



Obesity-Associated Severe Asthma Represents a Distinct Clinical Phenotype

Analysis of the British Thoracic Society Difficult Asthma Registry Patient Cohort According to BMI

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Background: Obesity has emerged as a risk factor for the development of asthma and it may also influence asthma control and airway inflammation. However, the role of obesity in severe asthma remains unclear. Thus, our objective was to explore the association between obesity (defined by BMI) and severe asthma.

Methods: Data from the British Thoracic Society Difficult Asthma Registry were used to compare patient demographics, disease characteristics, and health-care utilization among three BMI categories (normal weight: 18.5-24.99; overweight: 25-29.99; obese: ≥ 30) in a well-characterized group of adults with severe asthma.

Results: The study population consisted of 666 patients with severe asthma; the group had a median BMI of 29.8 (interquartile range, 22.5-34.0). The obese group exhibited greater asthma medication requirements in terms of maintenance corticosteroid therapy (48.9% vs 40.4% and 34.5% in the overweight and normal-weight groups, respectively), steroid burst therapy, and short-acting β_2 -agonist use per day. Significant differences were seen with gastroesophageal reflux disease (53.9% vs 48.1% and 39.7% in the overweight and normal weight groups, respectively) and proton pump inhibitor use. Bone density scores were higher in the obese group, while pulmonary function testing revealed a reduced FVC and elevated carbon monoxide transfer coefficient. Serum IgE levels decreased with increasing BMI and the obese group was more likely to report eczema, but less likely to have a history of nasal polyps.

Conclusions: Patients with severe asthma display particular characteristics according to BMI that support the view that obesity-associated severe asthma may represent a distinct clinical phenotype.

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Abbreviations: FENO = fraction of exhaled nitric oxide; GERD = gastroesophageal reflux disease; IQR = interquartile range; PPI = proton pump inhibitor; SABA = short-acting β_2 -adrenergic agonist

Obesity has been identified as a major risk factor for the development of asthma.¹ This is supported by prospective epidemiologic studies, almost all of which noted that obesity antedated a diagnosis of asthma.²⁻⁴ As BMI increases, the relative risk of developing asthma also increases.⁵ In addition, increasing BMI is associated with a reduced asthma-related quality of life, more frequent exacerbations, and a greater severity and frequency of respiratory symptoms.⁶⁻⁸

The link between the two appears to be multifactorial and is likely to involve a combination of in utero

conditions, genetic factors, comorbidities, and inflammation secondary to excess adipose tissue.⁹ Obesity-associated asthma may represent a distinct clinical phenotype,¹ characterized by later onset, female preponderance, and more symptoms than classic atopic asthma, with a relatively low degree of eosinophilic inflammation.¹⁰

There is evidence to support the presence of steroid resistance in patients with asthma who are overweight or obese. This stems from post hoc analyses of clinical trial data that have associated increasing BMI

with a reduced response to inhaled corticosteroids,¹¹⁻¹³ and by an in vitro study on peripheral blood mononuclear cells that found patients with asthma who were overweight or obese exhibited a reduced response to glucocorticoids.¹⁴

BMI is a simple index of weight for height and is calculated by dividing one's weight in kilograms by the square of one's height in meters (kg/m²). A BMI ≥ 25 is considered overweight, while people with BMI ≥ 30 are classified as obese. BMI is particularly useful because it is standardized, calculated in the same way for both sexes, and for adults of all ages.

The exact role of obesity in the pathophysiology of asthma and the relationship to severe asthma remains unclear. The aim of this study was to explore this relationship in a large, well-characterized population with refractory asthma by using data from the British Thoracic Society Difficult Asthma Registry to compare the demographics, clinical features, markers of inflammation, and health-care utilization in patients categorized by their BMI.

MATERIALS AND METHODS

The British Thoracic Society Difficult Asthma Network established a National Registry for dedicated UK Difficult Asthma Services in 2006. The aims were to define clinical phenotypes in subjects with well-characterized severe asthma, to facilitate research into the assessment and clinical management of difficult asthma, and to standardize specialist clinical services.¹⁵ There are currently seven dedicated Specialist Difficult Asthma Services submitting data to the British Thoracic Society Difficult Asthma Registry. The British Thoracic Society Difficult Asthma Registry is hosted online by Dendrite Clinical Systems Ltd and admits password-protected, anonymous data after fully informed written consent has been obtained. Ethical approval for the British Thoracic Society Difficult Asthma Registry was obtained from

the Office for Research Ethics Committees Northern Ireland (number 10/NIR02/37).

Patients at all centers underwent a multidisciplinary, systematic assessment of their asthma. Although there is not a standardized method of assessing patients with severe asthma in the United Kingdom at present, all patients underwent multiple investigations, including a thorough medical history and examination, pulmonary function tests, allergy assessment (skin-prick testing and/or radioallergen sorbent test), blood tests (incorporating serum eosinophil count and IgE), and bone densitometry. Investigations were performed according to protocols at individual centers and lung function % predicted values were calculated centrally. Skin-prick testing results were included for aeroallergens tested at all of the centers.

Subjects were entered into the British Thoracic Society Difficult Asthma Registry in a nonselected manner and were included if they fulfilled the American Thoracic Society definition of refractory asthma¹⁶ and had a recorded BMI. Patients were then divided into three groups according to their BMI (normal weight: 18.5-24.99; overweight: ≥ 25 ; obese: ≥ 30).

Statistical Analysis

Anonymous data were stored using Translational Medicine Mart, or tranSMART (tranSMART Consortium), a powerful, new, translational-informatics enterprise data warehouse developed by Johnson & Johnson in 2009. Statistical analysis was performed using GraphPad PRISM 5 (GraphPad Software Inc). BMI groups were compared using one-way analysis of variance and the Kruskal-Wallis test, with appropriate post hoc comparisons. Categorical variables were compared using χ^2 analysis with exact tests as appropriate.

RESULTS

The study population consisted of 666 patients with severe asthma. The median BMI was 29.8 (interquartile range [IQR], 22.5-34.0); 48.3% of the patients were obese, 29.3% were overweight, and 22.4% were of normal weight.

Group data comparisons and comparisons among BMI categories are shown in Tables 1-4. Values are presented as percent obese compared with percent overweight and percent normal weight.

Demographics

There was a predominance of female patients (65%) and white patients (91.1%) in all BMI groups (Table 1). Patients who were obese and had severe asthma were less likely to be in full-time employment than patients who were overweight or normal weight (34.9% compared with 39.3% and 44.2%, respectively), and this was more likely to be due to asthma-related ill health (33.3% vs 23.6% and 19.6%, respectively). The obese group was more likely to have a basic level of education (31.1% vs 20.7% and 17.0%, respectively) and appeared less likely to have achieved an advanced (19.7% vs 17.0% and 35.8%, respectively) or graduate level of education (9.6% vs 17.0% and 10.4%, respectively). More patients who were obese and had severe asthma were current smokers (10.5%) or ex-smokers (31.3%) than patients in the overweight

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Table 1—Patient Demographic Data

Characteristics	Overall	BMI			P Value ^a
		18.50-24.99	25.00-29.99	≥ 30.00	
Patients, No. (%)	666	149 (22.4)	195 (29.3)	322 (48.3)	...
BMI, median (IQR)	29.8 (22.5-34.0)	22.8 (18.9-24.9)	27.4 (26.3-28.5)	34.2 (31.8-38.9)	...
Female patients	435 (65)	107 (72)	111 (57)	217 (67)	.009
Race					
White	607 (91.2)	133 (89.3)	173 (89.6)	301 (94.4)	.31
Asian	36 (5.5)	12 (8.1)	13 (6.7)	11 (3.4)	...
Black	8 (1.2)	1 (0.7)	3 (1.6)	4 (1.3)	...
Other	10 (1.5)	3 (2.0)	4 (2.1)	3 (0.9)	...
Age at assessment, y	45.0 (37.0-54.0)	44.0 (34.0-54.0)	46.0 (38.0-57.0)	45.0 (38.0-54.0)	.3
Age at diagnosis, y	18.0 (3.0-35.0)	15.0 (3.0-35.0)	18.0 (3.0-36.0)	18.0 (4.0-34.0)	.94
Smoking status					
Never	394 (60.9)	92 (63.9)	120 (63.2)	182 (58.1)	.45
Ex-smoker	195 (30.1)	39 (27.1)	58 (30.5)	98 (31.3)	...
Current smoker	58 (9.0)	13 (9.0)	12 (6.3)	33 (10.5)	...
Ex-smoker or current smoker	253 (39.1)	52 (36.1)	70 (36.8)	131 (41.7)	.38
Smoking, median (IQR), pack-y	12 (5-26)	10 (4.3-23.8)	8.5 (5-20)	15 (5-30)	.08
Working status					
Full time	246 (38.2)	61 (44.2)	75 (39.3)	110 (34.9)	.0051
Not working, asthma related	177 (27.5)	27 (19.6)	45 (23.6)	105 (33.3)	...
Not working, other cause	176 (27.3)	38 (27.5)	62 (32.5)	76 (24.1)	...
Part time, asthma related	21 (3.3)	4 (2.9)	8 (4.2)	9 (2.9)	...
Part time, other cause	24 (3.7)	8 (5.8)	1 (0.5)	15 (4.8)	...
Educational achievement ^b					
Basic	117 (24.9)	18 (17.0)	28 (20.7)	71 (31.1)	.0016
Intermediate	165 (35.2)	32 (30.2)	52 (38.5)	81 (35.5)	...
Advanced	106 (22.6)	38 (35.8)	23 (17.0)	45 (19.7)	...
Graduate	56 (11.9)	11 (10.4)	23 (17.0)	22 (9.6)	...
Postgraduate	25 (5.3)	7 (6.6)	9 (6.7)	9 (3.9)	...
Family history of asthma	358 (55.2)	80 (54.4)	102 (54.5)	176 (55.9)	.91
Evidence of poor adherence	86 (13.3)	21 (14.9)	19 (10.1)	46 (14.6)	.3

Column 2 data are given as No. (%) unless otherwise indicated; age and BMI data are given as median (IQR). IQR = interquartile range; GCSE = General Certificate of Secondary Education; GNVQ = General National Vocational Qualification; NVQ = National Vocational Qualification.

^aBetween-group comparisons for continuous variables were made using the Kruskal-Wallis test; χ^2 exact testing was used for categorical variables.

^bBasic: level 1 NVQ, GCSE D-G, Foundation GNVQ; Intermediate: level 2 NVQ, 5 GCSE A*-C, Intermediate GNVQ; Advanced: level 3 NVQ, AS & A level, Advanced GNVQ; Graduate: level 4 NVQ, Graduate studies; Postgraduate: level 5 NVQ, Postgraduate studies.

group (6.3% and 30.5%, respectively) or normal-weight group (9% and 27.1%, respectively), although this did not reach statistical significance.

Medical History and Atopy

Patients who were obese and had severe asthma were more likely to report a history of eczema (31.9% vs 23.9% of the overweight group and 22.6% of the normal-weight group), gastroesophageal reflux disease (GERD) (53.9% vs 48.1% and 39.7%, respectively), and to have a documented, abnormal pH profile. Nasal polyposis (10.7% vs 17.4% and 18.4%, respectively) and previous nasal surgery were both reported less frequently with increasing BMI (Table 2).

Increasing BMI was associated with a lower *Aspergillus* sensitization (either a positive radioallergosorbent or skin-prick test) and a trend toward lower sensitization to house dust mites, cats, and mixed grasses (Table 2). Serum IgE levels were lower in the

overweight (median, 144; IQR, 46-384) and obese groups (median, 119; IQR, 46-418) compared with the normal BMI group (median, 266; IQR, 83-480) (Table 4).

Medications and Health-care Utilization

The use of maintenance oral steroids (48.9% of the obese group compared with 40.4% of the overweight and 34.5% of the normal-weight groups) and rescue courses of steroids over the preceding year were higher in the obese group. Nebulizer use, short-acting β_2 -adrenergic agonist (SABA) use per day, and proton pump inhibitor (PPI) use (45.4% of the obese group vs 30.7% of the overweight and 29.3% of the normal-weight groups) were all increased with increasing BMI. An insufficient number of patients were on steroid-sparing agents or anti-IgE treatment at the time of referral to specialist services for any meaningful results to be generated (Table 3). No significant difference

Table 2—Medical History and Allergen Testing

Medical History and Allergen Testing	Overall	BMI			P Value ^a
		18.50-24.99	25.00-29.99	≥ 30.00	
Patients, No. (%)	666	149 (22.4)	195 (29.3)	322 (48.3)	...
BMI, median (IQR)	29.8 (22.5-34.0)	22.8 (18.9-24.9)	27.4 (26.3-28.5)	34.2 (31.8-38.9)	...
Medical history					
Prior history of atopy	410 (62.6)	93 (63.7)	116 (61.4)	201 (62.8)	.9
Perennial rhinitis	225 (34.2)	51 (34.7)	68 (35.6)	106 (33.2)	.85
Seasonal rhinitis	263 (40.4)	57 (38.5)	75 (39.7)	131 (41.7)	.78
Eczema	178 (27.3)	33 (22.6)	45 (23.9)	100 (31.9)	<.05
Nasal polyps	94 (14.4)	27 (18.4)	33 (17.4)	34 (10.7)	.03
Prior nasal surgery	100 (16.3)	26 (17.7)	37 (19.8)	37 (11.7)	.036
GERD	321 (49.1)	59 (39.7)	91 (48.1)	171 (53.9)	.018
Prior EGD	27 (4.2)	5 (3.5)	8 (4.3)	14 (4.5)	.88
Prior pH profile (abnormal profile)	57 (30)	11 (2)	17 (11)	29 (17)	.036
Aspirin sensitivity	74 (11.7)	20 (14.1)	22 (11.6)	32 (10.7)	.59
Significant catamenial asthma	39 (9.0)	11 (10.6)	10 (9.3)	18 (8.1)	.76
Allergen testing					
Domestic exposures, pets	219 (34.2)	50 (34.7)	59 (31.4)	110 (35.7)	.61
<i>Aspergillus</i> ^b	234 (47.3)	65 (58.6)	68 (46.3)	101 (42.6)	.02
House dust mite ^b	300 (67.1)	68 (70.8)	90 (69.8)	142 (64.0)	.37
Cat ^b	256 (57.4)	59 (62.8)	75 (57.7)	122 (55.5)	.48
Dog ^b	237 (53.5)	50 (55.6)	71 (52.6)	116 (53.2)	.9
Mixed grasses ^b	238 (54.8)	59 (63.4)	66 (54.1)	113 (51.6)	.15

Data given as No. (%) except all BMI data, which are given as median (%), unless otherwise indicated. EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease. See Table 1 legend for expansion of other abbreviation.

^aBetween-group comparisons were made using χ^2 exact analysis.

^bThe data presented are for subjects with either a positive radioallergosorbent test or skin-prick test.

was noted in the number of previous ICU admissions, ED admissions, or unscheduled visits over the preceding 12 months among BMI groups.

Lung Function and Radiology

The obese group had a reduced mean prebronchodilator FVC (80.1%; 95% CI, 78.0-82.3) compared with both the overweight (86.7%; 95% CI, 83.7-89.8) and normal-weight groups (86.2.0%; 95% CI, 82.8-89.6). In those subjects for whom pre- and postbronchodilator study data were available, FVC was reduced in the obese group compared with the overweight group. In contrast, the mean FEV₁/FVC ratio was higher in the obese group (63.5%; 95% CI, 61.5-65.4) than the overweight group (59.3%; 95% CI, 56.6-61.9). The mean carbon monoxide transfer coefficient was greater in the obese group (104.5%; 95% CI, 102.1-106.9) than the normal weight group (97.0%; 95% CI, 93.5-100.7). The mean proportion of CT scans reported as normal by radiologists appeared to increase with BMI (20.9% in the obese group vs 15.1% and 13.1% in the overweight and normal-weight groups, respectively). Central bronchiectasis was reported less often in the obese group (6.7% vs 12.6% and 17.6%, in the overweight and normal-weight groups, respectively), although this did not achieve statistical significance (Table 4).

Inflammatory Markers and Bone Densitometry

No difference was seen in baseline peripheral blood eosinophil or sputum eosinophil counts among the groups. No significant difference in the level of fraction of exhaled nitric oxide (FENO) was seen among the groups.

Bone densitometry revealed a trend toward greater T scores at the lumbar spine with increasing BMI. The normal-weight group exhibited a lower T score at the femoral neck (-1.02 ± 1.21) compared with the overweight and obese groups (-0.32 ± 1.13 and $+0.074 \pm 1.19$, respectively).

DISCUSSION

Obesity is frequently encountered in severe asthma and was seen in just under one-half of this cohort compared with almost a quarter of the UK population aged ≥ 16 years.¹⁷ Determining whether obesity is a comorbidity affecting pathophysiology and response to therapy or secondary to disease-driven inactivity and/or systemic steroid therapy is often unclear.

The patients with severe asthma analyzed in this cohort were predominantly women, and the median BMI was just below the obese range. This compares with other cohorts of patients with severe asthma such as those in TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment

Table 3—Medications and Health-care Utilization

Medications and Health-care Utilization	BMI				P Value ^a
	Overall	18.50-24.99	25.00-29.99	≥ 30.00	
Patients, No. (%)	666	149 (22.4)	195 (29.3)	322 (48.3)	...
BMI, median (IQR)	29.8 (22.5-34.0)	22.8 (18.9-24.9)	27.4 (26.3-28.5)	34.2 (31.8-38.9)	...
Medications					
PPI use	244/654 (37.3)	43/147 (29.3)	58/192 (30.7)	143/315 (45.4)	.0002
Oral steroids, maintenance use	286/662 (43.2)	51/148 (34.5)	78/193 (40.4)	157/321 (48.9)	.009
Oral steroid, dose, median (range), mg	15 (10-20)	10 (10-20)	10 (10-20)	15 (10-22.5)	.19
Patients requiring rescue courses of steroids in past y	538/602 (89.4)	112/136 (82.4)	160/174 (92.0)	266/292 (91.1)	.01
Rescue courses of steroids in past y	4 (2.0-7.0)	4 (1.30-6.0)	4 (2.0-6.0)	5 (2.0-8.0)	.01
SABA use/d	8 (4.0-10.0)	6 (3.0-10.0)	8 (4.0-10.0)	8 (4.0-10.0)	.0084
Nebulizer use	314 (47.9)	58 (39.7)	89 (46.4)	167 (52.5)	.03
Beclomethasone equivalent dose, median (range), µg	2,000 (1,600-2,000)	2,000 (1,500-2,000)	2,000 (1,000-2,000)	2,000 (1,600-2,000)	0.015
Leukotriene receptor antagonists	303 (46.0)	61 (41.5)	82 (42.7)	160 (50.2)	0.12
Antihistamines	193 (29.4)	45 (30.4)	54 (28.4)	94 (29.6)	0.92
Nasal steroids	184 (27.9)	39 (26.4)	57 (29.7)	88 (27.5)	0.78
Theophylline	262 (39.7)	56 (38.1)	73 (37.8)	133 (41.6)	0.64
Steroid-sparing medications	23/664	4	6	13	0.61
None	628	142	181	305	...
Methotrexate	12	1	2	9	...
Cyclosporin	5	3	1	1	...
Azathioprine	4	0	1	3	...
Mycophenolate mofetil	1	...	1	...	...
Other	1	...	1	...	...
Anti-IgE treatment	15/652	4	3	8	0.72
Health-care utilization, No. (range)					
Unscheduled visits in past 12 mo	4 (2-6)	3.5 (2-6)	4 (2-6)	4 (2-7)	0.44
Admissions in past 12 mo	0 (0-2)	0 (0-2)	1 (0-2)	0 (0-2)	0.41
Total ICU admissions to date	0 (0-20)	0 (0-12)	0 (0-10)	0 (0-20)	0.94

Data given as No. (%), unless otherwise indicated. IQR = interquartile range; PPI = proton pump inhibitor; SABA = short-acting β_2 -adrenergic agonist. See Table 1 legend for expansion of other abbreviation.

^aBetween-group comparisons for continuous variables were made using the Kruskal-Wallis; χ^2 exact testing was used for categorical variables.

Regimens study) (adult mean BMI, 30.4)¹⁸ and is higher than in the ENFUMOSA (European Network for Understanding Mechanisms of Severe Asthma) cohort (male mean BMI, 26.5; female mean BMI, 27.2).¹⁹ The majority (77.6%) of patients in this cohort had a BMI ≥ 25 and just under half had a BMI ≥ 30 .

The overall percentage of current smokers in this cohort (9%) is lower than the rates in patients with asthma of all severities in the UK (slightly $< 25\%$)²⁰ and in the general population, in which the proportion of adults who are obese and who smoke is approximately 20%.²¹ Slightly $> 30\%$ of the cohort were exsmokers, which is higher than the 18%²² seen in subjects with asthma of all severity in a large cohort and 21% seen in the general population.²³ The overall difference may reflect the impact of disease severity on patients and greater clinical input from primary and secondary care regarding smoking cessation. The differences among BMI groups is harder to explain, but may be related to health beliefs and perceptions, or potential concerns regarding further weight gain following smoking cessation.

Increased inactivity and reduced mobility, potentially secondary to greater disease severity, may explain the lower levels of patients with asthma who are also obese in full-time employment and the fact that asthma was volunteered as the reason for not working in a third of this group (compared with $< 25\%$ of the overweight group and $< 20\%$ of the normal-weight group). However, the lower levels of educational achievement (33.3% in the obese group achieving an advanced, graduate, or postgraduate level vs 40.7% and 52.8% in the overweight and normal-weight groups, respectively) seen in the obese group are likely to play an important role. The relationship between employment and educational achievement is complex and a lack of information regarding the development of obesity and asthma diagnosis makes it difficult to infer causality.

The view that increasing BMI in severe asthma is associated with greater corticosteroid insensitivity is supported by the findings in this cohort. Corticosteroid burden was greatest in the obese group, where 48.9% of patients were on maintenance oral prednisolone and short-burst steroid use was increased.

Table 4—Lung Function and Radiology

Lung Function and Radiology	BMI				P Value ^a
	Overall	18.50-24.99	25.00-29.99	≥ 30.00	
Patients, No. (%)	666	149 (22.4)	195 (29.3)	322 (48.3)	...
BMI, median (IQR)	29.8 (22.5-34.0)	22.8 (18.9-24.9)	27.4 (26.3-28.5)	34.2 (31.8-38.9)	...
Lung function and FENO, mean (95% CI)					
FENO, ppb	33.0 (15-61)	34 (21-62.5)	35.5 (15.2-85.4)	31 (13.5-57.3)	.11
Prebronchodilator FEV ₁ , L	1.97 (1.9-2.0)	2.04 (1.9-2.2)	2.00 (1.9-2.1)	1.91 (1.8-2.0)	.43
FEV ₁ % predicted	67.7 (65.8-69.7)	69.6 (65.1-74.1)	67.8 (64.3-71.3)	66.9 (64.2-69.5)	.67
Prebronchodilator FVC, L	3.10 (3.0-3.2)	3.20 (3.0-3.4)	3.29 (3.1-3.5)	2.94 (2.8-3.1)	.0009
FVC % predicted	84.0 (81.9-85.0)	86.2 (82.8-89.6)	86.7 (83.7-89.8)	80.1 (78.0-82.3)	.0004
Subjects with baseline bronchodilator study, mean (95% CI)					
Prebronchodilator FEV ₁ , L	1.90 (1.8-2.0)	1.95 (1.8-2.1)	1.92 (1.8-2.1)	1.86 (1.8-2.0)	.94
FEV ₁ % predicted	65.5 (63.2-67.7)	67.0 (61.9-72.1)	65.3 (61.1-69.6)	64.8 (61.8-67.8)	.85
Prebronchodilator FVC, L	3.07 (3.0-3.2)	3.12 (2.9-3.3)	3.30 (3.1-3.5)	2.90 (2.8-3.0)	.013
FVC % predicted	82.6 (80.7-84.5)	84.5 (80.1-88.4)	87.1 (84.0-90.8)	78.8 (76.2-81.4)	.002
Postbronchodilator FEV ₁ , L	2.20 (2.1-2.3)	2.21 (2.0-2.4)	2.25 (2.1-2.4)	2.16 (2.1-2.3)	.67
FEV ₁ % predicted	76.0 (73.7-78.2)	76.4 (71.4-81.3)	76.5 (72.1-81.0)	75.4 (72.3-78.6)	.89
Bronchodilator response, % change FEV ₁	19.6 (17.4-21.7)	17.3 (13.3-21.2)	19.9 (15.8-24.0)	20.4 (17.1-23.7)	.34
Postbronchodilator FVC, L	3.33 (3.2-3.4)	3.35 (3.1-3.6)	3.53 (3.3-3.7)	3.19 (3.1-3.3)	.019
FVC % predicted	89.9 (88.2-91.7)	91.4 (87.7-95.1)	93.5 (89.9-97.0)	87.0 (84.7-89.3)	.0034
Prebronchodilator FEV ₁ /FVC ratio, %	61.8 (60.4-63.2)	61.6 (58.4-64.8)	59.3 (56.6-61.9)	63.5 (61.5-65.4)	.042
Postbronchodilator FEV ₁ /FVC ratio, %	65.7 (64.3-67.2)	65.1 (61.8-68.4)	63.4 (60.8-65.9)	67.5 (65.4-69.5)	.052
Total lung capacity % predicted, No.	103.0 (101.1-104.2)	106.4 (103.1-109.6)	103.6 (100.8-106.3)	100.3 (98.2-102.5)	.0028
Residual volume % predicted, No.	124.0 (123.6-131.3)	129.3 (121.2-137.3)	124.2 (117-131.5)	128.7 (123.1-134.3)	.45
Kco % predicted, No.	101.0 (100.3-103.7)	97.0 (93.5-100.7)	101.6 (98.6-104.6)	104.5 (102.1-106.9)	.002
Blood testing and radiology, median; IQR (No.)					
Blood eosinophil count × 10 ⁹ /L, No.	0.28; 0.11-0.53 (629)	0.30; 0.1-0.67 (141)	0.31; 0.11-0.60 (184)	0.26; 0.11-0.49 (304)	.21
Sputum eosinophil count, No.	2.9; 0.5-9.9 (174)	4.0; 0.38-14.0 (41)	2.8; 0-12.1 (49)	2.8; 1.0-9.7 (84)	.92
IgE kU/L, No.	158; 51-421 (610)	266; 83-480 (133)	144; 46-384 (181)	119; 46-418 (296)	.0049
Bone density T scores, mean ± SD (No.)					
L1 to L4	−0.71 ± 1.48 (239)	−1.08 ± 1.25 (50)	−0.73 ± 1.68 (70)	−0.55 ± 1.42 (119)	.051
Femoral neck	−0.27 ± 1.24 (233)	−1.02 ± 1.21 (48)	−0.32 ± 1.13 (72)	+0.074 ± 1.19 (113)	<.0001
HRCT scan, No. diagnosed/total CTs (%)					
Reported as normal by radiologist	68/392 (17.3)	11/84 (13.1)	19/126 (15.1)	38/182 (20.9)	.21
Abnormal HRCT	344/420 (81.9)	75/90 (83.3)	114/132 (86.4)	155/198 (78.3)	.16
Central bronchiectasis	34/306 (11.1)	12/68 (17.6)	13/103 (12.6)	9/135 (6.7)	.053
Other bronchiectasis	77/317 (24.3)	19/68 (27.9)	28/105 (26.7)	30/144 (20.8)	.42
Bronchial wall thickening	214/327 (65.4)	44/71 (62.0)	67/106 (63.2)	103/150 (68.7)	.52
Bronchial dilatation	58/318 (18.2)	12/67 (17.9)	21/104 (20.2)	25/147 (17.0)	.81
Ground glass	35/317 (11.0)	9/69 (13.0)	11/105 (10.5)	15/143 (10.5)	.84
Air trapping	63/319 (19.7)	12/69 (17.4)	19/106 (17.9)	32/144 (22.2)	.6
Mucus plugging	31/316 (9.8)	9/69 (13.0)	7/103 (6.8)	15/144 (10.4)	.38
Emphysema	15/333 (4.5)	4/73 (5.5)	4/109 (3.7)	7/151 (4.6)	.84

FENO = exhaled nitric oxide; HRCT = high resolution CT; Kco = carbon monoxide transfer coefficient; ppb = parts per billion. See Table 1 and 3 legends for expansion of other abbreviations.

^aBetween-group comparisons for continuous variables were made using Kruskal-Wallis testing.

However, there was no significant difference in the oral steroid dose among groups and the differences seen, in fact, may reflect increased BMI as a consequence of long-term steroid use. In addition to steroid use, SABA use per day was greater in the overweight and obese groups and nebulized bronchodilator use

increased alongside BMI, suggesting that asthma symptoms increase with increasing BMI.

PPI use and GERD were reported more often in the obese group, as was an abnormal 24-h esophageal pH study. The link between GERD and obesity in the general population remains unclear and a recent

meta-analysis of 30 studies found a weak to moderate association. However, subanalysis of subjects with a BMI >35 revealed that they were six times more likely to suffer with GERD than their normal-weight counterparts.²⁴ GERD was reported by 49.1% of this cohort, which is slightly higher than the 41% reported in patients with severe asthma in the SARP (Severe Asthma Research Program) cohort²⁵ and in contrast to 12.5% to 30% seen in unselected adult cohorts with a BMI $\geq$ 30.^{26,27} GERD in severe asthma is a common finding and is compounded by systemic corticosteroid use. This is particularly relevant given that steroid use in our cohort increased with BMI.

Obesity is associated with a lack of both eosinophilic and neutrophilic inflammation in the airways.¹ This is supported by the similar sputum eosinophil counts and FENO levels among groups in this cohort and has been noted in previous studies.²⁸ IgE levels decreased with BMI despite a lack of difference in a prior history of atopy. However, *Aspergillus* sensitization decreased with BMI and similar trends were seen with house dust mite, cat, and mixed grass sensitivity were noted. These findings fit well with the reduced atopy and lower IgE levels in conjunction with increased BMI that were factors in two of five clusters in the SARP cohort.²⁹

The obese group was more likely to report a history of eczema (31.4%) than the overweight or normal-weight groups. This is similar to the 33.9% of adults who were obese in a recent study that looked at patients presenting to an allergy clinic who were found to have atopic dermatitis.³⁰ However, both cohorts relied on self reporting and this may be a bias in the obese population. These collective findings, in addition to a nonsignificant difference in FENO and lower IgE levels noted in the obese group, are somewhat discordant, and it is possible that other skin complaints may have been misreported as eczema.

The lung function findings in this cohort follow similar trends to known obesity-related changes in lung physiology. Obesity is associated with increased intraabdominal pressure on the diaphragm and the chest wall, leading to lower tidal volumes, functional residual capacity, and expiratory reserve volume. FEV₁/FVC ratio may be normal, or elevated if gas trapping and airway closure reduce FVC.¹

Obesity appears to be associated with greater bone densitometry, particularly at the femoral neck. Previous studies have reported that obesity exerts a protective effect on bone density and this is felt to be secondary to several mechanisms, including increased levels of estrogens and adipokine imbalance.³¹

There are several limitations to this study that should be considered when interpreting these results. BMI is a crude population measurement and does not take body composition, fat distribution, and racial

variance into account, although these factors are not routinely measured in clinical practice. Increasing BMI is associated with comorbidities that may influence respiratory symptoms such as impaired ventilatory function (reduced FEV₁, FVC, total lung capacity, functional residual capacity, and expiratory reserve volume), sleep disordered breathing, reduced exercise tolerance, and GERD. This may result in a diagnostic bias in severe asthma. A previous study looking at 540 individuals with physician-diagnosed asthma found that although about a third of those assessed did not have objective evidence of asthma, there were no differences between the obese and normal-weight groups.³² Patients in our cohort, however, were subject to a detailed systematic assessment and multidisciplinary decision regarding their diagnosis prior to inclusion, which makes this unlikely to be a significant factor. This is supported by a mean bronchodilator reversibility for the entire cohort of 19.6% (95% CI, 17.4-21.7%) with no significant difference among BMI groups. In addition, while our previous study identified differences in severe asthma characteristics between different centers, BMI figures remained similar.

Although the use of BMI is convenient and widely accepted as a measure of adiposity, it may not be the best measure of the effect of adiposity on the lung.¹ Central body fat distribution may be a better associated factor with the mechanical effects of obesity on lung function.³³ The National Registry does not include data regarding exercise habits or levels of physical activity, which prevents any inferences regarding their role on BMI in severe asthma. In addition, the cohort of patients in this study did not have temporal information regarding the development of obesity. This would provide insight into the direction of causality for many of the factors discussed. It has been suggested that patients with early-onset asthma become obese following a diagnosis of severe asthma, while those with late-onset disease are more likely to have severe disease resulting from obesity.³⁴ Obesity-associated severe asthma is likely to comprise a spectrum of patients with two distinct ends: patients with severe asthma who gain weight secondary to disease-related inactivity and corticosteroid use, and patients in whom obesity predated the diagnosis of asthma, contributing to symptoms and relative corticosteroid insensitivity.

This study forms the largest cohort of patients with severe asthma that has been analyzed according to BMI to date. It provides evidence that patients who are obese and have severe asthma may represent a distinct clinical phenotype within the population with severe asthma. Further work looking at the mechanisms by which obesity affects asthma, as well as longitudinal studies designed to explore the temporal

role of obesity in asthma, will improve our understanding of this group of patients with the ultimate aim of providing targeted therapeutic interventions.

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Dr Gibeon: contributed to data abstraction, statistical analysis, writing the manuscript, revising and approving the final manuscript, and served as principal author.

Dr Batuwita: contributed to data abstraction, statistical analysis, and revising and approving the final manuscript.

Dr Osmond: contributed to data abstraction, statistical analysis, and revising and approving the final manuscript.

Prof Heaney: contributed to revising and approving the final manuscript.

Dr Brightling: contributed to revising and approving the final manuscript.

Dr Niven: contributed to revising and approving the final manuscript.

Dr Mansur: contributed to revising and approving the final manuscript.

Dr Chaudhuri: contributed to revising and approving the final manuscript.

Dr Bucknall: contributed to revising and approving the final manuscript.

Dr Rowe: contributed to data abstraction, statistical analysis, and revising and approving the final manuscript.

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Dr Bhavsar: contributed to revising and approving the final manuscript.

Prof Chung: contributed to revising and approving the final manuscript.

Dr Menzies-Gow: contributed to writing the manuscript, and revising and approving the final manuscript.

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