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Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD

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BACKGROUND: Obesity is prevalent in the United States; however, the impact of obesity on COPD morbidity is unclear. We hypothesized that obesity is associated with worse outcomes in COPD.

METHODS: We examined 3,631 participants from the multicenter prospective cohort study Genetic Epidemiology of COPD (COPDGene) who had spirometry-confirmed COPD, a postbronchodilator $FEV_1 < 80\%$ predicted, and a BMI ≥ 18.5 kg/m^2. We conducted logistic and linear regression analyses to determine the association between COPD outcomes and obesity class, adjusting for relevant confounders. The referent for obesity classes included normal/overweight individuals (BMI range, 18.5-29.9 kg/m^2).

RESULTS: Overall, 35% of participants were obese, with 21% class I (BMI range, 30-34.9 kg/m^2), 9% class II (BMI range, 35-39.9 kg/m^2), and 5% class III (BMI ≥ 40 kg/m^2). The number of comorbidities increased with increasing obesity class ($P < .001$). Increasing obesity class was independently associated with worse respiratory-specific and general quality of life (QOL) (St. George's Respiratory Questionnaire score and Short Form-36 score version 2, respectively), reduced 6-min walk distance (6MWD), increased dyspnea (Modified Medical Research Council score ≥ 2), and greater odds of severe acute exacerbation of COPD (AECOPD). The associations between obesity and worse outcomes were independent of the presence of comorbidities, except in the case of SF-36 and severe exacerbations.

CONCLUSIONS: Obesity is prevalent among individuals with COPD and associated with worse COPD-related outcomes, ranging from QOL and dyspnea to 6MWD and severe AECOPD. These associations were strengthened when obesity was analyzed as a dose-dependent response. Obesity in patients with COPD may contribute to a worse COPD-related course.

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KEY WORDS: COPD; dose response; exacerbation; morbidity; obesity

ABBREVIATIONS: 6MWD = 6-min walk distance; AECOPD = acute exacerbation of COPD; COPDGene = Genetic Epidemiology of COPD; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MCID = minimum clinically important difference; mMRC = Modified Medical Research Council; NHW = non-Hispanic White; QOL = quality of life; SF-36 = Short Form-36; SGRQ = St. George's Respiratory Questionnaire

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In the United States, 6% of adults have COPD[1] and 35% are obese[2-4]; however, the prevalence of obesity among patients with COPD is unclear, with estimates ranging from 6% to 54%.[5-9] Much attention has been given to the association between COPD and low BMI,[10-13] with studies suggesting a U-shaped relationship between weight and general health outcomes in individuals with COPD.[14-17] Obesity may be linked to adverse health consequences in patients with COPD[18-20]; however, these consequences are not well delineated.

Obesity is associated with myriad pulmonary decrements, including an increased prevalence and severity of asthma, rate of FEV_1 decline, prevalence of sleep-disordered breathing, and risk for perioperative complications.[19,21,22] Among those with COPD, obesity has demonstrated mixed effects, including worse quality of life (QOL), dyspnea, and exercise tolerance (6-min walk distance [6MWD]),[23] but also reduced mortality[14,24,25] and less severe airflow obstruction.[23,26]

Outcomes associated with risk for morbidity and mortality, such as COPD exacerbations, have not been consistently reported. Whether subpopulations of obese individuals with COPD, based upon sex and race for example, may be at greatest risk for worse outcomes is unknown. Despite emerging information regarding racial differences in the effect of weight on outcomes in chronic diseases,[27,28] representation of minorities in clinical COPD cohorts is lacking. Because women comprise a growing proportion of incident COPD cases and blacks incur greater mortality than whites,[29] the impact of race and sex on risk factors, such as obesity for COPD-related outcomes, needs investigation.

We examined a large well-characterized cohort of subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2 through 4 COPD from the multicenter Genetic Epidemiology of COPD (COPDGene) study to determine the impact of obesity on COPD morbidity.

Methods

Study Population

The COPDGene study details have been reported.[30] Briefly, the COPDGene study is a multicenter observational study including current and former smokers designed to identify genetic factors associated with COPD. Between January 2008 and April 2011, 10,192 non-Hispanic White (NHW) and black adults aged 45 to 80 years of age with a minimum 10 pack-year smoking history were enrolled. Participants were phenotyped by completing questionnaires, blood tests, imaging, and spirometry measurements. This study was conducted in accordance with the amended Declaration of Helsinki and approved by the institutional review board at each study center; all participants provided written, informed consent.

From the full cohort, 3,753 participants had spirometry-confirmed COPD at baseline, with an FEV_1 to FVC ratio < 0.70 and a postbronchodilator $FEV_1 < 80\%$ predicted. We excluded participants with a low BMI (BMI < 18.5 kg/m^2; n = 122) because these participants may represent a unique phenotype compared with normal or overweight individuals.[23,31]

Measurements

Weight and height were measured; BMI was calculated as mass in kilograms divided by height in meters squared. Demographic characteristics and comorbidities were self-reported through standardized study questionnaires. Level of education was defined as less than high school, high school ± some college, or college and beyond. Comorbidity count represented the number of the following conditions present: allergies, asthma, cancer, coronary heart disease, congestive heart failure, cerebrovascular attack/transient ischemic attack, diabetes, gastroesophageal reflux disease, hypertension, hyperlipidemia, OSA, osteoarthritis, osteoporosis, peptic ulcer disease, peripheral arterial disease, and rheumatoid arthritis.[32,33]

Continuous outcomes were analyzed using linear regression, including the St. George's Respiratory Questionnaire (SGRQ),[34,35] the Short Form-36 (SF-36) total score,[36,37] and the 6MWD.[38,39] Binary outcomes were analyzed using logistic regression, including Modified Medical Research Council (mMRC)[40,41] score ≥ 2 vs < 2, aligned with the GOLD[42] definition of more (vs less) symptoms, moderate acute exacerbation of COPD (AECOPD) defined as a self-reported exacerbation treated with antibiotics and/or oral corticosteroids in the last year, and severe AECOPD requiring ED visitation or hospital admission.[43] Accounting for FEV_1 percent predicted, mMRC score, and exacerbation history, GOLD 2013 ABCD[1] categories were defined as previously done by Han and colleagues.[44]

Statistical Analyses

Cohort characteristics are presented as frequencies, means (SDs), and medians (interquartile ranges). Comparisons were conducted using the *t* test for continuous variables or the χ^2 test for categorical variables. A two-sided *P* value $\leq .05$ defined statistical significance. The exposure

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of interest was obesity class. Exploratory data analyses examined BMI as a continuous vs categorical variable and explored univariable associations with obesity class. Histograms, locally weighted scatterplot smoothing plots, and univariate regressions demonstrated similar behavior for normal and overweight individuals. Therefore, the reference group included normal and overweight individuals (BMI range, 18.5-29.9 kg/m^2). Obesity was categorized into three classes: class I (BMI range, 30-34.9 kg/m^2), class II (BMI range, 35-39.9 kg/m^2), and class III (BMI ≥ 40 kg/m^2).[45,46]

Adjusted models accounted for age, sex, race, level of education, FEV_1 to height squared ratio,[47] smoking status (current/former), and smoking pack-years. Additional models also adjusted for comorbidity count. When FEV_1 was the outcome of interest, the FEV_1 to height squared ratio was removed from the covariates. Interaction terms were constructed between obesity status and race, sex, and lung function separately to determine if effect modification was present. Stratified analyses were conducted by race and sex to illustrate the impact of covariates on obesity class and the outcomes of interest.

Results

Participant Characteristics

Demographic and clinical characteristics are presented in Table 1, stratified by obesity class. Overall, 34% of participants were obese, with 21% in class I, 9% in class II, and 5% in class III. Age, sex, race, education, and smoking pack-years were similar across weight categories. Active tobacco use (current smoking) was most prevalent among the normal/overweight individuals (43%) and those with class III obesity (40%). Absolute and percent predicted FEV_1, and the FEV_1 to FVC ratio, were lowest among those who were normal/overweight. As obesity class increased, the proportion of GOLD A and C participants decreased and the proportion of GOLD B increased ($P < .001$ for trend across obesity class for each GOLD category). The proportion of GOLD D was not statistically different across obesity class ($P = .452$). Comorbidity count increased with increasing obesity class ($P < .001$), ranging from a mean of 2.6 comorbid conditions among normal/overweight individuals to a mean of 4.0 comorbid conditions among the most obese (Table 2). Across all obesity classes, gastroesophageal reflux disease, hypertension, and hyperlipidemia were the most prevalent comorbidities.

TABLE 1] Clinical and Demographic Characteristics of Study Participants

Characteristic	Normal/Overweight (18.5-29.9 kg/m^2)	Obesity Class I (30-34.9 kg/m^2)	Obesity Class II (35-39.9 kg/m^2)	Obesity Class III (≥ 40 kg/m^2)	*P* Value for Trend
Participants	2,383 (66)	748 (21)	316 (9)	184 (5)	
Age, y	63 ± 9	64 ± 9	62 ± 8	61 ± 9	.078
Male	1,365 (57)	423 (57)	133 (42)	70 (38)	.073
NHW race	1,850 ± 78	567 ± 76	240 ± 76	135 ± 73	.144
Education					.359
Less than high school	334 (14)	116 (16)	46 (15)	30 (16)	
High school ± some college	1,313 (55)	390 (52)	185 (59)	105 (57)	
College and beyond	735 (31)	242 (32)	85 (27)	49 (27)	
Current smoker	1,034 (43)	274 (37)	106 (34)	73 (40)	< .001
Smoking, pack-y	53 ± 28	53 ± 27	56 ± 28	51 ± 27	.246
FEV_1					
Absolute, L	1.4 ± 0.7	1.5 ± 0.6	1.5 ± 0.6	1.5 ± 0.5	.001
Percent predicted	49 ± 19	53 ± 17	53 ± 16	53 ± 14	< .001
FEV_1 to FVC ratio					
Absolute	0.48 ± 0.1	0.53 ± 0.1	0.54 ± 0.1	0.57 ± 0.1	< .001
GOLD category					
A	644 (27)	189 (25)	60 (19)	21 (11)	< .001
B	434 (18)	186 (25)	100 (32)	61 (33)	< .001
C	239 (10)	59 (8)	18 (6)	6 (3)	< .001
D	1,066 (45)	314 (42)	138 (44)	96 (52)	.452

Values are presented as mean ± SD, No. (%), or as otherwise indicated. GOLD = Global Initiative for Chronic Obstructive Lung Disease; NHW = non-Hispanic white.

TABLE 2] Self-Reported Comorbidities of Study Participants

Characteristic	Normal/Overweight (18.5-29.9 kg/m^2)	Obesity Class I (30-34.9 kg/m^2)	Obesity Class II (35-39.9 kg/m^2)	Obesity Class III (≥ 40 kg/m^2)	*P* Value for Trend
Participants	2,383 (66)	748 (21)	316 (9)	184 (5)	
Comorbidity count[a]	2.6 ± 2	3.4 ± 2	3.9 ± 2	4.0 ± 2	< .001
Comorbidity					
Allergies	555 (23)	187 (25)	95 (30)	50 (27)	.027
Asthma	502 (21)	207 (28)	96 (30)	59 (32)	< .005
Cancer	150 (6)	63 (8)	20 (6)	9 (5)	.218
CHD	373 (16)	131 (18)	71 (22)	30 (16)	.024
CHF	90 (4)	46 (6)	35 (11)	23 (13)	< .001
CVA/TIA	138 (6)	48 (6)	19 (6)	7 (4)	.864
Diabetes mellitus	198 (8)	145 (19)	92 (29)	50 (27)	< .001
GERD	657 (28)	269 (36)	110 (35)	65 (35)	< .001
Hypertension	1,080 (45)	432 (58)	210 (66)	125 (68)	< .001
Hyperlipidemia	918 (39)	352 (47)	162 (51)	91 (49)	< .001
OSA	243 (10)	182 (24)	113 (36)	93 (51)	< .001
Osteoarthritis	414 (17)	190 (25)	94 (30)	56 (30)	< .001
Osteoporosis	431 (18)	111 (15)	41 (13)	26 (14)	.004
Peptic ulcer disease	237 (10)	78 (10)	31 (10)	19 (10)	.764
Peripheral arterial disease	74 (3)	30 (4)	14 (4)	6 (3)	.157
Rheumatoid arthritis	187 (8)	81 (11)	35 (11)	22 (12)	.001

Values are presented as mean ± SD, No. (%), or as otherwise indicated. CHD = coronary heart disease; CHF = congestive heart failure; CVA = cerebrovascular attack; GERD = gastroesophageal reflux disease; TIA = transient ischemic attack.
[a]Count of the comorbidities listed in the table.

Association of Obesity Class With COPD Outcomes

In univariable analyses, increasing obesity class was associated with worse QOL, lower 6MWD, and higher odds of dyspnea, in a dose-dependent fashion (e-Table 1). In addition, class III obesity was associated with higher odds of severe AECOPD (OR, 1.57; $P = .007$).

In adjusted models, increasing severity of obesity remained statistically significantly associated with higher SGRQ score and lower SF-36 score (worse respiratory-specific and general QOL, respectively), reduced 6MWD, and higher odds of an mMRC score ≥ 2 (increased dyspnea) (Fig 1, Table 3). These associations increased in magnitude with increasing obesity class. For example, class I obesity was associated with a 1.4-fold increased odds of dyspnea, and class III obesity was associated with nearly a fourfold increased odds of dyspnea. Obesity was associated with increased odds of reporting severe exacerbations, and odds of severe AECOPD increased with increasing obesity class ($P = .005$). The link between obesity and risk of moderate exacerbations was apparent, but less consistent. Obesity class I was significantly associated with increased odds of moderate AECOPD (OR, 1.38; 95% CI, 1.08-1.75; $P = .009$); however, the trend across increasing obesity classes was not statistically significant ($P = .115$). Obesity was not associated with worse lung function (data not shown). On the contrary, those who were obese had slightly higher FEV_1 percent predicted compared with normal/overweight participants (obesity class I: $\beta = 4.05$; 95% CI, 2.64-5.46; obesity class II: $\beta = 4.92$; 95% CI, 2.89-6.96; obesity class III: $\beta = 3.76$; 95% CI, 1.15-6.38).

When also adjusting for comorbidity count, increasing obesity class remained significantly associated with higher SGRQ score, lower 6MWD, and increased odds of an mMRC score ≥ 2; however, effect sizes were attenuated. Again, the dose-dependent response was observed, with increasing obesity class associated with greater decrements in outcomes. Obesity was no longer associated with SF-36 score and exacerbations, suggesting that the effect of obesity on these outcomes may be mediated by comorbidity burden among obese individuals (Table 3). Adjusted models including individual comorbidities as covariates, rather than comorbidity count, demonstrated similar findings, with the exception of the moderate AECOPD-obesity class I

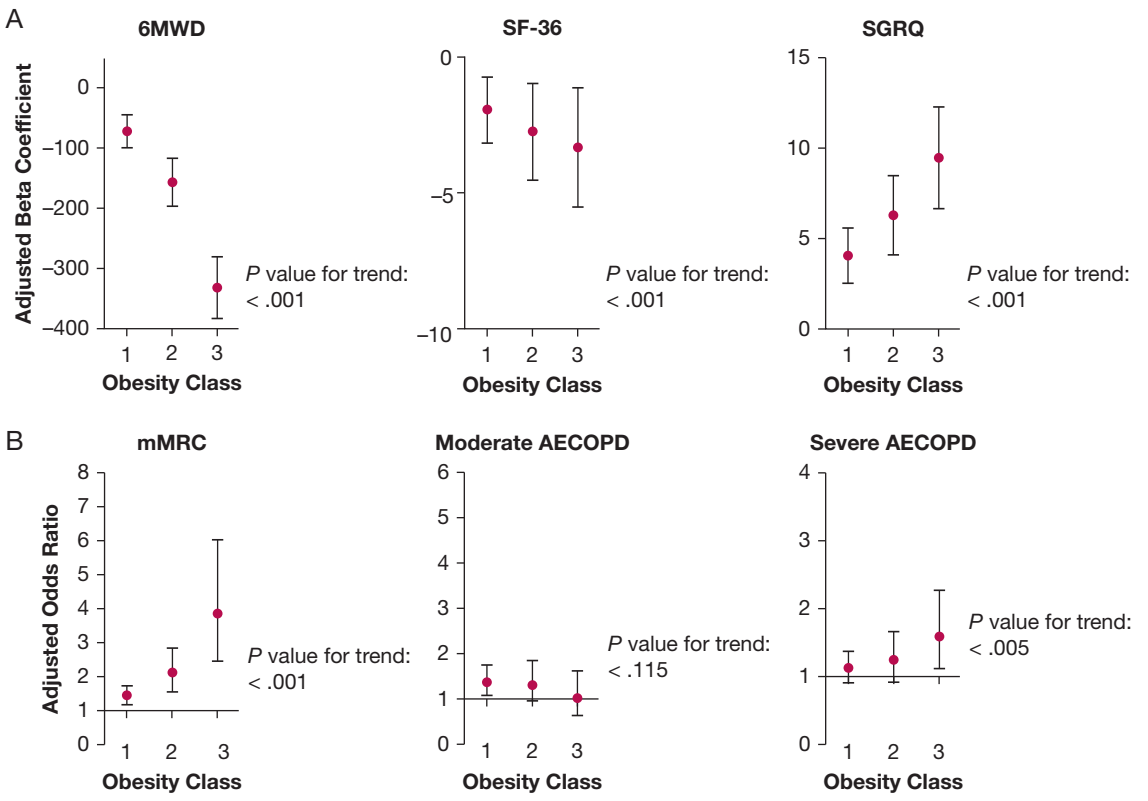

Figure 1 – *A, B, Dose-dependent response to higher obesity class. Adjusted for age, sex, race, education, FEV_1 to height squared ratio, smoking status, and smoking pack-y. Referent in all models includes normal/overweight individuals (BMI range, 18.5-29.9 kg/m^2). Markers represent the adjusted β coefficients (A) or adjusted ORs (B) for the association between each obesity class and the specified outcome. Bars represent the 95% CIs for each β coefficient (A) or OR (Panel B). The P values for trend represent the statistical significance of the increase or decrease in the outcome across obesity classes. 6MWD = 6-min walk distance; AECOPD = acute exacerbation of COPD; mMRC = Modified Medical Research Council; SF-36, Short Form-36; SGRQ, St. George's Respiratory Questionnaire.*

association, which was attenuated (e-Table 2). These models demonstrated the consistent negative impact of osteoporosis and cerebrovascular attack/transient ischemic attack. Separately examining the impact of metabolic (hypertension, diabetes, and hyperlipidemia) vs nonmetabolic comorbidities (remaining 13 conditions) did not alter our findings or suggest that metabolic disorders more strongly mediate the effect of BMI on outcomes compared with nonmetabolic comorbidities.

Race, Sex, and Lung Function Interactions With Obesity Class

A statistically significant interaction between obesity class and sex was observed for SGRQ score (interaction $P = .043$ for trend) (Table 4). Obesity was more strongly associated with worsening SGRQ score among women compared with men. The interaction between obesity and race was statistically significant for 6MWD (interaction $P = .011$ for overall trend) (Table 4). Increasing obesity class was associated with greater reduction in 6MWD among NHW compared with black participants. Finally, the interaction between obesity and lung function was statistically significant for both SGRQ score and severe AECOPD (Table 4). Increasing obesity class was associated with worse SGRQ scores and greater odds of severe AECOPD among those with healthier lung function (≥ 50% predicted) compared with those with lower lung function (< 50% predicted). The association between obesity and other outcomes did not vary significantly by race, sex, or lung function.

Discussion

In this large, well-characterized cohort of individuals with COPD and GOLD stages 2 through 4 severity of airflow obstruction, obesity was prevalent, affecting approximately one-third of the population. Increasing severity of obesity was associated with worse COPD morbidity. We show that obesity is not only linked to subjective outcomes, such as worse QOL and dyspnea, but also to increased risk of severe AECOPD. The link between obesity and exacerbations may be partly explained by increased prevalence of comorbidities

TABLE 3] Health Outcome Multivariable Models

	Base Models			Base Model + Comorbidity Count		
Outcome	β	95% CI	*P* Value	β	95% CI	*P* Value
SGRQ total score						
Obese class I	4.06	2.54 to 5.58	< .001	2.37	0.87 to 3.86	.002
Obese Class II	6.28	4.09 to 8.48	< .001	3.24	1.07 to 5.40	.003
Obese Class III	9.45	6.64 to 12.27	< .001	6.09	3.33 to 8.85	< .001
P value for trend			< .001			< .001
SF-36 total score						
Obese class I	−1.95	−3.17 to −0.73	.002	−0.90	−2.09 to 0.28	.135
Obese class II	−2.76	−4.54 to −0.97	.003	−0.74	−2.50 to 1.02	.412
Obese class III	−3.32	−5.51 to −1.12	.003	−1.03	−3.19 to 1.12	.347
P value for trend			< .001			.146
6MWD, ft						
Obese class I	−71.66	−99.25 to −44.07	< .001	−55.65	−83.39 to −27.90	< .001
Obese class II	−156.28	−196.08 to −116.47	< .001	−128.93	−169.11 to −88.76	< .001
Obese class III	−330.82	−382.21 to −279.43	< .001	−299.75	−351.43 to −248.07	< .001
P value for trend			< .001			< .001
	OR	95% CI	*P* value	OR	95% CI	*P* value
mMRC score ≥ 2						
Obese class I	1.42	1.16 to 1.72	.001	1.22	1.00 to 1.50	.052
Obese class II	2.09	1.54 to 2.83	< .001	1.66	1.21 to 2.27	.001
Obese class III	3.84	2.44 to 6.04	< .001	2.95	1.86 to 4.69	< .001
P value for trend			< .001			< .001
Moderate AECOPD						
Obese class I	1.38	1.08 to 1.75	.009	1.24	0.97 to 1.59	.082
Obese class II	1.31	0.93 to 1.85	.120	1.08	0.76 to 1.54	.669
Obese class III	1.02	0.64 to 1.62	.944	0.83	0.52 to 1.33	.433
P value for trend			.115			.916
Severe AECOPD						
Obese class I	1.12	0.91 to 1.38	.286	1.03	0.83 to 1.28	.772
Obese class II	1.24	0.92 to 1.66	.152	1.05	0.78 to 1.42	.734
Obese class III	1.59	1.12 to 2.27	.010	1.35	0.94 to 1.93	.102
P value for trend			.005			.172

Base models are adjusted for age, sex, race, education, FEV_1 to height squared ratio, smoking status, and smoking pack-years. Referent in all models includes normal/overweight individuals (BMI range, 18.5-29.9 kg/m^2). 6MWD = 6-min walk distance; AECOPD = acute exacerbation of COPD; mMRC = Modified Medical Research Council; SF-36 = Short Form-36; SGRQ = St. George's Respiratory Questionnaire.

among obese individuals compared with normal/overweight individuals. We also show that increasing severity of obesity adversely impacts outcomes in a dose-dependent fashion, including those with class I obesity, but most dramatically affecting those with class III obesity. Furthermore, obesity is more likely to be associated with worse QOL among women compared with men, and more likely to lead to decreased functional status among NHW compared with black participants; however, generally, the link between obesity and worse COPD outcomes was consistent regardless of sex or race.

Our findings add to the existing understanding of the obesity to COPD relationship by reporting the dose-dependent impact of obesity on markers of QOL, symptom burden, and disease severity of COPD. The clinical characteristics and size of our study population allow the reporting of prevalence and morbidity associated with obesity within a well-defined cohort of

TABLE 4] Interactions by Sex, Race, and Lung Function With Obesity Categories

Health Outcome	Stratified Models						Interaction Model
	Men			Women			
SGRQ total score	β	95% CI	*P* Value	β	95% CI	*P* Value	*P* Value
Obese class I	2.78	0.77 to 4.80	.007	5.71	3.37 to 8.05	< .001	
Obese class II	4.21	1.33 to 7.08	.004	9.00	5.56 to 12.44	< .001	
Obese class III	8.17	3.74 to 12.60	< .001	10.65	6.96 to 14.33	< .001	
P value for trend			< .001			< .001	.043
	NHW Race			Black Race			
6MWD, ft	OR	95% CI	*P* Value	OR	95% CI	*P* Value	
Obese class I	−83.84	−114.66 to −53.02	< .001	−29.95	−91.33 to 31.42	.338	
Obese class II	−175.89	−220.20 to −131.57	< .001	−80.67	−170.49 to 9.14	.078	
Obese class III	−359.45	−417.53 to −301.37	< .001	−245.55	−355.34 to −135.76	< .001	
P value for tend			< .001			< .001	.011
	FEV_1 ≥ 50% Predicted			FEV_1 < 50% Predicted			
SGRQ total score	β	95% CI	*P* Value	β	95% CI	*P* Value	*P* Value
Obese class I	4.84	2.61 to 7.06	< .001	2.37	0.12 to 4.62	.039	
Obese class II	8.53	5.36 to 11.70	< .001	2.03	−1.21 to 5.27	.218	
Obese class III	11.62	7.54 to 15.71	< .001	5.19	1.08 to 9.30	.013	
P value for tend			< .001			.003	.001
Severe AECOPD	OR	95% CI	*P* Value	OR	95% CI	*P* Value	*P* Value
Obese class I	1.35	1.00 to 1.83	.049	0.90	0.67 to 1.20	.470	
Obese class II	1.43	0.95 to 2.15	.089	0.95	0.63 to 1.42	.803	
Obese class III	1.81	1.11 to 2.95	.017	1.20	0.73 to 1.97	.474	
P value for tend			.004			.886	.050

Sex models are adjusted for age, race, obesity class, education, baseline FEV_1 to height squared ratio, smoking status, and smoking pack-y. Race models are adjusted for age, sex, obesity class, education, baseline FEV_1 to height squared ratio, smoking status, and smoking pack-y. Lung function models are adjusted for age, sex, race, obesity class, education, smoking status, and smoking pack-y. See Table 1 and 3 legends for expansion of other abbreviations.

patients with COPD. Estimates of obesity prevalence among individuals with COPD vary widely from 5% to 55%.[5-9] The prevalence of obesity may be higher in those with preserved ratio impaired spirometry compared with those with COPD.[48] The prevalence of obesity (34%) and severe obesity (BMI ≥ 40 kg/m^2; 5.1%) in our cohort was similar to the general US population.[2,3,49] Obese individuals reported worse COPD outcomes when compared with normal/overweight individuals, including respiratory-specific and general QOL, exercise tolerance, and dyspnea. These results are consistent with the literature linking obesity to reduced QOL,[50] impaired exercise tolerance,[50,51] and dyspnea.[50,52] Our findings extend prior reports through the observation of dose-dependent detriments in adverse effects in response to increasing obesity class, with significant impact occurring even at the lowest obesity class. The strength of obesity-COPD association is further supported by the magnitude of our results, which exceeded the minimum clinically important difference (MCID)[53] for several outcomes. For example, although individuals with class I obesity had a 4-point increase or worsening, in respiratory-specific QOL (SGRQ) compared with normal/overweight individuals (the SGRQ MCID is 4), those with class III obesity demonstrated a 9.5-point increase. Similarly, although those with class I obesity walked 72 fewer feet than their normal/overweight counterparts on the 6MWD (the 6MWD MCID in COPD is 98 ft), those with class III obesity exhibited remarkably reduced exercise capacity, walking 330 fewer feet than their normal/overweight counterparts, which is > 3 times the MCID for 6MWD.[54] Similarly, those with class I obesity were 1.4 times as likely to report greater levels of dyspnea (mMRC score ≥ 2, consistent with GOLD guidelines of symptomatic disease),[42] whereas those with class III obesity were nearly 4 times as likely to report greater levels of dyspnea.

Our results also expand previous research by highlighting that obesity was linked to severe COPD exacerbations—a novel finding to our knowledge. Severe obesity has been shown to increase health-care utilization in other populations, by increasing risk for hospitalization, death from respiratory infections,[55] and prolonging length of hospital stay.[56] Obese individuals had increased comorbidity burden, and accounting for comorbidities did not eliminate the impact of obesity on respiratory symptoms and QOL; however, the association between obesity and severe AECOPD was attenuated after adjusting for this comorbidity count. Therefore, the link between obesity and severe AECOPD may be driven by the complexity of overlapping conditions among obese patients. Obesity is increasingly recognized to correlate with increased comorbidity burden,[23,32,50] leading to complex management of multifactorial symptom expression and disease burden. Therefore, diagnosing comorbidities and understanding their role in the expression of COPD among obese individuals is critical to both their symptomatic and preventative management.

Overall, the contribution of obesity to worse outcomes was consistent across sex and race; however, the impact of obesity was greater in women compared with men regarding respiratory QOL and was greater among NHW compared with black participants regarding reduced functional status. Our findings support known sex imbalances in the experience of COPD.[57,58] A combination of smaller airway caliber and increased hyperresponsiveness,[59] along with greater anxiety and depression,[60] has been hypothesized to cause the disproportionate symptom burden experienced by women. Women also demonstrate altered leptin metabolism with higher secreted leptin levels per BMI strata.[61] These increases in leptin secretion may contribute to sex differences in COPD pathogenesis through a pathway of chronic systemic inflammation.[62-64] Race may further moderate the role of obesity in COPD. Variations in BMI and body fat distribution may explain the moderation by race/ethnicity[65]; however, there is a paucity of information regarding the role of obesity in COPD among black populations. Generally, obesity prevalence and severity were similar among black and NHW participants, and the impact of obesity on COPD morbidity was similarly impacted across race. The impact of race and sex on COPD-related morbidity among obese individuals requires further investigation of these understudied populations. In addition, we found that increasing obesity class was more strongly associated with worse respiratory-specific QOL and greater odds of severe AECOPD among those with healthier lung function. The reason that the negative impact of obesity on both symptomatic and severe exacerbation risk is greater among those with better lung function is unclear but provides a targeted population for more aggressive risk modification and further study.

This study has limitations. Participants were enrolled in an observational cohort; therefore, our findings may not be generalizable to the general clinical population. However, our recruitment from 21 centers did allow for a diverse sampling of the US population. Our cohort has relatively equal sex distribution and approximately 30% black participants, not typical of research cohorts often predominantly composed of NHW men, and allowed for the assessment of the impact of obesity by sex and race. Our results are cross sectional and cannot determine causality; however, biological mechanisms support the plausibility of our findings. Obesity alters lung mechanics and therefore may directly contribute to pulmonary symptoms and impairment.[19] In addition, increased adipose may cause local tissue hypoxia and lead to chronic inflammation,[20] which have been hypothesized to advance disease progression and worsen outcomes. BMI has been criticized as a crude marker of both weight and body habitus. The COPDGene study did not collect anthropometric measurements, such as waist-to-hip ratio, to allow a more in-depth examination of the role of body habitus; however, BMI is a readily available measurement routinely collected in the clinical arena; therefore, our findings may more easily be translated into practice.

Conclusions

Comorbid obesity and COPD is prevalent, and increasing obesity is associated with increased comorbidity, reduced QOL, impaired functional status, and increased risk for severe AECOPD. Importantly, even class I obesity adversely impacted COPD outcomes, with increasing severity of obesity associated with greater magnitude of deficits in a dose-dependent fashion. Patients with COPD should be assessed for comorbid obesity and closely monitored for COPD outcomes. Determination of the impact of weight loss on these outcomes in obese patients warrants investigation.

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Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

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