Original Article

Characterization of Obesity in Severe Asthma in the German Asthma Net

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What is already known about this topic? Obesity affects numerous patients with severe asthma, worsening quality of life, asthma control, and disease burden. Together with variable lung function changes and inflammation markers, they have not been uniformly elucidated in large cohorts.

What does this article add to our knowledge? Obesity in severe asthma is associated with lower lung function and increased disease burden, more frequent reflux, depression, older age, and any smoking. However, type 2 inflammation is similarly high as in patients without obesity.

How does this study impact current management guidelines? Severe asthma in patients affected by obesity is similar to—and to be treated just like in—unaffected patients, additionally to weight loss initiation, to improve associated changes and asthma control.

BACKGROUND: Asthma is increasingly recognized as heterogeneous, characterized by different endotypes, with obesity not only a distinct phenotype but a risk factor for severe asthma.

OBJECTIVE: We sought to understand the associations of obesity with relevant parameters of severe asthma, including asthma control, disease burden, and lung function.

METHODS: The German Asthma Net registry is a multicenter international real-life registry capturing long-term follow-up data. This analysis included 2213 patients (52 ± 16 years, 58% female, 29% with obesity [body mass index ≥30 kg/m^2], 4.2 ± 4.3 exacerbations/year). The primary analysis assessed relationships between BMI and variables through univariate tests, followed by a multiple regression model. Secondary outcomes regarded clinically relevant variables in relation to weight groups.

RESULTS: Patients with obesity were more frequently female, more likely to have depression and gastroesophageal reflux, and suffered from worse asthma control, lower quality of life, reduced static lung volumes, more pronounced hypoxemia, and higher blood neutrophil counts, all statistically significant. Blood eosinophils, exhaled nitric oxide, and total IgE were

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Abbreviations used
ACQ-5- Asthma Control Questionnaire-5
ACT- Asthma Control Test
BMI- Body mass index
CRSwNP- Chronic rhinosinusitis with nasal polyps
DLCO- Diffusing capacity for carbon monoxide
ERS/ATS- European Respiratory Society/American Thoracic Society
FeNO- Fraction of exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GAN- German Asthma Network
GERD- Gastroesophageal reflux disease
ICS- Inhaled corticosteroid
ISAR- International Severe Asthma Registry
mAQLQ- Mini Asthma Quality of Life Questionnaire
MEF- Mid-expiratory flow
OCS- Oral corticosteroids
pO_2- Partial pressure of oxygen
RV- Residual volume
SARP- Severe Asthma Research Program
SD- Standard deviation
TLC- Total lung capacity

independent of obesity. In the multiple regression analysis, obesity was significantly associated with more frequent reflux and depression, reduced static lung function values, older age, poor asthma control, and long-acting muscarinic antagonist therapy, and inversely associated with bronchiectasis and nonsmoking status.

CONCLUSION: In this large, well-characterized cohort, we identified the association of obesity with a significantly higher disease burden and a similar portfolio of inflammation type 2 markers in patients with and without obesity; therefore, patients with obesity seem similarly eligible for the treatment with biologics targeting these disease endotypes. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Severe asthma; Obesity; BMI; Registry; Comorbidities; Lung function; Asthma control; Exacerbations; Biomarker*

Obesity (body mass index [BMI] $\geq$30 kg/m^2) is both a relevant comorbidity of and a risk factor for the development of severe asthma,[1,2] affecting up to 60% of patients,[3-5] with an impact on disease control,[3,4,6] lung function values through increased abdominal fat,[7] and dyspnea through increased cardiorespiratory workload.[1] Closely associated comorbidities of obesity, such as sleep apnea and gastroesophageal reflux disease (GERD),[7,8] similarly increase disease burden and can facilitate weight gain together with asthma-related factors such as sedentary lifestyle and corticosteroid use.[1,3,4,9,10]

Several registry studies in severe asthma assessed characteristics of patients with increased disease burden, such as reduced asthma control,[11] frequent exacerbations,[12] extensive pharmacotherapy, and oral corticosteroid (OCS) dependence.[13-15] Obesity was highlighted as an important factor for asthma disease burden,[6,16,17] among others such as age, sex,[18-21] or comorbidities.[22,23] In cluster analyses of severe asthma, blood neutrophilia is often included with obesity, OCS dependence, and female sex,[18,24,25] but the source and relevance of neutrophilia to asthma remains questionable.[26-28] Variability remains in assessing the impact of obesity on lung function values,[29,30] and on type 2 airway inflammation and the presence or reduction of type 2 biomarkers, including eosinophilia, fraction of exhaled nitric oxide (FeNO), and total IgE,[3,13,31,32] which are essential in justifying targeted treatments.[33] A thorough analysis of patients with severe asthma and obesity was required to assess the inflammation markers, lung function changes, and highlight changeable aspects in this at-risk group of patients with severe asthma. For this purpose, we analyzed data from the Severe Asthma Registry of the German Asthma Net (GAN), an international registry created to record long-term patient epidemiology, therapy, and treatment outcomes in a real-life setting on a large scale,[15,34] with the primary aim of detecting parameters associated with obesity in patients with severe asthma and the secondary aim to find if differences in clinical characteristics relevant to asthma management arise in patient groups with and without obesity.

METHODS

The Severe Asthma Registry has recruited patients with severe asthma defined by European Respiratory Society/American Thoracic Society (ERS/ATS) criteria,[35] mainly from Germany but also from Austria[15,36] from centers included in the Severe Asthma Registry of the GAN study group (https://germanasthmanet.de/en/centers/). Patients were included if they had severe asthma, defined by the ERS/ATS guidelines as the requirement of high to very high doses of inhaled corticosteroids (ICS) and an additional inhalative therapy such as long-acting β-agonists or maintenance OCS therapy for over half of the previous year to control their asthma, were 12 to 90 years old, and had valid height and weight values. No patient with a current exacerbation was included.

This study was a cross-sectional analysis of baseline data from the Severe Asthma Registry, performed per the Declaration of Helsinki and approved by ethics committees of all respective countries (Germany and Austria). All adult participants or respective guardians

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provided written informed consent to be included in the registry. These analyses included all eligible patients from the registry, excluding only those with incomplete essential data regarding age, weight, or height (n = 4), aged <12 years (n = 66) due to differing obesity definitions and standard BMI values with age. Adolescents from age 12 were included to comply with cohorts of large studies in severe asthma;[37,38] an assessment including only adults was additionally performed. As this was a cross-sectional analysis, BMI was measured on the day when all the analyzed variables including laboratory and lung function results were acquired.

Consistent with international guidelines, overweight was defined as BMI ≥25 to <30 kg/m^2, obesity as BMI ≥30 kg/m^2, and morbid obesity as BMI ≥35 kg/m^2. We defined exacerbations as events requiring OCS for ≥3 days, doubling of current OCS dose, or hospitalization, and patients with frequent exacerbations were those with ≥2 exacerbations/year.[35] Controlled asthma was defined as an Asthma Control Questionnaire-5 (ACQ-5) score <1.5,[39] or an Asthma Control Test (ACT) score ≥20,[40] and good asthma quality of life by a score of ≥5.4 in the mini Asthma Quality of Life Questionnaire (mAQLQ).[41] Finally, hypoxemia was partial pressure of oxygen in the blood (pO_2) <72 mm Hg.

Statistics

All statistics were performed in R 3.5.1 (R Core Team, Vienna, Austria, 2021), SPSS version 27 (IBM, Armonk, NY), and Excel 2013 (Microsoft, Redmond, Wash). Obesity was assessed both as a continuous endpoint (BMI in kg/m^2) and as a binary outcome ("obesity," BMI ≥30 kg/m^2) for precision and for clinical application, see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org. As primary analysis, continuous endpoint BMI was used, and univariate *t* tests and linear regression analyses (reporting regression estimates, *t* statistics, *P* values, and Pearson correlation coefficients) were performed to assess the relationship with variables of interest. For binary endpoint obesity, χ^2 tests (asymptotic) and *t* tests were performed (where appropriate). All variables of interest with a univariate *P* value smaller than 0.00125 (Bonferroni boundary) and with less than 10% missing values were considered in a multiple analysis of covariance for continuous endpoint BMI. For the analysis of BMI and corticosteroid use, a nonparametric Spearman correlation was calculated. In addition, a secondary analysis was performed to analyze the difference between BMI subgroups <25, 25 to 30, 30 to 35, and ≥35 kg/m^2 with clinically relevant variables including OCS dose, exacerbations, mAQLQ, ACQ, forced expiratory volume in 1 second (FEV_1), and diffusing capacity for carbon monoxide (DLCO); a Kruskal-Wallis test was performed.

Because of the exploratory character of the study, no adjustment for multiple testing was performed, except that the Bonferroni method was used to select variables for the multiple analysis, and *P* values should therefore be interpreted descriptively. This report follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[42]

RESULTS

Of 2213 patients with severe asthma aged ≥12 years included in these analyses, 639 (28.9%) were affected by obesity (BMI mean ± standard deviation [SD] 35.0 ± 4.7 kg/m^2 [range: 30.0-58.8 kg/m^2]; the BMI of the comparator [nonaffected] group was mean ± SD: 24.4 ± 3.2 kg/m^2 [range: 15.8-29.9 kg/m^2]).

The patients with obesity were more likely to be female and to have GERD or depression than patients without obesity, but there were no differences in the prevalence of chronic obstructive pulmonary disease or chronic rhinosinusitis with nasal polyps (CRSwNP). Dominant type 2 inflammation was seen independently of obesity with high FeNO levels, total IgE, sputum, and blood eosinophil counts in both patient groups. Fittingly, approximately the same number of patients with and without obesity received anti-IL5 (*P* = .6), anti-IL4/13 (*P* = .6), anti-IgE therapy (*P* = .7), or biologic therapies (*P* = .7). Furthermore, the patients with obesity had a significantly lower arterial pO_2 and smaller lung volumes, including forced vital capacity (FVC) and total lung capacity (TLC), compared with patients without obesity, although the FEV_1/FVC ratio was significantly higher in these patients. The DLCO, mid-expiratory flow $(MEF)_{50\%}$, and $MEF_{75\%}$ were below predicted in both groups, but significantly higher in patients with obesity. Patients affected by obesity had significantly worse asthma control and quality of life, a higher blood neutrophil count, and were significantly more likely to be smokers or passive smokers than unaffected patients. BMI was positively correlated with OCS dose in all patients (r = 0.048, *P* = .02) and in OCS-dependent patients (r = 0.12, *P* < .001), as seen in Table I.

In the subsequent multiple linear regression analysis, there were persisting associations of obesity with GERD, depression, older age, the use of long-acting muscarinic antagonist therapy, and higher FEV_1/FVC ratio, and inverse associations with FVC, bronchiectasis, never-smoking, and asthma control (ACT; ACQ and mAQLQ needed to be excluded because of multicollinearity), as seen in Table II. Of the 2213 patients assessed, 2102 were adults in the current study. Excluding patients <18 years old yielded highly similar variables associated with higher BMI, aside of age (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

In order to analyze critical variables more accurately, we performed a Kruskal-Wallis test with patients in BMI subgroups <25, 25 to 30, 30 to 35, and ≥35 kg/m^2 with clinically relevant variables including OCS dose, exacerbations, mAQLQ, ACQ, and FEV_1, and univariate regression analyses with BMI as outcome variables, excluding the already analyzed variables from the multiple regression analysis.

In the univariate regression analyses, higher BMI was significantly associated with a higher number of exacerbations in the prior year, poorer asthma control and quality of life, and higher maintenance OCS intake. In contrast, blood eosinophil counts were not associated with BMI (Table III). In groupwise analysis, obstructive lung function impairment as measured by FEV_1 % predicted remained nonassociated with BMI. Poor asthma control and quality of life remained significantly associated with BMI category. Although overall maintenance OCS use was not associated with BMI category, when we restricted the analysis to patients on maintenance OCS, normal-weight patients were less OCS dependent (Table IV). In a further study on patients separated by intake of maintenance OCS, corticosteroid intake increased blood neutrophil counts to similar degrees in patients with and without obesity. Higher blood neutrophil counts were associated with maintenance OCS in patients with and without obesity (Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In the current cohort with severe asthma, 29% were affected by obesity, less than the International Severe Asthma Registry

TABLE I. Associations between obesity and baseline variables

Univariate tests of variables from severe asthma patients with the end point obesity (BMI ≥30 kg/m^2)	n	Obesity (BMI ≥30 kg/m^2) (n = 639), % (n)	No obesity (BMI <30 kg/m^2) (n = 1574), % (n)	BMI ≥30 kg/m^2 vs BMI <30 kg/m^2	
				P value‖	Point estimate; 95% CI‖
Female (% of total)*	2213	62 (396)	56 (879)	.009	—
CRSwNP (% of total)*	2200	51 (325)	54 (841)	.3	—
Bronchiectasis (% of total)*	2200	2 (14)	4 (55)	.14	—
GERD (% of total)*	2200	40 (252)	31 (489)	<.001	—
Depression (% of total)*	2200	20 (129)	12 (192)	<.001	—
COPD (% of total)*	2200	9 (60)	8 (127)	.4	—
Never smoking (% of total)*	2213	30 (192)	39 (616)	<.001	—
Passive smoking (% of total)*	2213	23 (145)	18 (283)	.013	—
Family history of asthma (% of total)*	1090	73 (226)	76 (596)	.3	—
Frequent exacerbations (% of total)*,†	1699	77 (382)	75 (900)	.5	—
Severe exacerbations (% of total)*	1708	57 (284)	52 (623)	.052	—
Near-lethal exacerbations (% of total)*	1701	9 (46)	9 (104)	.8	—
Anti-IgE therapy*	2213	17 (106)	16 (255)	.7	—
Anti-IL5 therapy*	2213	15 (97)	16 (258)	.6	—
Anti-IL4/13 therapy*	2213	2 (10)	1 (20)	.6	—
LAMA therapy*	2213	65 (415)	56 (878)	<.001	—
Beclomethasone equivalent ≥1000 μg/d*	2213	47 (302)	45 (709)	.4	—
Beclomethasone equivalent ≥2000 μg/d*	2213	25 (156)	24 (373)	.7	—
Maintenance OCS use (% of total)*	2213	35 (225)	35 (543)	.8	—
	n	Mean (SD)	Mean (SD)	*P* value	Point estimate; 95% CI‖
Mean BMI (SD)	2213	35.0 (4.7)	24.4 (3.2)	n/a	n/a
Maintenance OCS (mg)‡	2213	5.6 (13.4)	4.6 (10.4)	.09	−0.92; −2.08 to 0.25
pO_2 (mm Hg)	983	71.7 (8.9)	74.6 (10.6)	<.001	2.87; 1.57 to 4.18
pCO_2 (mm Hg)	982	36.2 (3.9)	36.1 (4.3)	.8	−0.08; −0.64 to 0.48
TLC (% of predicted)	774	102 (16)	107 (17)	<.001	5.16; 2.63 to 7.68
RV (% of predicted)	772	143 (46)	150 (47)	.056	−9.95; −14.08, 0.19
RV/TLC (%)	751	49 (12)	48 (13)	.6	−0.47; −2.41 to 1.48
Total IgE (IU/mL)	937	488 (1160)	428 (891)	.4	−60.1; −216.3 to 96.2
$MEF_{25\%}$ (% of predicted)	1806	47 (40)	45 (39)	.4	−1.87; −5.94 to 2.20
$MEF_{50\%}$ (% of predicted)	1906	49 (35)	44 (32)	.001	−5.30; −8.69 to −1.92
$MEF_{75\%}$ (% of predicted)	1638	57 (31)	51 (30)	.001	−5.36; −8.67 to −2.05
Age (y)	2213	52 (13)	51 (17)	.09	−1.24; −2.56 to 0.08
Age at asthma onset	1664	31 (19)	31 (20)	.8	0.32; −1.76 to 2.39
FEV_1 (% of predicted)	2074	66 (22)	67 (22)	.6	0.57; −1.52 to 2.66
FVC (% of predicted)	2048	79 (19)	83 (19)	<.001	4.32; 2.49 to 6.14
FEV_1/FVC (%)	1976	70 (14)	67 (14)	<.001	−3.23; −4.61 to −1.86
DLCO (% of predicted)	973	77 (19)	73 (18)	.005	−3.62; −6.19 to −1.05
FeNO (ppb)	1129	47 (44)	51 (48)	.2	4.13; −1.74 to 10.00
Exacerbations, mean (SD)	1699	4.4 (4.5)	4.1 (4.2)	.2	−0.32; −0.78 to 0.14
ACQ-5 score	1857	2.9 (1.5)	2.6 (1.5)	<.001	−0.33; −0.48 to −0.18
ACT score	2017	13.6 (5.5)	15.3 (5.6)	<.001	1.65; 1.12 to 2.19
mAQLQ score	1761	3.7 (1.3)	4.1 (1.3)	<.001	0.39; 0.26 to 0.53
Blood neutrophils (G/L)	1496	5.9 (2.6)	5.3 (2.5)	<.001	−0.57; −0.86 to −0.29
Blood eosinophils (G/L)	1506	0.4 (0.8)	0.5 (0.7)	.06	0.07; −0.01 to 0.16
Sputum eosinophils (%)§	66	11.6 (18.9)	14.6 (20.4)	.5	3.50; −1.40 to 5.50§

The analyses performed were 2-sample *t* tests, if not otherwise defined. Significance was determined by the χ^2 or *t* test.

ACQ-5, Asthma Control Questionnaire-5; *ACT*, Asthma Control Test; *BMI*, body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *DLCO*, diffusing capacity for carbon monoxide; *FeNO*, fraction of exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic antagonist; *mAQLQ*, Mini Asthma Quality of Life Questionnaire; *MEF*, mid-expiratory flow; *n/a*, not applicable; *OCS*, oral corticosteroids; *pCO_2*, partial pressure of carbon dioxide; *pO_2*, partial pressure of oxygen; *RV*, residual volume; *SD*, standard deviation; *TLC*, total lung capacity.

*χ^2 test.

†Frequent exacerbations were defined as ≥2 exacerbations/y in the past year.

‡The Spearman correlation coefficient between BMI and OCS was 0.048 ($P = .02$) and between BMI and OCS in mg (dose >0 mg) 0.12 ($P < .001$).

§Mann-Whitney test with actual difference and 95% CI of difference.

‖*P* values with CI were for the mean difference between the groups or categories from the χ^2 or *t* test. End point delineates: obesity (categoric).

TABLE II. Multiple linear regression analysis: variables associated with increased BMI values (kg/m^2)

Variable	Estimate	SE	*t* value	CI	*P* value
Age (y)	0.03	0.01	3.29	0.01 to 0.05	.001
GERD	1.00	0.30	3.36	0.42 to 1.58	<.001
Depression	1.40	0.39	3.58	0.63 to 2.17	<.001
Bronchiectasis	−2.48	0.80	−3.12	−4.05 to −0.92	.002
LAMA therapy	0.63	0.29	2.19	0.07 to 1.20	.029
Never smokers	−1.23	0.29	−4.19	−1.81 to −0.66	<.001
FVC (% of predicted)	−0.03	0.01	−3.24	−0.04 to −0.01	.001
FEV_1/FVC (%)	0.06	0.01	6.3	0.04 to 0.09	<.001
ACT score	−0.15	0.03	−5.41	−0.20 to −0.09	<.001

The significant results according to the Bonferroni boundary were included in a multiple linear regression analysis, excluding variables with multicollinearity or high missing value number.

ACT, Asthma Control Test; *BMI*, body mass index; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic antagonist; *SE*, standard error.

TABLE III. Univariate regression analysis of clinically relevant variables with BMI (kg/m^2)

Variable	n	Estimate	*t* value	Correlation coefficient	*P* value
Exacerbations, mean (SD)	1699	0.07	2.02	0.05	.04
ACQ-5 score	1857	0.67	7.17	0.16	<.001
mAQLQ score	1761	−0.82	−7.67	−0.18	<.001
FEV_1 (% of predicted)	2074	−0.01	−0.8	−0.02	.4
DLCO (% of predicted)	973	0.04	3.35	0.11	.001
Maintenance OCS (mg)	2213	0.03	3.02	0.06	.003
Blood eosinophils (G/L)	1506	−0.34	−1.49	−0.04	.14

ACQ-5, Asthma Control Questionnaire-5; *BMI*, body mass index; *DLCO*, diffusing capacity for carbon monoxide; *FEV_1*, forced expiratory volume in 1 second; *mAQLQ*, Mini Asthma Quality of Life Questionnaire; *OCS*, oral corticosteroids; *SD*, standard deviation.

(ISAR) cohort with 39% or the Australian cohort with 45%-46%,[43,44] although similar to the Italian ISAR subgroup.[45,46]

Patients with obesity were similar to several other cohorts including the Severe Asthma Research Program (SARP) study[19,47] in being predominantly middle-aged adults with poor lung function,[14,21,47-49] and showed similarities to cluster analysis phenoptypes marked by obesity, female sex, late onset, and highly symptomatic severe asthma.[24,33,34,47,50,51] A female preponderance in severe, symptomatic asthma with obesity[18] could be due to increased blood estrogen and reduced blood progesterone levels,[21,24] resulting in attenuated airway smooth muscle relaxation and airway inflammation.[1,21] However, BMI is a biased marker of adiposity, as constitutionally lean male patients may be wrongly included in the group with obesity through increased heavy muscle mass.[1,34] Few studies have used other obesity markers such as waist-to-hip ratio and show conflicting results.[6,17]

Corticosteroid use in patients with asthma could contribute to weight gain[1,6,23,48] and worsen the therapeutic morbidity.[10] OCS dose was correlated with BMI in the current study, and OCS-dependent patients with obesity required higher doses of maintenance corticosteroid therapy. In severe asthma, a British registry study detected comparable associations of obesity with more frequent OCS use, but not OCS dose, with the differences perhaps explained by lower OCS use in our cohort and differing definitions.[24] This was further corroborated in another study showing both increased ICS and OCS doses in patients with obesity.[52]

Some studies describe a late-onset nonatopic asthma that develops in patients already affected by obesity and may be resolved with weight loss,[22,26,27] or asthma with obesity and neutrophilia signaling chronic non−type 2 systemic inflammation.[28,48,53] This constellation of phenotypic parameters, in addition to increased neutrophilia, however, might not describe a distinct endotype of asthma but a consequence of inhalative and systemic corticosteroid therapy,[26,27] as corticosteroids increase survival time of neutrophils.[28] In our study, blood neutrophil counts were similarly increased in OCS-dependent patients with and without obesity, whereas no association of blood neutrophilia with higher BMI was detected in the multiple regression. The blood neutrophil and eosinophil counts in our analysis advocate against a defining role within severe asthma pathophysiology of patients with obesity.

Our study shows that patients with obesity did not have reduced blood or sputum eosinophil counts, total IgE, or CRSwNP, in fact displaying a similar level of clinical type 2 inflammation as patients without obesity. Furthermore, obesity had no effect on FeNO levels in the multivariate regression analysis in this cohort (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).[31] Other inflammation markers such as IL6,[54] vitamin D,[55,56] or TNF-α[54,57] were not assessed in the current study. A study in patients with asthma of any severity and with and without obesity showed mostly poor prediction power of all 3 type 2 biomarkers for sputum eosinophilia, with correlations of r = 0.17 to 0.22,[58] and patients with obesity had lower thresholds for all type 2 biomarkers predicted and had no association of blood with sputum eosinophils in that study.[58] However, eosinophilic airway inflammation was similarly present in patients with obesity as in lean or overweight patients, similar to the current study.[58] In clinical practice, in the light of similar eosinophilic airway inflammation in patients of any weight, it is relevant to consider these biomarkers as auxiliary information; however, conditions such as CRSwNP, allergies, or atopy remain an essential decision aid in therapy choice, independent of weight in patients with severe asthma.

The current study confirmed that FVC is inversely associated with BMI as reported in eminent studies of patients with severe asthma and obesity,[24] and participants without asthma,[30] and that the FEV_1/FVC ratio is associated with higher BMI because of the effect on FVC.[9,24,30] In asthma of any severity, a meta-analysis did not detect similarly pronounced associations of obesity with FVC, and differential effects on TLC, with a mean difference within 5% predicted.[29] A small effect of obesity on TLC was also shown by a review of studies in participants without asthma, which reflects the current results in patients with severe asthma.[30] Residual volume (RV) was high in the current severe asthma cohort, but unchanged by obesity. A large study reporting respiratory healthy participants similarly showed no reduction through obesity,[30] in contrast to other studies in patients with less severe asthma.[24,29,59,60] A possible explanation could be that an intact RV and RV/TLC with simultaneously decreased FVC could hint at an additional air trapping aspect in patients with severe asthma and obesity.[30]

TABLE IV. Groupwise comparison of patients with severe asthma separated according to BMI

	BMI category				
Variable	Normal (n = 846)	Overweight (n = 728)	Obesity (n = 406)	Morbid obesity (n = 233)	*P* value
Exacerbations/y	3.0 [1.0, 5.0]	3.0 [2.0, 5.0]	3.0 [2.0, 5.0]	3.0 [2.0, 6.0]	.051
ACQ-5 score	2.4 [1.4, 3.6]	2.8 [1.6, 4.0]	3.0 [1.6, 4.0]	3.2 [2.0, 4.2]	<.001
mAQLQ score	4.2 [3.2, 5.2]	3.8 [2.9, 4.9]	3.5 [2.8, 4.5]	3.5 [2.5, 4.4]	<.001
FEV_1 (% of predicted)	68 [52, 84]	64 [49, 80]	64 [49, 81]	66 [53, 80]	.11
DLCO (% of predicted)	74 [63, 84]	75 [63, 86]	78 [65, 90]	78 [65, 90]	.042
Maintenance OCS (mg)	0.0 [0.0, 5.0]	0.0 [0.0, 7.0]	0.0 [0.0, 5.0]	0.0 [0.0, 6.1]	.14
OCS (mg) (>0 mg)	7.5 [5, 15] (n = 278)	10 [5, 20] (n = 261)	10 [5, 20] (n = 137)	10 [5, 20] (n = 87)	.001

A Kruskal-Wallis test was performed with patients in groups with BMI of <25 (normal weight), 25-30 (overweight), 30-35 (obesity), and ≥35 kg/m^2 (morbid obesity). Data are presented as medians [interquartile range] and *P* values.

ACQ-5, Asthma Control Questionnaire-5; *BMI*, body mass index; *DLCO*, diffusing capacity for carbon monoxide; *FEV_1*, forced expiratory volume in 1 second; *mAQLQ*, Mini Asthma Quality of Life Questionnaire; *OCS*, oral corticosteroids.

$MEF_{50\%}$ and $MEF_{75\%}$ were firmly below predicted values in the current study, but positively associated with obesity, while FEV_1 was unaffected. Prior studies did not see effects of obesity on MEFs in asthma of any severity;[59-61] however, studies were not well comparable, as the current study focused on severe asthma and had a larger cohort. Overall, obesity itself causes mechanical changes in lung function,[30] aggravating asthma without causing further obstructive lung function issues.

DLCO in patients with severe asthma was lower than predicted, yet positively associated with obesity, similar to studies in respiratory healthy participants,[62] and a British cohort study showing an association of BMI with high carbon monoxide transfer quotients.[24] The higher cardiac output and blood volume necessary for increased body weight maintenance could provide an explanation.[62,63]

In univariate analyses, the current study detected an association of BMI with exacerbation rates, confirming the results of other studies where this effect was more pronounced,[24,52,64] including subgroups with early-onset severe asthma[65] and an all-female cohort,[66] and contrary to other studies not detecting associations of obesity with severe exacerbations,[8,56] or asthma control, which was probably due to differences in methodology or cohort characteristics.[64] Frequent exacerbations increase the corticosteroid burden and associated side effects, including weight gain.[13,67] Proinflammatory mediators and mechanical stress through comorbidities link obesity to severe, difficult-to-control asthma.[3,7,9,64]

We showed the association of depression and GERD with obesity, which are known, along with obstructive sleep apnea, to impact asthma pathophysiology and control[8,23] through microaspiration,[3] mechanical effects on lung function, and systemic inflammation.[7,53] Our results confirmed other studies, which additionally showed depression causing the highest impact on quality of life,[3,8,24] as well as cluster phenotypes of older, predominately female subjects with obesity and frequent comorbidities including GERD.[50,51] The current study showed an inverse association of bronchiectasis with obesity, consistent with the British severe asthma cohort.[24] This relation persisted if DLCO was added as a factor to our analysis, and DLCO was independently positively correlated with BMI, as seen in Table E6 in this article's Online Repository at www.jaci-inpractice.org. In the present study, patients with obesity were more frequently ex-smokers or passively exposed, unlike a SARP cohort result, which however excluded patients with high pack-year values or current smokers and performed different analyses.[19,65]

Identifying and treating comorbidities is essential to maximizing disease control;[3] however, the current study confirms the independent impact of increased BMI on asthma control and quality of life,[6,11,24,57,64] which were shown with any asthma severity,[8] or age at asthma onset,[6,65] and less clearly if assessed as visceral obesity by the waist-to-hip ratio.[6,17] Weight loss of as little as 5% body weight was repeatedly reported to significantly improve asthma control, exacerbation rate, and lung function values in patients with severe asthma and overweight or obesity. Clinicians can promote this by adding in-person or remote weight loss interventions to routine examinations.[22,68,69]

The strengths of the GAN are its focus on patients with severe asthma, large cohort size, and meticulous and comprehensive clinical assessments conducted on patient inclusion resulting in a representative and well-characterized real-life study cohort. The limitations of our specific analyses as a registry arise from the definition of obesity. The most predominant definition is based on BMI,[24,29] which can be biased by factors like muscle mass or proportion of visceral fat. Overall, no viable alternative to BMI has emerged to date for registry studies; however, future focus on visceral adipose tissue with other measurements such as waist and hip circumferences or whole-body composition scans is warranted.[70] Another potential limitation is the real-world nature of the study, including patients both with and without obesity on OCS or targeted therapies, which could bias the blood eosinophil count, among other biomarkers. The current analyses were performed with the goal of mitigating the effect of current maintenance OCS therapy; however, recent OCS courses with potential for biomarker alteration were not assessed.

CONCLUSION

In the GAN, a large, real-life, carefully characterized cohort of patients with severe asthma and obesity was associated with sex, age, asthma control, lung function values, therapy, and comorbidities. A similar portfolio of inflammation type 2 markers in patients with and without obesity was detected. The current results do not necessarily support an "asthma in obesity" distinct endotype, as changes in inflammation markers and lung function values might be therapy-induced or influenced by altered breathing mechanics[26,27,29] and cause additional effects on top of the underlying endotype. We postulate that severe asthma in

patients affected by obesity is like—and to be treated just like—in unaffected patients. Most importantly, patients with severe asthma and obesity need to be initiated into weight loss interventions to alleviate the disease burden.[22,68,69]

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REFERENCES

1. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006;110:83-102.
2. Tashiro H, Shore SA. Obesity and severe asthma. Allergol Int 2019;68:135-42.
3. Dixon AE, Holguin F. Metabolic dysfunction and severe asthma. In: Chung KF, Israel E, Gibson PG, editors. Severe Asthma. Sheffield, UK: European Respiratory Society (ERS); 2019.
4. Al Heialy S, Ramakrishnan RK, Hamid Q. Recent advances in the immunopathogenesis of severe asthma. J Allergy Clin Immunol 2022;149:455-65.
5. Buhl R, Bel E, Bourdin A, Dávila I, Douglass JA, FitzGerald JM, et al. Effective management of severe asthma with biologic medications in adult patients: a literature review and international expert opinion. J Allergy Clin Immunol Pract 2022;10:422-32.
6. Barros LL, Souza-Machado A, Correa LB, Santos JS, Cruz C, Leite M, et al. Obesity and poor asthma control in patients with severe asthma. J Asthma 2011;48:171-6.
7. Dias-Junior SA, Reis M, de Carvalho-Pinto RM, Stelmach R, Halpern A, Cukier A. Effects of weight loss on asthma control in obese patients with severe asthma. Eur Respir J 2014;43:1368-77.
8. Vortmann M, Eisner MD. BMI and health status among adults with asthma. Obesity (Silver Spring) 2008;16:146-52.
9. Garcia-Rio F, Alvarez-Puebla MJ, Esteban-Gorgojo I, Barranco P, Olaguibel JM. Obesity and asthma: key clinical questions. J Investig Allergol Clin Immunol 2019;29:262-71.
10. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016;71:339-46.
11. Schatz M, Zeiger RS, Yang S-J, Chen W, Sajjan S, Allen-Ramey F, et al. Prospective study on the relationship of obesity to asthma impairment and risk. J Allergy Clin Immunol Pract 2015;3:560-5.e1.
12. Yang F, Busby J, Heaney LG, Menzies-Gow A, Pfeffer PE, Jackson DJ, et al. Factors associated with frequent exacerbations in the UK Severe Asthma Registry. J Allergy Clin Immunol Pract 2021;9:2691-701.e1.
13. Graff S, Vanwynsberghe S, Brusselle G, Hanon S, Sohy C, Dupont LJ, et al. Chronic oral corticosteroids use and persistent eosinophilia in severe asthmatics from the Belgian severe asthma registry. Respir Res 2020;21:214.
14. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax 2010;65:787-94.
15. Korn S, Milger K, Skowasch D, Timmermann H, Taube C, Idzko M, et al. The German severe asthma patient: baseline characteristics of patients in the German Severe Asthma Registry, and relationship with exacerbations and control. Respir Med 2022;195:106793.
16. Goudarzi H, Konno S, Kimura H, Makita H, Matsumoto M, Takei N, et al. Impact of abdominal visceral adiposity on adult asthma symptoms. J Allergy Clin Immunol Pract 2019;7:1222-9.e5.
17. Musaad SM, Patterson T, Ericksen M, Lindsey M, Dietrich K, Succop P, et al. Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant. J Allergy Clin Immunol 2009;123:1321-7.e12.
18. Wu W, Bang S, Bleecker ER, Castro M, Denlinger L, Erzurum SC, et al. Multiview cluster analysis identifies variable corticosteroid response phenotypes in severe asthma. Am J Respir Crit Care Med 2019;199:1358-67.
19. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. J Allergy Clin Immunol Pract 2018;6:545-54.e4.
20. Jenkins CR, Boulet L-P, Lavoie KL, Raherison-Semjen C, Singh D. Personalized treatment of asthma: the importance of sex and gender differences. J Allergy Clin Immunol Pract 2022;10:963-71.e3.
21. Senna G, Latorre M, Bugiani M, Caminati M, Heffler E, Morrone D, et al. Sex differences in severe asthma: results from Severe Asthma Network in Italy-SANI. Allergy Asthma Immunol Res 2021;13:219-28.
22. Gaffin JM, Castro M, Bacharier LB, Fuhlbrigge AL. The role of comorbidities in difficult-to-control asthma in adults and children. J Allergy Clin Immunol Pract 2022;10:397-408.
23. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. Respirology 2017;22:651-61.
24. Gibeon D, Batuwita K, Osmond M, Heaney LG, Brightling CE, Niven R, et al. Obesity-associated severe asthma represents a distinct clinical phenotype: analysis of the British Thoracic Society Difficult Asthma Registry Patient cohort according to BMI. Chest 2013;143:406-14.
25. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218-24.
26. Nguyen LT, Lim S, Oates T, Chung KF. Increase in airway neutrophils after oral but not inhaled corticosteroid therapy in mild asthma. Respir Med 2005;99:200-7.
27. Saffar AS, Ashdown H, Gounni AS. The molecular mechanisms of glucocorticoids-mediated neutrophil survival. Curr Drug Targets 2011;12:556-62.
28. Crisford H, Sapey E, Rogers GB, Taylor S, Nagakumar P, Lokwani R, et al. Neutrophils in asthma: the good, the bad and the bacteria. Thorax 2021;76:835-44.
29. Forno E, Han Y-Y, Mullen J, Celedón JC. Overweight, obesity, and lung function in children and adults—a meta-analysis. J Allergy Clin Immunol Pract 2018;6:570-581.e10.
30. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med 2018;12:755-67.
31. Bal C, Idzko M, Škrgat S, Koch A, Milger K, Schulz C, et al. Fraction of exhaled nitric oxide is associated with disease burden in the German Asthma Net severe asthma cohort. Eur Respir J 2022;59:2101233.
32. Al Khathlan N, Salem AM. The effect of adiposity markers on fractional exhaled nitric oxide (FeNO) and pulmonary function measurements. Int J Gen Med 2020;13:955-62.
33. Denton E, Price DB, Tran TN, Canonica GW, Menzies-Gow A, FitzGerald JM, et al. Cluster analysis of inflammatory biomarker expression in the international severe asthma registry. J Allergy Clin Immunol Pract 2021;9:2680-8.e7.
34. Milger K, Korn S, Buhl R, Hamelmann E, Herth FJ, Gappa M, et al. Age- and sex-dependent differences in patients with severe asthma included in the German Asthma Net cohort. Respir Med 2020;162:105858.
35. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
36. Lommatzsch M, Suhling H, Korn S, Bergmann KC, Schreiber J, Bahmer T, et al. Safety of combining biologics in severe asthma: asthma-related and unrelated combinations. Allergy 2022;77:2839-43.
37. Lemiere C, Taillé C, Lee JK, Smith SG, Mallett S, Albers FC, et al. Impact of baseline clinical asthma characteristics on the response to mepolizumab: a post hoc meta-analysis of two Phase III trials. Respir Res 2021;22:184.
38. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128-41.
39. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47:76-83.
40. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117:549-56.
41. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.
42. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806-8.
43. Harvey ES, Langton D, Katelaris C, Stevens S, Farah CS, Gillman A, et al. Mepolizumab effectiveness and identification of super-responders in severe asthma. Eur Respir J 2020;55:1902420.
44. Gibson PG, Reddel H, McDonald VM, Marks G, Jenkins C, Gillman A, et al. Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. Intern Med J 2016;46:1054-62.

45. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. Chest 2020;157:790-804.
46. Maio S, Baldacci S, Bresciani M, Simoni M, Latorre M, Murgia N, et al. RItA: the Italian severe/uncontrolled asthma registry. Allergy 2018;73:683-95.
47. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 2010;181:315-23.
48. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy 2012;67:1060-8.
49. Graff S, Brusselle G, Hanon S, Sohy C, Dupont L, Peche R, et al. Anti-interleukin-5 therapy is associated with attenuated lung function decline in severe eosinophilic asthma patients from the Belgian Severe Asthma Registry. J Allergy Clin Immunol Pract 2022;10:467-77.
50. Patrawalla P, Kazeros A, Rogers L, Shao Y, Liu M, Fernandez-Beros ME, et al. Application of the asthma phenotype algorithm from the Severe Asthma Research Program to an urban population. PLoS One 2012;7:e44540.
51. Baan EJ, de Roos EW, Engelkes M, de Ridder M, Pedersen L, Berencsi K, et al. Characterization of asthma by age of onset: a multi-database cohort study. J Allergy Clin Immunol Pract 2022;10:1825-34.e8.
52. Tang M, Henderson RJ, Holbrook JT, Que LG, Mathews AM, Wise RA, et al. Does obesity increase respiratory tract infections in patients with asthma? J Allergy Clin Immunol Pract 2019;7:954-61.e6.
53. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol 2018;141:1169-79.
54. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir Med 2016;4:574-84.
55. Korn S, Hübner M, Jung M, Blettner M, Buhl R. Severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency. Respir Res 2013;14:25.
56. Schatz M, Zeiger RS, Zhang F, Chen W, Yang S-J, Camargo CA Jr. Overweight/obesity and risk of seasonal asthma exacerbations. J Allergy Clin Immunol Pract 2013;1:618-22.
57. Oliveira MJ, Vieira M, Coutinho D, Ladeira I, Pascoal I, Ferreira J, et al. Severe asthma in obese patients: improvement of lung function after treatment with omalizumab. Pulmonology 2019;25:15-20.
58. Lugogo N, Green CL, Agada N, Zhang S, Meghdadpour S, Zhou R, et al. Obesity's effect on asthma extends to diagnostic criteria. J Allergy Clin Immunol 2018;141:1096-104.
59. Lessard A, Turcotte H, Cormier Y, Boulet L-P. Obesity and asthma: a specific phenotype? Chest 2008;134:317-23.
60. Deesomchok A, Fisher T, Webb KA, Ora J, Lam YM, Lougheed MD, et al. Effects of obesity on perceptual and mechanical responses to bronchoconstriction in asthma. Am J Respir Crit Care Med 2010;181:125-33.
61. Pisi R, Aiello M, Tzani P, Marangio E, Olivieri D, Pisi G, et al. Overweight is associated with airflow obstruction and poor disease control but not with exhaled nitric oxide change in an asthmatic population. Respiration 2012;84:416-22.
62. Saydain G, Beck KC, Decker PA, Cowl CT, Scanlon PD. Clinical significance of elevated diffusing capacity. Chest 2004;125:446-52.
63. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol (1985) 2010;108:206-11.
64. Juel CT, Ulrik CS. Obesity and asthma: impact on severity, asthma control, and response to therapy. Respir Care 2013;58:867-73.
65. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. J Allergy Clin Immunol 2011;127:1486-93.e2.
66. Von Behren J, Lipsett M, Horn-Ross PL, Delfino RJ, Gilliland F, McConnell R, et al. Obesity, waist size and prevalence of current asthma in the California Teachers Study cohort. Thorax 2009;64:889-93.
67. Moitra S, Carsin A-E, Abramson MJ, Accordini S, Amaral AFS, Anto J, et al. Long-term effect of asthma on the development of obesity among adults: an international cohort study. ECRHS. Thorax 2023;78:128-35.
68. Johnson O, Gerald LB, Harvey J, Roy G, Hazucha H, Large C, et al. An online weight loss intervention for people with obesity and poorly controlled asthma. J Allergy Clin Immunol Pract 2022;10:1577-86.e3.
69. Kolinsky NC, Weare-Regales N, Lockey RF. A practical approach to assist asthmatics to lose weight. J Allergy Clin Immunol Pract 2021;9:2245-54.
70. Ofenheimer A, Breyer-Kohansal R, Hartl S, Burghuber OC, Krach F, Schrott A, et al. Reference charts for body composition parameters by dual-energy X-ray absorptiometry in European children and adolescents aged 6 to 18 years—results from the Austrian LEAD (Lung, hEart, sociAl, boDy) cohort. Pediatr Obes 2021;16:e12695.

ONLINE REPOSITORY

TABLE E1. Associations between BMI as a linear variable and baseline parameters

Variable	Category	Category Yes—BMI (kg/m^2)	Category No—BMI (kg/m^2)	*t* value	Category: Yes vs No	
					P value‡	Point estimate and 95% CI‡
Female (% of total)*	Yes/No	27.38	27.56	0.73	.5	0.18; −0.31 to 0.67
CRSwNP (% of total)*	Yes/No	27.36	27.65	1.11	.3	0.29; −0.22 to 0.80
Bronchiectasis (% of total)*	Yes/No	25.00	27.57	4.01	<.001	2.57; 1.30 to 3.85
GERD (% of total)*	Yes/No	28.50	26.98	−5.54	<.001	−1.52; −2.05 to −0.98
Depression (% of total)*	Yes/No	29.21	27.20	−5.18	<.001	−2.01; −2.77 to −1.24
COPD (% of total)*	Yes/No	27.96	27.45	−1.15	.3	−0.51; −1.39 to 0.37
Never smoking (% of total)*	Yes/No	26.44	28.08	6.27	<.001	1.64; 1.13 to 2.15
Passive smoking (% of total)*	Yes/No	28.18	27.31	−2.63	.009	−0.87; −1.51 to −0.22
Family history of asthma (% of total)*	Yes/No	27.26	28.20	2.16	.032	0.94; 0.08 to 1.79
Frequent exacerbations (% of total)*,†	Yes/No	27.70	27.26	−1.29	.2	−0.45; −1.12 to 0.23
Severe exacerbations (% of total)*	Yes/No	27.82	27.31	−1.77	.08	−0.52; −1.09 to 0.06
Near-lethal exacerbations (% of total)*	Yes/No	27.64	27.59	−0.08	.9	−0.05; −1.09 to 1.00
LAMA therapy*	Yes/No	27.94	26.84	−4.26	<.001	−1.10; −1.60 to −0.59
Beclomethasone equivalent ≥1000 μg/d*	≥1000 μg/d	27.59	27.39	−0.79	.4	−0.20; −0.71 to 0.30
Beclomethasone equivalent ≥2000 μg/d*	≥2000 μg/d	27.84	27.36	−1.55	.1	−0.48; −1.09 to 0.13
Maintenance OCS use (% of total)*	Yes/No	27.78	27.32	−1.69	.09	−0.46; −0.99 to 0.07

Variable	n	Estimate	*t* value	*P* value	Correlation coefficients
pO_2 (mm Hg)	983	−0.08	−4.32	<.001	−0.14
pCO_2 (mm Hg)	982	0.01	0.31	.8	0.01
TLC (% of predicted)	774	−0.05	−3.90	<.001	−0.14
RV/TLC (%)	751	0.01	0.39	.7	0.01
Total IgE (IU/mL)	937	0.00	1.02	.3	0.03
MEF25 (% of predicted)	1806	0.00	0.41	.7	0.01
MEF50 (% of predicted)	1906	0.01	3.20	.001	0.07
MEF75 (% of predicted)	1638	0.01	2.22	.027	0.06
Age (y)	2213	0.03	4.16	<.001	0.09
Age at asthma onset	1664	0.01	1.82	.07	0.05
FVC (% of predicted)	2048	−0.03	−4.66	<.001	−0.1
FEV_1/FVC (%)	1976	0.04	3.72	<.001	0.08
FeNO (ppb)	1129	−0.01	−2.23	.026	−0.07
ACT score	2213	−0.19	−8.04	<.001	−0.18
Blood neutrophils	1496	0.34	5.42	<.001	0.14

To address statistical clarity and completeness, Tables E1 and E2 are shown as the counterparts to Tables I and II.

ACT, Asthma Control Test; *BMI*, body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *DLCO*, diffusing capacity for carbon monoxide; *FeNO*, fraction of exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic antagonist; *MEF*, mid-expiratory flow; *OCS*, oral corticosteroids; *pCO_2*, partial pressure of carbon dioxide; *pO_2*, partial pressure of oxygen; *RV*, residual volume; *TLC*, total lung capacity.

*Chi-square test.

†Frequent exacerbations were defined as ≥2 exacerbations/year in the past year.

‡*P*-values with CI were for the mean difference between groups or categories from the Chi-square or t-test. Endpoint delineates: respective parameter, category (Yes/No or ≥1000 μg/d or ≥2000 μg/d)

TABLE E2. Multiple linear regression analysis: parameters associated with obesity (BMI $\geq$30 kg/m^2)

Variable	Odds ratio	95% CI	*P* value
Age (y)	1.005	1.00, 1.01	.2
GERD	1.331	1.06, 1.67	.012
Depression	1.607	1.22, 2.13	.001
Bronchiectasis	0.722	0.37, 1.40	.3
LAMA therapy	1.266	1.01, 1.59	.041
Never smokers	0.741	0.59, 0.94	.012
FVC (% of predicted)	0.987	0.98, 0.99	<.001
FEV_1/FVC (%)	1.026	1.02, 1.03	<.001
ACT score	0.958	0.94, 0.98	<.001

ACT, Asthma Control Test; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic antagonist.

TABLE E3. Multiple linear regression analysis in adults: parameters associated with increased BMI values (kg/m^2) (n = 2102)

Parameter	Estimate	*t* value	*P* value
GERD	0.99	3.29	.001
Depression	1.34	3.40	.001
Bronchiectasis	−2.46	−3.06	.002
LAMA therapy	0.63	2.13	.033
Never-smokers	−0.92	−3.05	.002
FVC (% of predicted)	−0.03	−3.36	.001
FEV_1/FVC (%)	0.07	6.70	<.001
ACT score	−0.13	−4.75	<.001

ACT, Asthma Control Test; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *LAMA*, long-acting muscarinic antagonist.

TABLE E4. Blood neutrophilia in patients separated by obesity and OCS dependence

Patients separated by obesity	*t* test, *P*	OCS dependent	No daily OCS	n
In nonobese patients	<.001	6.48 (2.81) G/L	4.63 (1.90) G/L	1066
In obese patients	<.001	6.72 (2.80) G/L	5.35 (2.23) G/L	430
Patients separated by OCS dependence	*t* test, *P*	Obese	Nonobese	n
In non−OCS-dependent patients	<.001	5.35 (2.23) G/L	4.63 (1.90) G/L	925
In OCS-dependent patients	.3	6.72 (2.80) G/L	6.48 (2.81) G/L	571

Patients who did not take daily OCS showed a significant association between obesity and neutrophilia. OCS intake increased blood neutrophil numbers to a similar degree in obese and nonobese patients.
OCS, Oral corticosteroid.

TABLE E5. Multiple linear regression analysis: parameters associated with increased BMI values (kg/m^2), explicit inclusion of FeNO (exclusion reason: high missing number of values)

Parameter	Estimate	Standard error	*t* value	*P* value
FeNO (ppb)	−0.01	0.005	−1.17	.244
GERD	1.23	0.44	2.79	.005
Bronchiectasis	−3.17	1.35	−2.35	.019
Never smokers	−1.24	0.45	−2.74	.006
FVC (% of predicted)	−0.05	0.01	−3.95	<.001
FEV1/FVC (%)	0.06	0.02	3.41	<.001
ACQ-5 score	0.48	0.16	3.07	.002

ACQ-5, Asthma Control Questionnaire-5; *BMI*, body mass index; *FeNO*, fraction of exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease.

TABLE E6. Multiple linear regression analysis: parameters associated with increased BMI values (kg/m^2), explicit inclusion of DLCO (exclusion reason: high missing number of values)

Parameter	Estimate	Standard error	*t* value	*P* value
DLCO (% of predicted)	0.06323	0.01335	4.738	.000
GERD	1.17	0.4617	2.534	.011
Bronchiectasis	−3.78717	1.39886	−2.707	.007
Never smokers	−1.25069	0.47574	−2.629	.009
FVC (% of predicted)	−0.04062	0.01339	−3.034	.002
FEV_1/FVC (%)	0.03837	0.01684	2.279	.023
ACQ-5 score	0.56182	0.15934	3.526	.000
Depression	1.56304	0.6144	2.544	.011
Blood neutrophils (G/L)	0.28839	0.09188	3.139	.002

ACQ-5, Asthma Control Questionnaire-5; *BMI*, body mass index; *DLCO*, diffusing capacity for carbon monoxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease.