

Obesity and asthma: An association modified by age of asthma onset

Fernando Holguin, MD, MPH,^a Eugene R. Bleeker, MD,^b William W. Busse, MD,^c William J. Calhoun, MD,^d Mario Castro, MD, MPH,^e Serpil C. Erzurum, MD,^f Anne M. Fitzpatrick, PhD, RN, MS,^g Benjamin Gaston, MD,^h Elliot Israel, MD,ⁱ Nizar N. Jarjour, MD,^c Wendy C. Moore, MD,^b Stephen P. Peters, MD,^b Michael Yonas, DrPH,^j W. Gerald Teague, MD,^k and Sally E. Wenzel, MD^l Pittsburgh, Pa, Winston-Salem, NC, Madison, Wis, Galveston, Tex, St Louis, Mo, Cleveland, Ohio, Atlanta, Ga, Charlottesville, Va, and Boston, Mass

Background: Studies of asthma phenotypes have identified obesity as a component of a group characterized by a high proportion of subjects with adult-onset asthma. However, whether age of asthma onset modifies the association between obesity and asthma is unknown.

Objectives: We sought to compare the associations between body mass index (BMI) categories with physiological, inflammatory, and clinical parameters across age of asthma onset phenotypes; and to compare the rate of BMI change in relation to asthma duration, by age of onset asthma phenotypes.

From ^athe Asthma Institute, Pulmonary Allergy and Critical Care Medicine, University of Pittsburgh; ^bthe Center for Genomics and Personalized Medicine Research, Pulmonary Critical Care Allergy and Immunologic Medicine, Wake Forest University, Winston-Salem; ^cAllergy Pulmonary and Critical Care Medicine, University of Wisconsin, Madison; ^dthe Division of Pulmonary and Critical Care Medicine, University of Texas, Galveston; ^ePulmonary and Critical Care Medicine, Washington University, St Louis; ^fPulmonary and Critical Care Medicine/Cancer Biology, Cleveland Clinic; ^gAsthma Clinical Research Program, Pulmonary Allergy & Immunology Cystic Fibrosis and Sleep, Emory University, Atlanta; ^hthe Division of Respiratory Medicine, Department of Pediatrics, University of Virginia, Charlottesville; ⁱthe Department of Medicine, Harvard University, Boston; ^jthe Department of Family Medicine, University of Pittsburgh; ^kthe Division of Respiratory Medicine, Department of Pediatrics, University of Virginia, Charlottesville; ^lPulmonary Allergy and Critical Care Medicine, University of Pittsburgh.

Supported by National Institutes of Health grant HL-069174.

Disclosure of potential conflict of interest: W. W. Busse has served on the advisory boards for Centocor and Merck; has consulted for AstraZeneca, Boehringer Ingelheim, Novartis, TEVA, GlaxoSmithKline, (GlaxoSmithKline) Amgen, Pfizer, MedImmune, and Genentech; and has received research support from the National Institutes of Health (NIH; National Institute of Allergy and Infectious Diseases [NIAID] and National Heart, Lung, and Blood Institute [NHLBI]), Novartis, AstraZeneca, GlaxoSmithKline, MedImmune, and Cepion. M. Castro has consulted for Electrocore, NKTT, Schering, Astmatx, and Cephalon; has served on an advisory board and given talks for Genentech; has given talks for AstraZeneca, Boehringer Ingelheim, Pfizer, Merck, and GlaxoSmithKline; has received research support from Astmatx, Amgen, Cepion, Genentech, MedImmune, Merck, Novartis, the NIH, and GlaxoSmithKline; and has received royalties from Elsevier. A. M. Fitzpatrick has received research support from the NIH (NHLBI and National Institute of Nursing Research). B. Gaston has served on an advisory board for Gilead. E. Israel has consulted for Abbott, Amgen, Cowen & Co, GlaxoSmithKline, IcaGen, MedImmune, Merck, NewMentor, NKT Therapeutics, Ono Pharmaceuticals US, Schering-Plough, and TEVA; has received research support from Aerovance, Amgen, Biota, Cepion Therapeutics, Genentech, MedImmune, the NIH, and Novartis; and has provided legal consultation or expert witness testimony on the topic of asthma. N. N. Jarjour has consulted for Astmatx and Genentech and has received research support from GlaxoSmithKline, Merck, Genentech, and MedImmune. S. P. Peters has received research support from the NIH (NHLBI). W. G. Teague has given talks for Merck and Genentech and has received research support from the NIH (NIAID and NHLBI) and the American Lung Association. The rest of the authors have declared that they have no conflict of interest.

Received for publication December 7, 2010; revised March 18, 2011; accepted for publication March 22, 2011.

Reprint requests: Fernando Holguin, MD, MPH, Asthma Institute at UPMC, UPMC Montefiore 9NW, 3459 Fifth Ave, Pittsburgh, PA 15213. E-mail: holguinf@upmc.edu. 0091-6749/\$36.00

© 2011 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2011.03.036

Methods: From the Severe Asthma Research Program, we defined age of asthma onset as early (<12 years of age) and late (≥ 12 years of age). Comparisons of BMI categories were done within age-of-onset groups, and obesity was also compared across these groups. Multivariable logistic regression analysis was done to evaluate the association between BMI categories with health care use and respiratory symptoms and multivariable linear regression for the association between duration of asthma and weight gain (BMI change per year). An interaction between obesity and age of asthma onset was included in the multivariable analyses.

Results: The study population consisted of 1049 subjects, and the median age for asthma onset was 10 years (interquartile range, 4-25 years); 48% had late-onset asthma (≥ 12 years of age), and 52% had early-onset asthma (<12 years of age). Compared with obese subjects with late-onset asthma, obese subjects with early-onset asthma had more airway obstruction, bronchial hyperresponsiveness, and higher odds ratios of ever having 3 or more previous oral steroid tapers per year or intensive care unit admissions for asthma per preceding year (interactions between obesity and age of asthma onset were $P = .055$ and $P = .02$, respectively). In subjects with early-onset asthma but not in subjects with late-onset asthma, there was a significant association between increasing BMI and duration of asthma after adjusting for confounders. The interaction between asthma duration and age of asthma onset was a P value of less than .01. **Conclusion:** Asthmatic subjects are differentially affected by obesity based on whether they had asthma early (<12 years of age) or later in life. These results highlight the need to understand obesity as a comorbidity that affects specific clinical phenotypes and not all asthma subjects alike. (*J Allergy Clin Immunol* 2011;127:1486-93.)

Key words: Severe, asthma, obesity, Severe Asthma Research Program

Compared with lean and overweight subjects with asthma, obese asthmatic subjects have more severe and frequent respiratory symptoms, greater exacerbation rates, and reduced asthma-related quality of life.¹ Several mechanisms have been postulated as potential explanations to understand how obesity affects asthma, including increased airway resistance, abnormal respiratory mechanics, increased bronchial hyperresponsiveness, and reduced inhaled corticosteroid effectiveness.²⁻⁶ However, in clinical studies obesity has not been consistently associated with increased airway inflammation and clinical impairment.⁷⁻¹⁰ This lack of consistency might be partly determined by our inability to determine in which asthmatic subjects obesity is a comorbidity that affects the underlying pathophysiology of asthma or the

Abbreviations used

ATS: American Thoracic Society
BMI: Body mass index
FVC: Forced vital capacity
ICU: Intensive care unit
IQR: Interquartile range
SARP: Severe Asthma Research Program

response to therapy versus being primarily a driver of increased respiratory symptom burden. Evidence that obesity does not equally affect all asthmatic subjects is supported by cluster analysis studies, which have identified obesity as part of a clinical asthma phenotype characterized by a higher proportion of female subjects and subjects with late-onset disease.^{11,12} Having late-onset asthma, typically during early adolescence or adulthood, is associated with a different clinical phenotype. Although subjects with late-onset asthma are characterized by having less atopy and a higher degree of airway eosinophilic inflammation, subjects with early-onset asthma have more allergic symptoms, atopy, higher IgE levels, and proportionately less eosinophilic inflammation.^{13,14} On the basis of obesity being predominantly associated with the late-onset asthma phenotype, we hypothesized that the influence of obesity on asthma control and severity characteristics is modified by the age of asthma onset (early onset vs late onset). We also explored whether age of asthma onset would differentially affect the degree of body mass index (BMI) change over time and the risk of being obese. A cross-sectional analysis with data from the National Institutes of Health Severe Asthma Research Program (SARP) was used to address these questions.

METHODS

Study population

The study population consisted of participants aged 18 years or older from the multicenter SARP study that met the criteria for asthma, which included either a 12% increase in FEV₁ after a short-acting bronchodilator or a 20% decrease in FEV₁ after inhalation of methacholine (PC₂₀, 25 mg/mL). The SARP study has been previously described in detail.¹⁵ Briefly, the study population consisted of subjects recruited at each of the SARP-participating academic centers through the use of local advertisements who met the eligibility criteria, including being a current nonsmoker with asthma and having less than 5 pack-years of tobacco use.

Study participants were classified as having mild, moderate, or severe asthma. According to the American Thoracic Society (ATS) definition, severe asthma was defined as having at least 1 of the major criteria (1) use of high-dose inhaled steroids for more than 50% of the preceding year or (2) use of continuous or near-continuous oral steroids and at least 2 of the minor criteria (1) use of daily controller medication in addition to inhaled steroids, (2) β -agonist required daily or near daily, (3) persistent airway obstruction, (4) 1 or more urgent care visits for asthma per year, (5) 3 or more oral corticosteroid bursts per year, (6) clinical deterioration with reduction in oral steroid dose, and (7) history of a near-fatal asthma event. Subjects with nonsevere asthma included those with moderate (prebronchodilator FEV₁ <80% with or without use of inhaled corticosteroids) or mild (FEV₁ $\geq$ 80% with or without use of inhaled corticosteroids) asthma.¹⁶ For the purposes of this study, subjects with mild and moderate asthma were analyzed together as "not severe." Age of onset was dichotomized into early childhood (<12 years of age) and adolescence/late onset ($\geq$ 12 years of age) based on data showing that this age dichotomy differentiates severe asthma into distinct inflammatory phenotypes.¹⁴

Clinical data

After signing an informed consent form, study participants provided demographic information, smoking history, past medical history, and

frequency of respiratory symptoms in the 3 months preceding enrollment, including cough, sputum production, chest tightness, nighttime asthma symptoms, wheezing, and shortness of breath. Subjects also completed the Juniper Asthma Quality of Life Questionnaire.¹⁷

Allergy skin test. All participants underwent allergy skin testing for tree mix, grass mix, ragweed, weed mix, dogs, cats, molds, dust mites, and cockroach. Diluting fluid and histamine were used as negative and positive controls, respectively, to control for validity. The presence of atopy was defined as having at least 1 skin test reaction of 3 mm or larger than that elicited by the saline control.

Lung function testing. Spirometry was done according to ATS guidelines. Postbronchodilator FEV₁ was recorded as the maximum bronchodilator change between 4 and 8 puffs of albuterol.¹⁸ Patients with a baseline FEV₁ of greater than 50% and an FEV₁ of 1.5 L or greater underwent methacholine challenge according to a 7-dose algorithm of incremental doses from 0.078 mg/mL to a maximum of 25 mg/mL. A PC₂₀ of less than 25 mg/mL was considered positive. This high value was chosen because of the high and prolonged steroid doses in the population. Because of FEV₁ criteria, methacholine tests were only performed in a subset of the subjects.

Inflammatory biomarkers. Total serum IgE level and complete blood count measurements with cell count differential were done with standard clinical laboratory procedures. In subjects with an FEV₁ percent predicted value of greater than 55%, sputum induction and processing were performed by using a standardized protocol based on the Fahy method with 3% saline for induction.¹⁹ Sputum eosinophils were counted by a single reader and presented as a percentage of total white blood cells in sputum. Similar to methacholine, sputum was only obtained from a subset of subjects. Online exhaled nitric oxide measurement was performed according to the ATS recommendations in a subset of study subjects.²⁰

Statistical analysis

Given that the majority of continuous variables in Table I did not achieve normality by using the Kolmogorov-Smirnov test for both the late- and early-onset asthma groups, comparisons of continuous variables within and between groups were done with a more conservative nonparametric analysis, with the Kruskal-Wallis test used for the BMI categories or the Wilcoxon rank sum test used for comparison of obesity categories across asthma age-of-onset groups. Fisher exact or χ^2 tests were used for comparison of proportions. Some comparisons across age-of-onset groups were done on smaller subsets of patients in whom the comparison test was not performed in the entire group. A Bonferroni correction with an α value of .05/ κ (κ = number of BMI categories) was used to reduce the likelihood of false-positive results because of multiple-group comparisons. The Bonferroni-corrected *P* value is set at less than .016.

Multivariable and univariable logistic regression analysis combined subjects with severe and nonsevere asthma to model the association between BMI categories (main exposure) and asthma morbidity measures in the preceding 12 months from SARP enrollment. Subjects with asthma of different severities were combined, given that the categories of asthma severity were included as part of the outcome evaluated by the model. The dichotomous outcomes for the logistic regression analyses included the following events in the preceding year of SARP enrollment: 3 or more steroid bursts, visited the emergency department for asthma, spent at least 1 night in a hospital for breathing reasons, and any intensive care unit (ICU) admissions for asthma, as well as having ever been mechanically ventilated for asthma-related reasons and having received a diagnosis of pneumonia. Modeling was done by means of backward elimination, with retention of variables in the model based on a significance level of .1 or less or a $\pm$ 10% change in the model estimate. These models were adjusted for asthma duration in years, atopy (yes/no), and race (white, African American, or "other") and use of asthma controller medications (current use vs no use, including inhaled steroids, long-acting β -agonists, or leukotriene blockers); age and sex were not significant and thus were not included in the final model. Multivariable logistic analysis was also used to model having continuous respiratory symptoms (in the 3 months before SARP enrollment), which was defined as having any of the following: cough, sputum production, chest tightness, wheeze, dyspnea, and nocturnal asthma symptoms 2 or more times per week. Other outcomes included having an Asthma Quality

TABLE I. Characteristics of the study population by age of asthma onset and BMI categories

BMI categories	Late-onset asthma (n = 506)				Early-onset asthma (n = 543)				Between age of onset obesity comparison
	>30 (n = 245)	>25 < 30 (n = 125)	≤25 (n = 134)	P value	>30 (n = 201)	>25 < 30 (n = 153)	≤25 (n = 189)	P value	P value*
N = 1047 (%)	245 (48)	125 (25)	134 (27)		201 (38)	153 (28)	189 (34)		
Demographic and clinical characteristics									
BMI (kg/m ²)	35.5 (33-41)	27 (26-28)	23 (21-24)		36 (33-40)	27 (26-28)	22 (20-23)		
Age (y), median (range)	45 (20-79)	43 (19-74)	39 (18-78)	.01	35 (18-75)	33 (18-66)	26 (18-69)	<.01	<.01
Female sex (%)	74	65	69	.1	65	49	64	<.01	.03
Age at asthma onset (y)	27 (15-37)	26 (18-35)	22 (19-31)	<.01	4 (1-7)	4 (1-7)	5 (2-7)	.1	
Median asthma duration (y [IQR])	14 (6-24)	11 (6-21)	12 (6-23)	.40	31 (22-42)	30 (19-39)	22 (17-30)	<.01	<.01
Race									
White (%)	61	70	72	<.01	50	68	75	<.01	.01
African American (%)	34	24	13		42	24	17		
Other (%)	5	6	15		8	8	8		
Exsmoker (%)	20	23	26	.20	21	17	14	.70	.70
Median amount smoked (PPY [IQR])	4 (1-5)	4 (1-8)	3 (0-10)	.20	2 (1-5)	1 (0-4)	2 (1-4)	.40	.60
Severity									
Mild (%)	23	36	44	<.01	25	44	50	<.01	.70
Moderate	23	23	18		24	22	25		
Severe	54	41	38		51	34	25		
Exercise provokes asthma symptoms (%)	82	83	76	.30	87	86	88	.80	.10
Medications									
Any ICS steroid use (%)	75	69	69	.40	69	59	65	.40	.20
High-dose ICS (%)	54	40	37	<.01	50	34	26	<.01	.10
OCS steroid use (%)	20	12	8	<.01	17	9	7	<.01	.10
LABA use (%)	72	60	62	.04	69	61	55	.02	.40
Leukotriene blockers (%)	44	30	30	<.01	31	26	21	.07	.02
Any anti-IgE use (%)	10	1	2.2	<.01	16	4	5	.3	.60
Lung function test									
FEV ₁ (L), median (IQR)	2.1 (1.7-2.7)	2.5 (1.7-2.9)	2.5 (1.7-3.3)	<.01	2.2 (1.6-2.7)	2.9 (2.1-3.7)	2.8 (2.3-3.4)	<.01	.80
FEV ₁ (% predicted), median (IQR)	75 (57-86)	76 (59-89)	81 (58-95)	.04	70 (54-83)	82 (66-94)	82 (69-97)	<.01	.09
FVC (L), median (IQR)	2.9 (3.4-3.6)	3.4 (2.7-4.1)	3.6 (2.8-4.2)	<.01	3.1 (2.5-3.8)	4 (3.1-4.7)	3.8 (3.2-4.6)	<.01	.10
Base FVC (% predicted), median (IQR)	79 (69-94)	85 (75-97)	90 (78-101)	<.01	83 (71-94)	94 (82-105)	94 (71-94)	<.01	.20
Base FEV ₁ /FVC ratio, median (IQR)	0.73 (0.63-0.8)	0.71 (0.60-0.80)	0.72 (0.60-0.80)	.10	0.69 (0.59-0.76)	0.72 (0.62-0.78)	0.73 (0.64-0.82)	<.01	<.01
Maximum FEV ₁ reversal (%), median (IQR)	12 (5-22)	11 (5-21)	10 (4-19)	.50	14 (6-26)	12 (7-19)	10 (6-18)	<.01	.06
PC ₂₀ (mg/mL),* median (IQR)	1.5 (0.4-5)	1.4 (0.4-3)	1.6 (0.5-6)	.70	0.7 (0.3-2.2)	1 (0.2-4)	1 (0.3-3)	.20	<.01
Biomarkers for allergy									
IgE (IU/mL),† median (IQR)	165	194	284	.10	540	255	348	.80	<.01
Exhaled NO (ppb), median (IQR)	36	38	43	.20	33	43	46	.08	.80
Atopic (%),‡	72	82	79	.07	86	93	92	.09	<.01
Percentage of eosinophils in blood,§ median (IQR)	4 (2-6)	3 (1-5)	3 (1-6)	.50	3 (2-5)	3 (2-5)	4 (2-6)	.40	.60

(Continued)

TABLE I. (Continued)

BMI categories	Late-onset asthma (n = 506)				Early-onset asthma (n = 543)				Between age of onset obesity comparison P value*
	>30 (n = 245)	>25 < 30 (n = 125)	≤25 (n = 134)	P value	>30 (n = 201)	>25 < 30 (n = 153)	≤25 (n = 189)	P value	
Percentage of eosinophils in sputum, median (IQR)	1.5 (0.4-5)	1 (0.2-4)	3 (0.2-14)	.20	1 (0.2-4)	0.6 (0.1-4)	0.8 (0.3-5)	.20	.60

Boldfaced results indicate statistical significance. Obesity comparison is between age-of-onset groups and limited to BMI of greater than 30 kg/m². Except where stated, continuous variables are shown as medians and IQRs (25th-75th).

ICS, Inhaled corticosteroids; LABA, long-acting β -blockers; NO, nitric oxide; OCS, oral corticosteroids; PPY, pack-per-year.

*Based on a subset of 665 asthmatic subjects (359 with early-onset and 306 with late-onset asthma).

†Based on a total of 406 subjects with early-onset and 361 with late-onset asthma.

‡Positive reaction to at least 1 skin allergen: sample limited to 468 subjects with early-onset and 435 subjects with late-onset asthma.

§Based on a total of 819 asthmatic subjects (438 with early-onset and 381 with late-onset asthma).

||Based on a subset of 492 asthmatic subjects (232 with late-onset and 260 with early-onset asthma).

of Life Questionnaire score of less than the population's median level (4.6) and being labeled as having severe asthma (yes/no). These models were adjusted for atopy (yes/no), asthma duration (years), sex, and race (white, African American, or "other"). Results are presented as univariable and adjusted estimates. All multivariable logistic models included an interaction term between obesity and age of asthma onset.

The linear association between years of having asthma (main exposure) and BMI as a continuous variable (model outcome) was modeled adjusting for sex, race, and asthma severity to determine whether age of asthma onset is a risk factor for weight gain. The interaction between age of asthma onset and BMI was evaluated to determine whether a statistically significant differential weight pattern exists between early or late asthma phenotypes.

RESULTS

The study population consisted on 1049 adult subjects with asthma of whom 63% were female, 65% were white, 27% were African American, and 8% were of "other" race. The median age for asthma onset was 10 years (interquartile range [IQR], 4-24 years), 48% had late-onset asthma (25 years; range, 12-69 years), and 52% had early-onset asthma (4 years; range, 0-11 years). The median BMI was 28 kg/m² (IQR, 23-34 kg/m²); 42% were obese, 27% were overweight, and 31% were lean. Within the late-onset group, 48% were obese (BMI, 35 kg/m²; IQR, 32.7-40.7 kg/m²), 25% were overweight (BMI, 27 kg/m²; IQR, 26-28.5 kg/m²), and 26% were lean (BMI, 22.8 kg/m²; IQR, 21.2-23.8 kg/m²). BMI was correlated with age among the late-onset group (Spearman rho = 0.12, $P < .01$) and to a greater extent within the early-onset group (Spearman rho = 0.23, $P < .01$). Age was also associated with asthma duration in the late-onset (Spearman rho = 0.4, $P < .01$) and early-onset (Spearman rho = 0.9, $P < .01$) asthma groups. The proportion of subjects with severe and nonsevere asthma was 42% and 58%, respectively, for the entire study population. Among subjects with late-onset asthma, these proportions were 47% and 53%, respectively, and among the subjects with early-onset asthma, these proportions were 37% and 63%, respectively.

Demographic, functional, and phenotypic comparisons between obese and nonobese asthmatic subjects within each asthma age-of-onset category

Table I shows the distribution of demographic markers, lung function markers, and biomarkers of allergic inflammation by

age of asthma onset. Among subjects with early-onset asthma, the obese and overweight were older, included a larger proportion of African American subjects, and had asthma for a longer period of time than lean asthmatic subjects. Compared with leaner counterparts, a larger proportion of obese subjects with early-onset asthma were taking controller medications. There was a trend for lower FEV₁ and forced vital capacity (FVC) percent predicted values with increasing BMI categories (P for trend for both = .001) and a trend for greater airway obstruction (determined by FEV₁/FVC ratio) and maximal FEV₁ reversal after short-acting bronchodilators (P trend < .001 and $P = .002$, respectively). There was a marginal inverse trend (P trend = .06) between exhaled nitric oxide levels and BMI categories (based on a subset of 411 subjects with early-onset asthma).

Among the late-onset category, obese and overweight asthmatic subjects were older, and asthma onset occurred at an older age when compared with leaner asthmatic subjects. The race distribution differed across the late-onset BMI categories, with a greater proportion of African Americans being in the obese category. Obese subjects with late-onset asthma were also more likely to be classified as having severe asthma and required more asthma control medications. Among the subjects with late-onset asthma, there was a trend for lower FEV₁ and FVC percent predicted values (P trend for both = .001) with increasing BMI categories.

Demographic, functional, and phenotypic comparisons between asthma age-of-onset categories

Obese subjects with early-onset asthma were younger and included a lower proportion of female subjects than obese subjects with late-onset asthma. Also, obese subjects with early-onset asthma had greater airway obstruction and a marginally higher maximal FEV₁ reversal when compared with obese subjects with late-onset asthma. Among a subset of SARP participants with methacholine testing (early-onset asthma, $n = 359$; late-onset asthma, $n = 306$), obese subjects with early-onset asthma had significantly greater bronchial hyperresponsiveness when compared with that seen in obese subjects with late-onset asthma ($P = .0009$). Nonobese subjects with early-onset asthma also had greater bronchial responsiveness than nonobese subjects with late-onset asthma, although to a lesser extent ($P = .049$). Also, obese subjects with

TABLE II. Examination of morbidity association by age of asthma onset with BMI categories

	Late-onset asthma, OR (95% CI)		Early-onset asthma, OR (95% CI)	
	Univariable (n = 506)	Multivariable (n = 435)*	Univariable (n = 543)	Multivariable (n = 468)*
Cough				
Lean	1.0	1.0	1.0	1.0
Overweight	1.3 (0.7-2.2)	1.1 (0.6-2)	1.02 (0.6-1.8)	0.9 (0.5-1.8)
Obese	1.9 (1.6-4.2)	1.7 (1.01-2.9)	2.6 (1.6-4.2)	2.2 (1.3-3.9)
Sputum				
Lean	1.0	1.0	1.0	1.0
Overweight	0.7 (0.4-1.3)	0.6 (0.3-1.2)	1.2 (0.7-2.4)	1.2 (0.6-2.4)
Obese	1.3 (0.8-2)	1.1 (0.7-1.9)	2.8 (1.6-4.7)	2.5 (1.3-2.5)
Chest tightness				
Lean	1.0	1.0	1.0	1.0
Overweight	0.9 (0.5-1.6)	0.8 (0.4-1.6)	1.0 (0.6-1.9)	0.9 (0.5-1.6)
Obese	1.6 (0.9-2.6)	1.4 (0.8-2.4)	1.4 (1.4-3.5)	1.8 (1.05-3)
Wheeze				
Lean	1.0	1.0	1.0	1.0
Overweight	1.0 (0.5-1.9)	1.1 (0.6-2.5)	1.0	0.7 (0.4-1.4)
Obese	2.2 (1.3-3.6)	2.2 (1.3-3.4)	3 (1.9-5)	2.7 (1.6-4.7)
Dyspnea				
Lean	1.0	1.0	1.0	1.0
Overweight	0.8 (0.5-1.3)	0.8 (0.4-1.3)	1.0 (0.6-1.7)	0.8 (0.4-1.4)
Obese	2.4 (1.5-3.7)	1.7 (1.02-3.3)	2.4 (1.5-3.7)	2 (1.2-3.3)
Nocturnal symptoms				
Lean	1.0	1.0	1.0	1.0
Overweight	1.0 (0.5-1.9)	0.9 (0.5-1.9)	0.8 (0.4-1.6)	0.7 (0.4-1.3)
Obese	2 (1.2-3.3)	2.1 (1.1-3.6)	2.1 (1.4-3.4)	1.7 (1.02-3.3)
Low AQLQ score				
Lean	1.0	1.0	1.0	1.0
Overweight	1.9 (0.9-3.5)	2.3 (1.3-4.7)	0.9 (0.5-1.6)	0.8 (0.4-1.6)
Obese	2.8 (1.6-4.8)	2.8 (1.5-5.4)	2.9 (1.8-4.8)	2.4 (1.4-4.3)
Severe asthma				
Lean	1.0	1.0	1.0	1.0
Overweight	1.1 (0.6-1.8)	1.23 (0.7-2.2)	1.1 (0.7-1.8)	0.9 (0.5-1.6)
Obese	1.9 (1.2-2.9)	1.85 (1.1-3)	1.9 (1.2-2.9)	2.1 (1.3-3.5)

Adjusted for age, sex, race, atopy, and asthma duration. Boldfaced estimates are significant at a *P* value of less than .05. This significance is for the comparison of either overweight or obese status in reference to the lean category within age of asthma categories. Across age of asthma categories, comparisons were done by using an obesity/age-of-onset interaction in the model. No significant interactions were observed.

AQLQ, Asthma Quality of Life Questionnaire.

*Limited to asthmatic subjects with atopy documented by means of skin testing.

early-onset asthma had higher IgE levels when compared with obese subjects with late-onset asthma (based on a subset of 406 subjects with early-onset and 361 subjects with late-onset asthma); IgE levels were not significantly different between nonobese subjects with early- and late-onset asthma. The proportion of atopic asthmatic subjects was higher among obese and nonobese subjects with early-onset asthma compared with that seen among obese and nonobese subjects with late-onset asthma.

Respiratory symptoms, quality of life, and asthma severity

Obese subjects with early-onset asthma were more likely to have continuous cough, sputum production, chest tightness, wheeze, dyspnea, asthma-induced nocturnal symptoms, lower asthma-related quality of life, and severe asthma when compared with the leaner early-onset categories. Obese subjects with late-onset asthma were also more likely than the leaner late-onset BMI categories to have increased continuous respiratory symptoms, to have reduced quality of life, and to be labeled as having severe asthma. Unlike the early-onset asthma category, sputum production and chest tightness were not associated with

obese or overweight late-onset asthma. The magnitude of associations between BMI categories with respiratory symptoms, quality of life, and asthma severity was similar across asthma age-of-onset categories (no significant interactions, Table II and see Table E1 in this article's Online Repository at www.jacionline.org).

Asthma morbidity

Obese subjects with early-onset asthma were more likely than nonobese subjects to have had asthma exacerbations requiring oral steroids and to use health care resources, including emergency department visits, hospitalizations, ICU admissions, and mechanical ventilation (Table III and see Table E2 in this article's Online Repository at www.jacionline.org). In contrast, obese subjects with late-onset asthma were only more likely to have been admitted to the emergency department or the ICU when compared with nonobese subjects with late-onset asthma. Between categories of age of asthma onset, obese subjects with early-onset asthma had marginally greater odds for requiring 3 or more steroid tapers in the preceding year (interaction *P* = .055) and being admitted to the ICU in the preceding year for asthma-related problems (interaction *P* = .02).

TABLE III. Association between age of asthma onset with asthma morbidity outcomes

	Late-onset asthma, OR (95% CI [n = 435])*		Early-onset asthma, OR (95% CI [n = 468])*	
	Univariable (n = 506)	Multivariable (n = 435)*	Univariable (n = 543)	Multivariable (n = 468)*
≥3 Steroid tapers/y				
Lean	1.0	1.0	1.0	1.0
Overweight	1.2 (0.7-2)	1.04 (0.6-1.5)	1.4 (0.8-2.4)	1.3 (0.7-2.5)
Obese	1.5 (0.9-2.4)	1.11 (0.6-1.9)	2.7 (1.6-4.4)	2.4 (1.3-4.2)
Visited ED preceding year				
Lean	1.0	1.0	1.0	1.0
Overweight	1.3 (0.8-2.4)	1.6 (0.9-3)	1.2 (0.7-2)	1.06 (0.6-1.9)
Obese	2.2 (1.3-3.5)	2.0 (1.1-3.4)	2.4 (1.5-3.9)	1.8 (1.5-2.3)
Spent the night in the hospital for breathing reasons in the preceding year				
Lean	1.0	1.0	1.0	1.0
Overweight	1.6 (0.7-3.4)	1.9 (0.8-4)	2.4 (1.1-5.3)	1.8 (0.8-4)
Obese	2.6 (1.3-5)	2.2 (0.9-5)	4 (1.9-8.3)	3.3 (1.5-7)
Admitted to ICU for asthma reasons/preceding year				
Lean	1.0	1.0	1.0	1.0
Overweight	2.2 (0.6-7)	2.2 (0.6-7)	3 (0.7-11)	2 (0.4-8)
Obese	2.3 (0.7-7)	1.3 (1.4-5)	6.5 (2-22)	6 (1.7-22)
Mechanical ventilation ever				
Lean	1.0	1.0	1.0	1.0
Overweight	1.0 (0.4-2.6)	1.0 (0.4-2.6)	1.3 (0.6-2.8)	1.0 (0.4-2.3)
Obese	1.2 (0.6-2.6)	0.99 (0.2-2.2)	2.6 (1.4-5)	2.08 (1.1-4.3)
Pneumonia diagnosis ever				
Lean	1.0	1.0	1.0	1.0
Overweight	1.1 (0.6-1.9)	1.1 (0.6-1.9)	1.2 (0.8-2)	1.3 (0.8-2.2)
Obese	1.6 (1.03-2.5)	1.5 (0.9-2.4)	2.4 (1.6-3.4)	2.2 (1.4-3.7)

Adjusted for age, sex, race, atopy, and asthma duration. This significance is for the comparison of either overweight or obese status in reference to the lean category within asthma age-of-onset categories. Across asthma age-of-onset categories, comparisons were done by using an obesity/age-of-onset interaction in the model. Obesity and age-of-onset interactions: 3 or more steroid tapers, $P = .055$; admitted to the ICU for asthma, $P = .02$. Boldfaced estimates are significant at a P value of less than .05.

ED, Emergency department.

*Limited to asthmatic subjects with documented atopy by means of skin testing.

Association between BMI and duration of asthma

The association between BMI and asthma duration was modeled and adjusted for sex, race, and asthma severity while testing for an interaction with the asthma age-of-onset group. The rate of BMI increase for every year of having asthma among the early-onset group had a β value of 0.20 (95% CI, 0.07-0.33; $P = .002$) in comparison with the late-onset group, which had a β value of -0.05 (95% CI, -0.17 to 0.33 ; $P = .4$; the interaction between asthma duration and age of onset on BMI change was significant at $P < .008$, Fig 1).

DISCUSSION

Given its high prevalence in the general population, obesity is one of the most frequent comorbidities among subjects with asthma. Yet remarkably, the association between obesity and asthma severity has been inconsistent. This might be explained by a combination of factors, which include the fact that not every asthmatic subject is equally affected by increases in BMI and the fact that age of asthma onset might lead to differential weight-gain patterns. In other words, clinical or epidemiologic studies have likely involved heterogeneous groups of asthmatic phenotypes, which have different degrees of susceptibility to being overweight or for being overweight. The results from this study support this assertion by showing that the association between being overweight or obese as a comorbidity for asthma varies depending on whether asthma was acquired early in childhood

(<12 years of age) or later in life (≥ 12 years of age). Although the proportion of subjects with severe asthma and use of oral steroids and controller medications increases in relation to BMI categories in both groups, there are several important differences between them. Obese subjects with early-onset asthma were more likely to have increased airway obstruction (as determined by FEV₁/FVC ratio), greater bronchial hyperresponsiveness, and FEV₁ reversal after bronchodilators. Also, obese subjects with early-onset asthma had greater IgE levels. These differences across asthma age-of-onset groups were either not significant or less significant (ie, bronchial hyperresponsiveness) when restricting the analysis to nonobese asthmatic subjects.

In both groups being overweight or obese was associated with greater odds for several comorbid outcomes and respiratory symptoms when compared with lean asthmatic subjects. However, subjects with early-onset asthma had a marginal increase in the odds of having a high number of steroid bursts per year and were significantly more likely to be admitted to the ICU for asthma-related problems. Also, in contrast to obese subjects with late-onset asthma, obese subjects with early-onset asthma showed significantly increased odds for continuous chest tightness and sputum production. Interestingly, subjects with early-onset asthma had a steeper BMI increase for every year of having asthma after adjusting for asthma severity, atopy, age, and race.

Early- and late-onset asthma are recognized as distinct asthma phenotypes with unique clinical and genetic features.²¹ Subjects with early-onset asthma (<12 years of age) have a higher

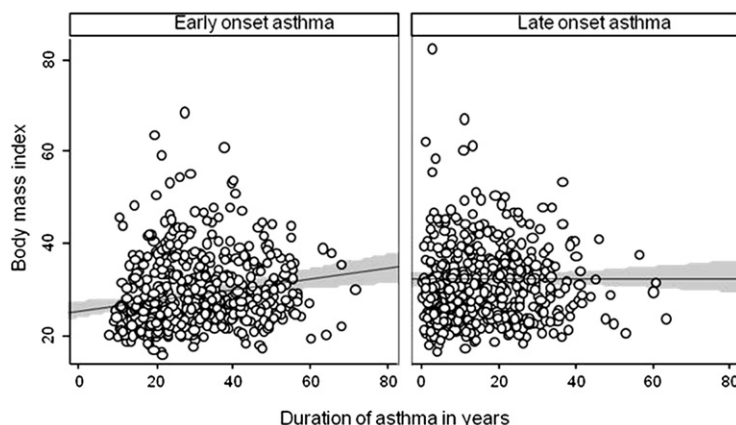


FIG 1. Association between BMI and years of having asthma by age of asthma onset. Linear regression models are adjusted for sex, race, and asthma severity. Early-onset asthma linear slope: $\beta = 0.20$; 95% CI, 0.07 to 0.33; $P = .002$. Late-onset asthma slope: $\beta = -0.05$; 95% CI, -0.17 to 0.33; $P = .4$. Interaction of BMI and asthma duration by age of onset of asthma: $P < .008$.

likelihood of allergic sensitization and reactions and a history of eczema and tend to have higher IgE levels; in contrast, subjects with late-onset asthma have less atopy but greater airway eosinophilic inflammation.²² Early-onset asthma has also been associated with single nucleotide polymorphisms that bear no association with a later-onset phenotype.²³ A sequence variant near *ORMLD3*, a gene on chromosome 17q21 previously associated with childhood asthma, was confined to subjects with early-onset asthma only, an association replicated in 6 European cohorts and 1 Asian cohort.

On the basis of early and late-onset asthma appearing to be different phenotypes, it is reasonable to hypothesize that they are differentially affected by increases in BMI. Although the longitudinal or cumulative effects of obesity on asthma are not known, in subjects with early-onset asthma, obesity has been shown to be an independent risk factor for unremitting asthma beyond puberty.²⁴ This suggests that there is an early-onset asthma phenotype in which obesity plays a role in the development of persistent asthma. In subjects with late-onset asthma, especially during adulthood, there are no studies to date that have evaluated the longitudinal effect of obesity on asthma outcomes or biomarkers of disease activity because the overwhelming majority of information is derived from cross-sectional studies. However, recent studies suggest that obesity might be an important factor among asthmatic subjects with specific phenotypic characteristics. Cluster analysis was used to identify specific asthma clusters in SARP participants based on demographic, clinical, and lung function variables. Of the clusters identified, the largest proportion of obese asthmatic subjects was observed in a cluster characterized by a higher female predominance, very late-onset asthma, and less atopy. Similar to the SARP cluster study, Halder et al¹² identified obesity as a component of a cluster characterized by a larger proportion of female subjects with less atopy and later-onset asthma. Although our study did not find a significant sex-based interaction between obesity, age of asthma onset, and sex, the majority of obese subjects with late-onset asthma were also female.

In evaluating whether age of asthma onset modifies the pattern of BMI increase, a cross-sectional analysis stratified by age of asthma onset was done to evaluate the slope of BMI change in relation to the years of having asthma. These models were adjusted for sex, race, atopy and asthma severity categories. Age

was not included in the model because of its high correlation with asthma duration in the early-onset group ($r^2 = 0.9$, $P < .01$). Subjects with early-onset asthma exhibited a steeper BMI increase for every year after being given a diagnosis of asthma, even after adjusting for asthma severity (change in BMI for every year of having asthma with adjustment for asthma severity: $\beta = 0.2$ [95% CI, 0.07–0.33]; without severity adjustment: $\beta = 0.3$ [95% CI, 0.2–0.45]). In contrast, subjects with late-onset asthma did not show a significant linear change in BMI with duration of asthma, even when restricting analysis to those with severe asthma (data not shown). These results might imply that in subjects with early-onset asthma, the association between obesity with increased asthma morbidity is the result of subjects with more severe asthma gaining weight and becoming obese, whereas in subjects with late-onset asthma, the association between obesity and increased asthma severity is more likely to be one of cause (obesity) and effect (severity).

Interestingly, there were notable differences in the associations between lung function and biomarkers of inflammation with increasing BMI across age-of-onset groups. Increasing BMI categories in the early-onset group were associated with more airway obstruction and a trend for lower exhaled nitric oxide levels but higher IgE levels, relationships not seen in the late-onset group.

There are several limitations to consider when interpreting these results. There is likely some degree of recall bias in ascertaining the age of asthma onset; however, this bias is likely not related to BMI categories. However, the strength of the association of duration with BMI in the early-onset group (and the lack of any relationship in late onset disease) argues that even for early-onset disease, there is reasonably good recall. Also, given that this is a cross-sectional study, it is impossible to fully ascertain the relationship between BMI and asthma at the time of asthma diagnosis. The SARP study does not include data on physical activity or exercise habits; therefore it is not possible to determine to what extent differences in weight gain and obesity risk across age-of-onset groups are driven by physical activity patterns. Although being obese might lead to an asthma diagnostic bias,²⁵ this is very unlikely to occur within the SARP study, given that all subjects with asthma are given rigorous diagnoses with a standardized algorithm.

Recent data suggest that in the United States there are approximately 5 million adults and more than 2 million children with current asthma who are obese (<http://www.cdc.gov/asthma/asthma.htm>). On the basis of the results of this and other studies, adult asthmatic subjects experience higher-end health care use, which translates into an enormous economic burden. Future studies to evaluate mechanisms by which obesity affects asthma should consider stratifying by age of asthma onset because the relationship appears to be very different. Understanding the implications and mechanisms of obesity as it relates to asthma will allow targeted therapeutic interventions.

Clinical implications: These results suggest that in subjects with early-onset asthma, obesity and increased asthma severity result from subjects with severe asthma becoming obese, whereas in subjects with late-onset asthma, obesity and increased asthma severity are potentially more likely to be causatively associated.

REFERENCES

1. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008; 63:14-20.
2. Sutherland TJ, Cowan JO, Taylor DR. Dynamic hyperinflation with bronchoconstriction: differences between obese and nonobese women with asthma. *Am J Respir Crit Care Med* 2008;177:970-5.
3. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008;178:682-7.
4. Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, et al. An Official American Thoracic Society workshop report: obesity and asthma. *Proc Am Thorac Soc* 2010;7:325-35.
5. Holguin F, Cribbs S, Fitzpatrick AM, Ingram RH Jr, Jackson AC. A deep breath bronchoconstricts obese asthmatics. *J Asthma* 2010;47:55-60.
6. Celedon JC, Palmer LJ, Litonjua AA, Weiss ST, Wang B, Fang Z, et al. Body mass index and asthma in adults in families of subjects with asthma in Anqing, China. *Am J Respir Crit Care Med* 2001;164:1835-40.
7. Sutherland ER, Lehman EB, Teodorescu M, Wechsler ME. National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2009;123:1328-34, e1321.
8. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy* 2008;63:570-4.
9. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37:1049-54.
10. Kazaks A, Uriu-Adams JY, Stern JS, Albertson TE. No significant relationship between exhaled nitric oxide and body mass index in people with asthma [letter]. *J Allergy Clin Immunol* 2005;116:929-30, author reply 930.
11. 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.
12. 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.
13. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;368: 804-13.
14. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101-8.
15. Moore WC, Bleecker ER, Curren-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al, for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Characterization of the severe asthma phenotype by the National Heart, Lung and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:405-13.
16. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000;162:2341-51.
17. 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.
18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
19. Fahy JV. A safe, simple, standardized method should be used for sputum induction for research purposes. *Clin Exp Allergy* 1998;28:1047-9.
20. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912-30.
21. Srivastava A, Cotton C, Paterson AD. Sex- and age-of-onset-based locus heterogeneity in asthma. *Genet Epidemiol* 2001;21(suppl 1):S154-9.
22. Dizier MH, Besse-Schmittler C, Guilloud-Bataille M, Selinger-Leneman H, Kauffmann F, Clerget-Darpoux F, et al. Indication of linkage and genetic heterogeneity of asthma according to age at onset on chromosome 7q in 107 French EGEA families. *Eur J Hum Genet* 2001;9:867-72.
23. Halapi E, Gudbjartsson DF, Jonsdottir GM, Bjornsdottir US, Thorleifsson J, Helgadóttir H, et al. A sequence variant on 17q21 is associated with age at onset and severity of asthma. *Eur J Hum Genet* 2010;18:902-8.
24. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004;170:78-85.
25. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest* 2008;134:317-23.

TABLE E1. Proportion of asthmatic subjects with persistent respiratory symptoms by BMI category and age of asthma onset (no. [%])

	Late onset (n = 506)	Early onset (n = 543)
Cough		
Lean	32 (20)	29 (25)
Overweight	37 (23)	24 (20)
Obese	91 (57)	64 (55)
	<i>P</i> = .02	<i>P</i> < .01
Sputum		
Lean	36 (26)	24 (22)
Overweight	27 (19)	24 (23)
Obese	78 (55)	58 (55)
	<i>P</i> = .09	<i>P</i> < .01
Chest tightness		
Lean	28 (23)	32 (26)
Overweight	24 (19)	28 (23)
Obese	72 (58)	62 (51)
	<i>P</i> = .04	<i>P</i> < .01
Wheeze		
Lean	27 (19)	28 (23)
Overweight	26 (19)	23 (19)
Obese	88 (62)	71 (58)
	<i>P</i> < .01	<i>P</i> < .01
Dyspnea		
Lean	37 (21)	43 (26)
Overweight	32 (19)	35 (22)
Obese	101 (60)	83 (51)
	<i>P</i> < .01	<i>P</i> < .01
Nocturnal symptoms		
Lean	24 (20)	31 (28)
Overweight	23 (19)	22 (20)
Obese	74 (61)	59 (52)
	<i>P</i> < .01	<i>P</i> < .01
Low AQLQ score		
Lean	19 (15)	29 (24)
Overweight	30 (24)	21 (17)
Obese	77 (61)	70 (59)
	<i>P</i> < .01	<i>P</i> < .01
Severe asthma		
Lean	52 (22)	48 (24)
Overweight	52 (22)	51 (25)
Obese	133 (56)	102 (51)
	<i>P</i> < .01	<i>P</i> < .01

Boldfaced results indicate statistical significance.

AQLQ, Asthma Quality of Life Questionnaire.

TABLE E2. Proportion of morbidity outcomes by BMI categories within each age-of-onset category (no. [%])

	Late onset (n = 506)	Early onset (n = 543)
≥3 Steroid tapers		
Lean	32 (22)	29 (23)
Overweight	34 (24)	30 (24)
Obese	78 (54)	66 (53)
	<i>P</i> = .2	<i>P</i> < .01
Visited ED in preceding year		
Lean	30 (18)	37 (25)
Overweight	36 (22)	34 (23)
Obese	94 (60)	75 (51)
	<i>P</i> < .01	<i>P</i> < .01
Spent the night in the hospital for breathing		
Lean	12 (15)	10 (15)
Overweight	17 (22)	18 (28)
Obese	50 (63)	37 (57)
	<i>P</i> = .04	<i>P</i> < .01
Admitted to ICU for asthma reasons/preceding year		
Lean	4 (14)	3 (10)
Overweight	8 (28)	7 (24)
Obese	16 (57)	19 (66)
	<i>P</i> < .3	<i>P</i> < .01
Mechanical ventilation		
Lean	10 (24)	15 (22)
Overweight	10 (24)	16 (23)
Obese	22 (52)	37 (54)
	<i>P</i> < .8	<i>P</i> < .01
Pneumonia diagnosis ever		
Lean	44 (22)	73 (28)
Overweight	45 (23)	67 (26)
Obese	108 (55)	122 (47)
	<i>P</i> < .01	<i>P</i> < .01

Boldfaced results indicate statistical significance.

ED, Emergency department.