lack of concordance between tissue eosinophilia, inflammation and FeNO levels {Komakula, 2007 #279;Holguin, 2013 #350}. We postulate that the mechanisms that mediate inflammation in a proportion of eosinophilic asthmatics that are obese is similar to lean asthmatics. However obese subjects are at higher risk of inaccurate phenotyping on the basis of surrogate markers of inflammation. These surrogate markers are indirect measures of inflammation that may be influenced by conditions in the lungs of obese subjects such as the presence of higher levels of oxidative stress{Holguin, 2010 #722} and adipokine mediated alterations of eosinophil chemotaxis and survival {Kato, 2011 #1539;Takeda, 2012 #1540;Kim, 2014 #1557}. These unique influences of obesity have the potential to influence the accuracy of surrogate markers at detecting compartmental eosinophilia.

Additionally, our study was limited by the reliance on sputum and not tissue eosinophils, as the gold standard test for eosinophilic inflammation in the lung. The variability in sputum eosinophilia on repeated measures and the potential discordance with tissue eosinophilia, particularly in obesity, has been reported and could be a confounding variable {Desai, 2013 #349;Peters, 2013 #418;van der Wiel, 2014 #423;McGrath, 2012 #289}. Therefore, we cannot be reassured that sputum eosinophilia reliably reflects lung tissue eosinophils; this remains a subject for future study. Other limitations include the retrospective data analysis of a cross sectional rather than longitudinal dataset.

We determined the ability of FeNO, blood eosinophils and IgE to predict sputum eosinophils (>2%). Sputum eosinophils have been shown to predict response to inhaled corticosteroids and elevations in this marker are associated with increased exacerbations {Bacci, 2006 #119;Brightling, 2005 #408;Petsky, 2007 #404}. Given the potential clinical importance of these markers in identifying treatment responders, adjusting therapies and predicting outcomes, we performed nominal logistic regression modeling to determine the ROC characteristics of each biomarker. None of the inflammation markers (FeNO, blood eosinophils and IgE) significantly predicted high sputum eosinophils. We noted a decrease

in the ROC AUC with each of these biomarkers with increasing obesity with only blood eosinophils having an AUC > 0.70 for overweight subjects. From the standpoint of precision medicine, these results suggest that obese patients could be inaccurately assigned to non-eosinophilic phenotypes and possibly be excluded from receiving therapies for their asthma that could facilitate improved outcomes. Indeed, most targeted therapies currently in development rely on surrogate biomarkers to identify potential responders to therapy {Pavord, 2012 #113;Ortega, 2014 #372;Castro, 2014 #365}.

In conclusion, asthma is a heterogeneous disease regardless of the presence of obesity. However, obesity has a significant impact on the ability of currently available biomarkers of inflammation to accurately detect the type of underlying inflammation present in the lung. It is, therefore, imperative that the potential confounding effect of obesity be taken into consideration when interpreting the results of FeNO, IgE, blood and sputum eosinophil measurements. Moreover, these results underscore the need to identify more sensitive biomarkers in this population, perhaps serum periostin, Dipeptidyl Peptidase 4 (DPP4) or specific cytokine measurements that might permit more precise and individualized therapy {Marijsse, 2014 #422;Bobolea, 2015 #1401;Y. Zhang, 2014 #1426}.

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Trial Registration: ClinicalTrials.gov number: NCT00495157 and NCT00565266.

Abbreviations

ACRN	Asthma Clinical Research Network
BMI	Body mass index
IgE	Immunoglobulin E
FeNO	Fraction of exhaled nitric oxide
CD4	Cluster of differentiation 4
IL	Interleukin
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
PC_{20}	provocative concentration of methacholine that causes a 20% drop in FEV_1.
AEQ	Asthma Evaluation Questionnaire
ACQ	Asthma Control Questionnaire
ASUI	Asthma Symptom Utility Index

ICS	Inhaled corticosteroids
AUC	Area under the curve
OR	Odds ratio
DPP4	Dipeptidyl peptidase 4

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Clinical Implications

The reliance on inflammatory markers to identify responders to various asthma therapies and thus to enable personalized treatment of asthma patients makes accurate characterization of inflammation essential in obese asthma.

Capsule Summary

Obesity is associated with decreased sensitivity of blood eosinophils, IgE and FeNO in characterizing eosinophilia. Reliance on peripheral markers to make decisions regarding therapies targeting eosinophilia should therefore be approached with caution in obese asthma.

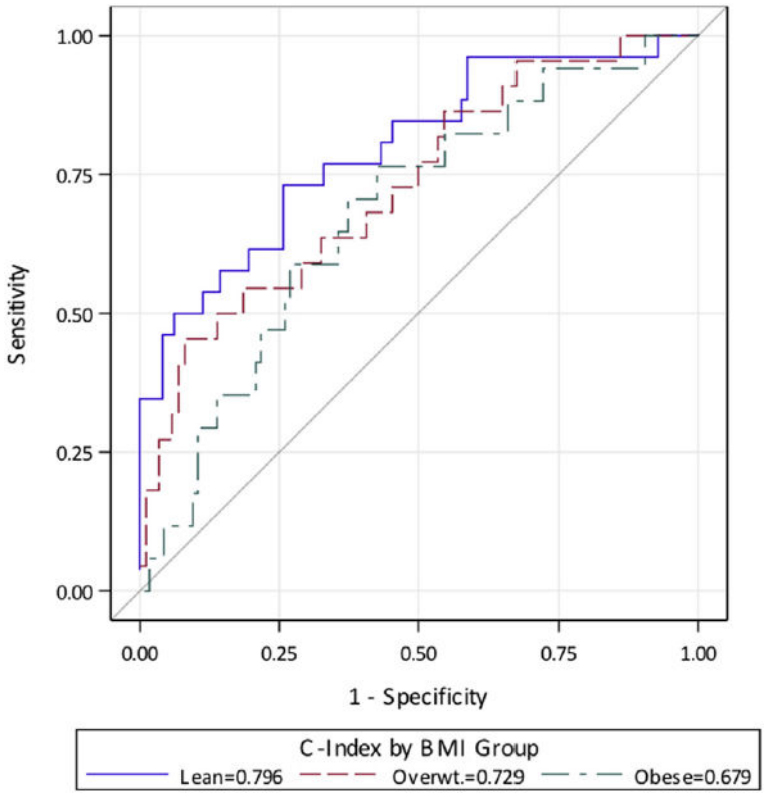

FIG 1.

Receiver operating characteristic curves by weight group adjusted for all biomarkers of inflammation.

Table 1

Demographic Data of Participants by Weight Group

	Lean (N=211)	Overweight (N=198)	Obese (N=243)	P-value
Female Gender (%)	148 (70.1)	118 (59.6)	175 (72.0)	0.014 *
Age (years)	30 (24, 42)	36 (27, 47)	40 (30, 49)	<0.001 *
Caucasian Race (%)	147 (69.7)	133 (67.2)	116 (47.7)	<0.001 *
Age at Asthma Diagnosis (years)	9 (4, 18)	12 (5, 24)	13 (5, 25)	0.012 *
Age ≥12 years at Asthma Diagnosis (%)	83 (39.3)	100 (50.5)	135 (55.6)	0.002 *
Asthma Duration (years)	19 (11, 26)	21 (14, 29)	21 (13, 32)	0.052
No Smoking History (%)	169 (80.1)	149 (75.2)	186 (76.5)	0.474
No Inhaled corticosteroid use at baseline (%)	204 (96.7)	194 (98.0)	236 (97.1)	0.718
Positive Skin Prick Test (%)	N=207 191 (92.3)	N=194 180 (92.8)	N=235 211 (89.8)	0.483

* Denotes a statistically significant difference across BMI categories. Data are presented as n (%) or as median (25^{th} percentile, 75^{th} percentile).

Lean=BMI ≤24.9; Overweight=BMI 25–29.9; Obese=BMI ≥30.

Table 2

Comparison of Biomarkers by Weight Group

	Lean (N=211)	Overweight (N=198)	Obese (N=243)	P-value
Blood Eosinophils (cells/μl)	N=200	N=191	N=231	0.796
Median (Q1, Q3)	178 (100, 251)	171 (100, 290)	174 (100, 260)	
Sputum Eosinophils (%)	N=138	N=126	N=150	0.358
Median (Q1, Q3)	0.6 (0.1, 2.0)	0.6 (0.0, 1.7)	0.4 (0.0, 1.2)	
IgE (IU/mL)	N=199	N=182	N=225	0.042 *
Median (Q1, Q3)	145 (61, 350)	125 (59, 360)	96 (38, 274)	
FENO (ppb)	N=194	N=175	N=216	<0.001 *
Median (Q1, Q3)	20.1 (14.3, 29.2)	22.9 (14.4, 33.1)	16.5 (11.8, 24.2)	

* Denotes a statistically significant difference across BMI categories. Data are presented as n (%) or as median (25th percentile, 75th percentile). Pairwise group differences are described in the text.

IgE=Immunoglobulin E; FENO=Fraction of exhaled nitric oxide; Lean=BMI ≤24.9; Overweight=BMI 25–29.9; Obese=BMI ≥30.

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Table 3

Baseline Lung Function Measurements by Weight Group

	Lean (N=211)	Overweight (N=198)	Obese (N=243)	P-value
FVC Pre-bronchodilator (L)	N=204	N=188	N=230	<0.001 *
Median (Q1, Q3)	3.8 (3.3, 4.4)	3.9 (3.3, 4.7)	3.3 (2.7, 3.9)	
FEV_1 Pre-bronchodilator (L)	N=204	N=188	N=230	<0.001 *
Median (Q1, Q3)	2.9 (2.4, 3.4)	2.7 (2.3, 3.2)	2.3 (1.9, 2.9)	
FEV_1 Pre-bronchodilator (% predicted)	N=204	N=188	N=230	<0.001 *
Mean (SD)	85.2 (13.6)	80.6 (14.7)	76.4 (13.3)	
FEV_1 Post-albuterol (L)	N=192	N=173	N=215	<0.001 *
Median (Q1, Q3)	3.2 (2.7, 3.6)	3.0 (2.6, 3.5)	2.6 (2.2, 3.2)	
FEV_1 Post-albuterol (% predicted)	N=192	N=173	N=215	<0.001 *
Mean (SD)	93.8 (12.9)	90.5 (13.7)	85.3 (13.3)	
Reversibility to Albuterol (%)	N=192 59 (30.7%)	N=173 74 (42.8%)	N=215 87 (40.5%)	0.038 *
FEV_1 Post-ipratropium (L)	N=202	N=192	N=235	<0.001 *
Median (Q1, Q3)	3.2 (2.6, 3.6)	3.0 (2.5, 3.5)	2.6 (2.2, 3.1)	
FEV_1 Post-ipratropium (% predicted)	N=202	N=192	N=235	<0.001 *
Mean (SD)	93.2 (12.8)	89.1 (13.7)	84.4 (13.0)	
Reversibility to Ipratropium (%)	N=196 62 (31.6%)	N=182 77 (30.3%)	N=223 84 (37.7%)	0.098
Methacholine PC_{20} (mg/ml)	N=153	N=141	N=179	0.750
Median (Q1, Q3)	1.2 (0.5, 4.0)	1.1 (0.5, 2.8)	1.2 (0.6, 3.4)	
Response to Methacholine (≤8 mg/ml) (%)	N=153 145 (94.8%)	N=141 133 (94.3%)	N=179 170 (95.0%)	0.967

* Denotes a statistically significant difference across BMI categories. Data are presented as n (%), mean (standard deviation) or as median (25^{th} percentile, 75^{th} percentile).

FEV_1=Forced expiratory volume in one second; FVC=Forced vital capacity; Reversibility is defined as an improvement of 12% and 200 ml in FEV_1 or FVC; PC_{20}=Provocative concentration of methacholine that causes a 20% drop in FEV_1.

Table 4

Asthma Symptom and Quality of Life Questionnaire Scores

	Lean (N=211)	Overweight (N=198)	Obese (N=243)	P-value
Average AEQ Score	N=211	N=198	N=242	0.010 *
Median (Q1, Q3)	0.33 (0.00, 0.67)	0.33 (0.00, 1.00)	0.67 (0.00, 1.00)	
Average ACQ Score	N=207	N=197	N=240	<0.001 *
Median (Q1, Q3)	0.67 (0.33, 1.17)	0.83 (0.50, 1.33)	1.00 (0.50, 1.67)	
Average ASUI Score	N=207	N=197	N=240	0.005 *
Median (Q1, Q3)	0.75 (0.50, 1.11)	0.75 (0.57, 1.00)	0.88 (0.57, 1.25)	
Average AQLQ Score	N=211	N=198	N=243	<0.001 *
Median (Q1, Q3))	6.38 (5.78, 6.62)	6.19 (5.56, 6.62)	6.09 (5.19, 6.53)	

* Denotes a statistically significant difference across BMI categories. Pairwise group differences are described in the text. Data are presented as median (25^{th} percentile, 75^{th} percentile).

ACQ=Asthma Control Questionnaire; AEQ=Asthma Evaluation Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index.

Table 5

Prevalence of Eosinophilic Inflammation by FeNO Threshold

	Lean (N=211)	Overweight (N=198)	Obese (N=243)	P-value
FeNO Threshold >25 ppb	N=191	N=177	N=212	0.010 *
Eosinophilic	99 (51.8)	103 (58.2)	91 (42.9)	
FeNO Threshold >50 ppb	N=189	N=137	N=165	0.311
Eosinophilic	68 (35.9)	59 (33.3)	61 (28.9)	

* Denotes a statistically significant difference across BMI categories. Data are presented as n (%). Eosinophilic if FENO >25 ppb or >50 ppb (two thresholds); or sputum eosinophils >2%; or blood eosinophils >300 cells/μl. The absence of all three denotes non-eosinophilic status.

Table 6

Correlation of the Eosinophilia Markers Overall and by Weight Group

Weight Category	Marker	Sputum Eosinophils	FENO	IgE
Overall	**Blood Eosinophils**	0.22 * (0.13, 0.31)	0.18 * (0.09, 0.26)	0.19 * (0.11, 0.27)
	Sputum Eosinophils		0.22 * (0.13, 0.32)	0.12 * (0.02, 0.22)
	FeNO			0.17 * (0.08, 0.25)
Lean	**Blood Eosinophils**	0.31 * (0.15, 0.46)	0.31 * (0.18, 0.44)	0.15 * (0.01, 0.29)
	Sputum Eosinophils		0.43 * (0.28, 0.56)	0.09 (−0.08, 0.26)
	FENO			0.32 * (0.18, 0.44)
Overweight	**Blood Eosinophils**	0.33 * (0.16, 0.48)	0.16 * (0.01, 0.30)	0.11 (−0.03, 0.26)
	Sputum Eosinophils		0.16 (−0.03, 0.33)	0.41 * (0.24, 0.55)
	FeNO			0.11 (−0.05, 0.26)
Obese	**Blood Eosinophils**	0.00 (−0.16, 0.16)	0.01 (−0.12, 0.15)	0.33 * (0.20, 0.44)
	Sputum Eosinophils		−0.02 (−0.19, 0.14)	−0.02 (−0.19, 0.14)
	FeNO			0.03 (−0.11, 0.17)

* Denotes a statistically significant correlation. Data presented as the Pearson correlation coefficient with 95% confidence intervals.

Table 7

Predicting High Sputum Eosinophils (>2%) by Weight Category Utilizing the Natural Log of each Inflammation Biomarker

Biomarker	BMI Category	OR	Lower 95% CI	Upper 95% CI	P-value	C-index
Log(IgE)	Overall	1.25	1.03	1.51	0.024*	0.646
	Lean	1.28	0.93	1.76	0.125	0.684
	Overweight	1.14	0.83	1.56	0.434	0.623
	Obese	1.32	0.89	1.96	0.161	0.659
Log(FeNO)	Overall	2.06	1.32	3.23	0.002*	0.662
	Lean	3.89	1.56	9.65	0.004*	0.762
	Overweight	1.61	0.75	3.44	0.220	0.639
	Obese	1.58	0.67	3.77	0.298	0.632
Log(Blood Eosinophils)	Overall	1.44	1.06	1.96	0.018*	0.667
	Lean	1.67	0.98	2.85	0.059	0.744
	Overweight	3.01	1.35	6.73	0.007*	0.718
	Obese	0.96	0.67	1.38	0.838	0.607

*Denotes a statistically significant correlation. Each logistic regression model is adjusted for study, gender, race, age, and BMI.

Table 8

Cut Points for Predicting High Sputum Eosinophils (>2%) by Weight Category

		Maximize AUC			Maximize Sensitivity			Maximize Specificity		
Biomarker	**BMI Category**	**Cut Point**	**SENS**	**SPEC**	**Cut Point**	**SENS**	**SPEC**	**Cut Point**	**SENS**	**SPEC**
Log(IgE)	**Overall**	268	0.46	0.73	5	1.00	0.02	5000	0.01	0.997
	Lean	277	0.43	0.75	10	1.00	0.04	5000	0.04	0.99
	Overweight	605	0.35	0.88	5	1.00	0.01	2841	0.00	0.99
	Obese	268	0.53	0.76	15	1.00	0.12	4761	0.00	0.99
Log(FeNO)	**Overall**	17.1	0.78	0.43	9.2	1.00	0.09	166.9	0.01	1.00
	Lean	17.1	0.93	0.44	9.5	1.00	0.07	166.9	0.03	1.00
	Overweight	31.2	0.42	0.78	11.0	1.00	0.19	103.9	0.04	1.00
	Obese	14.5	0.79	0.42	9.2	1.00	0.10	94.7	0.00	0.99
Log(Blood Eosinophils)	**Overall**	195	0.70	0.57	1	1.00	0.00	897	0.00	0.997
	Lean	195	0.75	0.66	1	1.00	0.00	630	0.04	1.00
	Overweight	400	0.36	0.95	70	1.00	0.13	897	0.00	0.99
	Obese	96	0.25	0.85	486	1.00	0.02	1	0.10	0.97

AUC=Area under the receiver operator characteristics (ROC) curve; SENS=Sensitivity; SPEC=Specificity.