Differential Impact of Low Fat-Free Mass in People With COPD Based on BMI Classifications

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Differential Impact of Low Fat-Free Mass in People With COPD Based on BMI Classifications

Results From the COPD and Systemic Consequences-Comorbidities Network

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BACKGROUND: Alterations in body composition, including a low fat-free mass index (FFMI), are common in patients with COPD and occur regardless of body weight.

RESEARCH QUESTION: Is the impact of low FFMI on exercise capacity, health-related quality of life (HRQL), and systemic inflammation different among patients with COPD stratified in different BMI classifications?

STUDY DESIGN AND METHODS: We analyzed baseline data of patients with COPD from the COPD and Systemic Consequences-Comorbidities Network (COSYCONET) cohort. Assessments included lung function, bioelectrical impedance analysis, 6-min walk distance (6MWD), HRQL, and inflammatory markers. Patients were stratified in underweight, normal weight (NW), preobese, and obese according to BMI and as presenting low, normal, or high FFMI using 25th and 75th percentiles of reference values. Linear mixed models were used to investigate the associations between fat-free mass (FFM) and fat mass with secondary outcomes in each BMI group.

RESULTS: Two thousand one hundred thirty-seven patients with COPD (Global Initiative for Chronic Obstructive Lung Disease stages 1-4; 61% men; mean ± SD age, 65 ± 8 years; mean ± SD FEV_1, 52.5 ± 18.8% predicted) were included. The proportions of patients in underweight, NW, preobese, and obese groups were 12.3%, 31.3%, 39.6%, and 16.8%, respectively. The frequency of low FFMI decreased from lower to higher BMI groups (underweight, 81%; NW, 53%; preobese, 42%; and obese, 39%). FFM was associated with the 6MWD in the underweight group, even when adjusting for a broad set of covariates ($P < .05$). HRQL was not associated with FFM after adjustment for lung function or dyspnea ($P > .32$). Fat mass was associated with higher systemic inflammation in the NW and preobese groups ($P < .05$).

INTERPRETATION: In patients with COPD with lower weight, such as underweight patients, higher FFMI is associated independently with better exercise capacity. In contrast, in preobese and obese patients with COPD, a higher FFMI was not consistently associated with better outcomes.

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KEY WORDS: body composition; COPD; exercise tolerance; health status; systemic inflammation

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ABBREVIATIONS: 6MWD = 6-min walk distance; BIA = bioelectrical impedance analysis; COSYCONET = COPD and Systemic Consequences-Comorbidities Network; CRP = C-reactive protein; FFM = fat-free mass; FFMI = fat-free mass index; HRQL = health-related quality of life; SGRQ = Saint George's Respiratory Questionnaire for COPD; TLCO = lung transfer factor for CO

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Take-home Points

Study Question: Is the impact of low fat-free mass index (FFMI) on exercise capacity, health-related quality of life (HRQL), and systemic inflammation different among patients with COPD stratified in different BMI classifications?

Results: Normal weight patients with high FFMI showed the lowest degree of airflow limitation, covered the lowest proportion of patients with increased symptoms, and demonstrated the highest levels of physical activity, best exercise capacity, and HRQL. In underweight patients, normal and high FFMI was associated with better exercise capacity when compared with low FFMI. In preobese patients, individuals with normal and high FFMI showed better lung function, exercise capacity, and physical activity when compared with their low-FFMI counterparts. No significant differences were found among obese patients after stratification for low, normal, or high FFMI.

Interpretation: Clinicians and researchers should consider screening patients with COPD for body composition abnormalities through a combination of BMI and FFMI classifications, rather than each of the two indexes alone.

COPD is defined by presence of chronic airflow limitation in patients with persistent respiratory symptoms and significant exposure to noxious stimuli.[1] Patients with COPD exhibit extrapulmonary manifestations and comorbidities that contribute to the clinical presentation of the disease.[2-4] Alterations in body composition, including low fat-free mass index (FFMI), are recognized predictors of mortality and future acute exacerbation risk in these patients[5,6] and may occur regardless of changes in body weight. Thus, patients with comparable BMI may differ considerably in body composition.[7-9] Therefore, interest is growing in understanding whether and to what extent alterations in body composition are related to patients' physical condition and health status.

Although previous studies demonstrated that low FFMI is associated with lower exercise capacity in patients with COPD,[10,11] ambiguous results are reported on the independent association between FFMI and health-related quality of life (HRQL).[12-14] Additionally, higher fat mass has been shown to be associated with higher systemic inflammation[15,16] and worse exercise capacity[10] in clinically stable patients with COPD. However, these prior studies were conducted in selected and relatively small samples of patients. Associations of FFMI, exercise capacity, HRQL, and markers of systemic inflammation were not investigated in a large and well-characterized multicenter COPD cohort. Importantly, whereas previous studies focus on the individual impact of BMI or FFMI on different outcomes. No previous study has provided a comprehensive stratification of patients with COPD based on a combination of BMI and FFMI classifications and has considered the potential interplay between these indexes. In addition, how the association between body composition and these outcomes is impacted when the effects of age, sex, lung function, and dyspnea are considered is still not studied sufficiently. We hypothesized that patients within the same BMI classification may be stratified further into clinically relevant subgroups according to the amount of FFMI.

Thus, this study aimed (1) to investigate whether stratification of patients with COPD from the same BMI group into different FFMI groups discriminates patients with distinct characteristics and (2) to explore the independent associations between fat-free mass (FFM) and fat mass with exercise capacity, HRQL, and systemic inflammation in each BMI group. Furthermore, we expect that FFM and fat mass are associated differently with the impairment on exercise capacity, HRQL, and degree of systemic inflammation depending on the BMI classification.

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Study Design and Methods

Participants and Study Design

We used data from the baseline visit of the prospective, observational, multicenter German COPD and Systemic Consequences—Comorbidities Network (COSYCONET) study, which recruited 2,741 participants in 31 study centers across Germany.[2] This study was conducted in accordance with the tenets of the amended Declaration of Helsinki and is registered at ClinicalTrials.gov (Identifier: NCT01245933). All participants gave written informed consent, and the study was approved by the Ethics Committee of the University of Marburg as coordinating center and the ethics committees of all study centers (see e-Appendix 1 for details). Detailed information about the inclusion and exclusion criteria, recruitment process, and methodology are available elsewhere.[2]

From the 2,741 patients recruited in COSYCONET, we excluded 450 patients with Global Initiative for Chronic Obstructive Lung Disease stage 0 disease or missing Global Initiative for Chronic Obstructive Lung Disease stage. Of the remaining 2,291 patients with COPD (Global Initiative for Chronic Obstructive Lung Disease stages 1-4), two patients showed missing values for BMI. We report the results of 152 patients in obesity classes II and III (BMI, $\geq$ 35 kg/m^2) in e-Table 1 because bioelectrical impedance analysis (BIA) must be interpreted with caution in these individuals because this technique is valid up to 34 kg/m^2 and its results require further validation in these obesity classes.[17]

Assessments

Age, sex, smoking status, and number of exacerbations within the year before the visit were assessed in standardized interviews. The lung function assessments included measurement of FEV_1 and FVC by spirometry after bronchodilator administration and single breath maneuver for the measurement of lung transfer factor for CO (TLCO). Procedures were performed according to standard operating procedures following international guidelines and recommendations.[2] All parameters were taken as percent of their Global Lung Function Initiative predictive values.[18-20] The modified Medical Research Council scale was used to evaluate the level of functional limitation in activities of daily living resulting from dyspnea.[21]

BMI was calculated as body mass in kilograms divided by height in square meters. Preobese (BMI, 25-< 30 kg/m^2) and obese class I (BMI, 30-< 35 kg/m^2) were defined as proposed by the World Health Organization criteria. We chose BMI of < 21 kg/m^2 for the stratification of underweight patients because this value was useful to discriminate patients with COPD with worse prognosis.[22] Normal weight patients were classified as BMI of 21 to < 25 kg/m^2. For the assessment of body composition, the study centers were equipped with identical instruments to perform BIA (Nutribox; Data Input).[2] A standard operating procedure was issued with a recommended order of the scheduled assessments and tests. BIA was performed after assessment of anthropometric data, clinical history, blood gas analysis, and pulmonary function, following The European Society for Clinical Nutrition and Metabolism recommendations for BIA in clinical practice published by Kyle et al.[17] FFM was estimated and used to calculate FFMI (FFM in kilograms divided by height in square meters) and fat mass (total body mass minus FFM). Patients were classified with low (FFMI, < 25th percentile), normal (FFMI, 25th-< 75th percentile), or high (FFMI, $\geq$ 75th percentile) FFMI according to reference values of the UK Biobank from the general population.[23] Values corresponding to the 25th and 75th percentiles of FFMI that were applied in this study are presented in e-Table 2.

Functional exercise capacity was assessed using the 6-min walk distance (6MWD) after standard recommendations.[24] References values for 6MWD were those from Troosters et al.[25] The 6-min walk work was calculated as the product of 6MWD and total body mass. Self-reported physical activity was assessed using the International Physical Activity Questionnaire, and overall physical activity was reported using a metabolic equivalent scored in minutes per week (MET min/wk).[26] HRQL was assessed using the disease-specific Saint George's Respiratory Questionnaire for COPD (SGRQ).[27] The BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index was determined following recommendations.[22] Several markers in the blood were assessed to evaluate systemic inflammation. WBC count and C-reactive protein (CRP) were determined in the laboratories of the study centers using quality-controlled procedures. Concentrations of fibrinogen, IL-6, IL-8, and tumor necrosis factor α were determined in the central biobank following the manufacturers' instructions (e-Appendix 1).

Statistical Analysis

Quantitative data are described as mean $\pm$ SD or median (interquartile range). Qualitative data are presented as absolute and relative frequencies. Comparisons between BMI groups and FFMI groups were performed using the one-way analysis of variance, Kruskal-Wallis test, or χ^2 test, as appropriate. We determined whether FFM and fat mass were associated independently with exercise capacity, HRQL, and systemic inflammation using linear mixed models with study centers entered as a random effect. Because CRP was elevated in preobese and obese patients, we opted to use this marker of systemic inflammation as the dependent variable. Because the distribution of CRP was skewed, the variable was $\log_{10}$-transformed to yield normal distribution before entering analyses. Associations were adjusted for potential confounders in four models: model 1, crude; model 2, adjusted for demographic confounders (age and sex); model 3, additionally adjusted for lung function (FEV_1 % predicted and TLCO % predicted) and pack-years of smoking; and model 4, additionally adjusted for limitations resulting from dyspnea (modified Medical Research Council scale). A general linear model (general linear model univariate regression analysis) was used to investigate the differences among low, normal, or high FFMI in each BMI group. In the general linear model univariate regression analysis, the normal weight and high FFMI group was set as the reference group. All analyses were performed using SPSS version 25.0 software (SPSS, Inc.) and GraphPad Prism version 9.2.0 software (GraphPad Software, Inc.). The level of significance was set at $P < .05$ (two-sided); analyses were corrected for multiple comparisons using Bonferroni correction.

Results

Overall, data from 2,137 patients (1,306 men [61%]) with COPD grades 1 through 4 (n = 197, n = 887, n = 812, and n = 241, respectively) were available for analysis. e-Figure 1 displays the baseline distribution of patients by study center. Patients' characteristics are given in Table 1. Most patients were stratified as preobese (39.6%) and normal weight (31.3%), whereas a

TABLE 1] Baseline Characteristics of Patients With COPD Stratified Into BMI Groups

Variable	Missing (%)	All Patients (N = 2,137)	Underweight (< 21 kg/m^2; n = 262)	Normal Weight (21-< 25 kg/m^2; n = 668)	Preobese (25-< 30 kg/m^2; n = 847)	Obese (30-< 35 kg/m^2; n = 360)
Male sex	0	1,306 (61)	98 (37)[a]	395 (59)	568 (67)[a]	245 (68)[a]
Age, y	0	65 ± 8	63 ± 9[a]	65 ± 8	66 ± 8	65 ± 8
BMI, kg/m^2	0	25.8 ± 4.1	18.9 ± 1.6[b]	23.2 ± 1.1	27.3 ± 1.4[b]	32.0 ± 1.4[b]
FFMI, kg/m^2	5.0	18.0 ± 2.8	14.5 ± 1.7[b]	16.8 ± 1.9	18.8 ± 2.0[b]	20.8 ± 2.5[b]
FMI, kg/m^2	5.0	7.8 ± 2.8	4.5 ± 1.6	6.4 ± 1.8[b]	8.5 ± 2.0[b]	11.2 ± 2.4[b]
FEV_1, % predicted	0	52.5 ± 18.8	45.7 ± 19.4[b]	51.4 ± 19.6	54.1 ± 18.0[b]	55.7 ± 17.5[b]
TLCO, % predicted	5.8	51.9 ± 20.3	39.8 ± 18.3[b]	49.3 ± 19.5	54.7 ± 20.0[b]	58.4 ± 19.8[b]
Current smokers	0.1	532 (25)	93 (36)	179 (27)	170 (20)[a]	90 (25)
Smoking history, pack-years	0.6	40 (19-62)	34 (14-55)	38 (17-60)	42 (19-64)	45 (22-70)[a]
Exacerbations ≥ 2	0	1,065 (50)	141 (54)	334 (50)	409 (48)	181 (50)
mMRC ≥ 2	0	986 (46)	129 (49)	281 (42)	392 (46)	184 (51)[a]
IPAQ, MET min/wk	3.7	2,718 (815-5,706)	2,623 (825-5,541)	2,772 (951-5,790)	2,778 (824-6,030)	2,079 (577-5,160)
6MWD						
Meters	3.1	420 ± 106	419 ± 101	429 ± 110	423 ± 105	400 ± 100[a]
% Predicted	3.1	65 ± 16	63 ± 16[b]	66 ± 17	66 ± 16	64 ± 16
6MWW, kg/m	3.1	31,898 ± 10,442	22,699 ± 6,734[b]	29,295 ± 8827	34,182 ± 9,888[b]	38,151 ± 4,620[b]
Fibrinogen, g/L	10.1	2.4 (1.8-3.2)	2.3 (1.8-3.2)	2.5 (1.8-3.2)	2.5 (1.8-3.3)	2.3 (1.7-3.1)
CRP, mg/dL	1.2	0.4 (0.2-0.7)	0.3 (0.1-0.6)	0.3 (0.1-0.6)	0.5 (0.2-0.8)[b]	0.5 (0.3-1.0)[b]
IL-6, pg/mL	7.2	2.9 (0.6-8.7)	2.0 (0.3-11.0)	2.8 (0.4-6.9)	3.0 (0.6-8.8)	3.8 (0.9-9.9)[a]
IL-8, pg/mL	7.2	8.3 (5.5-12.1)	9.1 (6.0-13.3)	8.1 (5.5-11.8)	8.3 (5.4-11.9)	7.8 (5.6-11.9)
TNFα, pg/mL	7.2	8.0 (4.9-12.4)	6.9 (4.1-11.7)	7.8 (4.9-11.6)	8.6 (5.3-13.3)[a]	7.8 (4.9-12.7)
WBC count, 10^9/mL	1.7	7.6 (6.4-9.1)	7.6 (6.3-9.4)	7.5 (6.3-9.0)	7.7 (6.4-9.1)	7.6 (6.5-9.0)
SGRQ, points						
Symptoms	0.6	56 ± 21	57 ± 20	55 ± 22	55 ± 22	57 ± 21
Activity	0.7	58 ± 26	60 ± 25	56 ± 27	56 ± 25	64 ± 23[b]
Impact	0.5	30 ± 21	32 ± 21	29 ± 21	30 ± 20	33 ± 22[b]
Total	0.9	43 ± 20	45 ± 20	42 ± 20	42 ± 20	47 ± 20[b]
BODE index	5.7	2 (1-4)	4 (2-5)[b]	2 (1-4)	2 (1-3)	2 (1-3)

Data are presented as No. (%), mean ± SD, or median (interquartile range). 6MWD = 6-min walk distance; 6MWW = 6-min walk work; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity index; CRP = C-reactive protein; FFMI = fat-free mass index; FMI = fat mass index; IPAQ = International Physical Activity Questionnaire; MET = metabolic equivalent; mMRC = modified Medical Research Council dyspnea scale; SGRQ = St. George Respiratory Questionnaire; TNFα = tumor necrosis factor α; TLCO = lung transfer factor for CO.

[a] $P < .05$ vs normal weight.

[b] $P < .01$ vs normal weight.

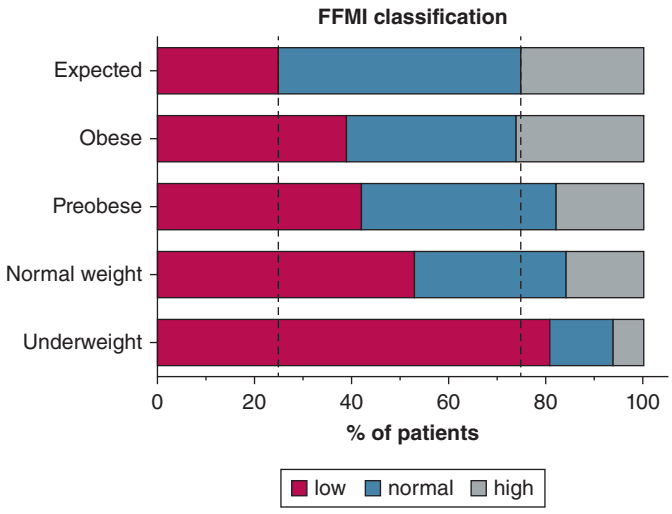

Figure 1 – *Bar graph showing the proportion of patients with COPD stratified into low, normal, or high FFMI within BMI groups. First row shows the expected proportion according to the reference values. FFMI = fat-free mass index.*

small proportion of patients were obese class I (16.8%) and underweight (12.3%). Compared with the normal weight group, underweight patients were slightly younger with a greater proportion of women and showing worse lung function and exercise capacity. Preobese and obese groups included a greater proportion of men and showed better lung function and higher levels of CRP compared with the normal weight group. Generally, obese patients demonstrated the most impaired exercise capacity, HRQL, and limitations in daily activities resulting from dyspnea.

The use of BMI-adjusted cutoffs allowed the identification of patients with low, normal, and high FFMI in patients from all BMI groups (e-Fig 2). However, as displayed in Figure 1, the proportion of patients with low FFMI decreased according to the increase in BMI (from underweight to obese groups: 81%, 53%, 42%, and 39%). The comparison of the characteristics among patients with low, normal, or high FFMI stratified for sex is presented in e-Table 3. We compared the characteristics among patients with low, normal, or high FFMI within each BMI group (Table 2). Patients with normal weight and high FFMI showed lowest degree of airflow limitation (FEV_1, 59.5 ± 20.7% predicted), lowest proportion of patients with modified Medical Research Council scale of > 2 (27%), highest levels of physical activity (International Physical Activity Questionnaire, 3,732 MET min/wk [IQR, 1,386-7,391 MET min/wk]), best exercise capacity (6MWD, 77 ± 17% predicted), and HRQL (SGRQ total score, 37 ± 22 points). Underweight patients with normal and high FFMI showed better exercise capacity compared with underweight patients with low FFMI. Preobese patients with normal and high FFMI showed better lung function, exercise capacity, and physical activity compared with preobese patients with low FFMI. No significant differences were found among obese patients after stratification for low, normal, or high FFMI. Patients with COPD with low FFMI regardless of the BMI classification and obese patients regardless of the FFMI classification showed lower 6MWD and higher SGRQ total scores compared with normal weight patients with high FFMI (reference group) (Fig 2).

Table 3 presents the unstandardized regression coefficients and CIs from the different models designed to explore the associations between FFM and fat mass with exercise capacity, quality of life, and markers of systemic inflammation. FFM was associated with the 6MWD in the underweight group, even when adjusting for all the covariates (model 4 - β coefficient: 3.68 m for each kg of FFM [95% CI, 1.50-5.85]). In the normal weight and preobese group, FFM was not associated with the 6MWD after adjustment for FEV_1, TLCO, and pack-years of smoking ($P \geq .129$). In the obese group, fat mass was associated negatively with 6MWD even after adjustment for all the covariates (model 4 β coefficient: –2.08 m for each kg of fat mass [95% CI, –3.40 to –0.75]). Moreover, associations between FFM and SGRQ total score were found in normal weight and underweight patients, which were not statistically significant after adjustment for FEV_1, TLCO, and pack-years of smoking. Finally, in normal weight and

preobese patients, fat mass was associated independently with log-transformed CRP (model 4 - β coefficient: 0.017 Log_{10} mg/dL for each kg of fat mass [95% CI, 0.007-0.027] and 0.008 Log_{10} mg/dL for each kg of fat mass [95% CI, 0.0001-0.015/kg fat mass, respectively). The complete results of model 4 are shown in e-Tables 4-6.

Discussion

The main finding of our study is that patients with COPD with low FFMI, obesity, or both showed worse exercise capacity and HRQL compared with normal weight patients with high FFMI. Moreover, body composition was associated differently with exercise capacity, HRQL, and markers of systemic inflammation depending on the BMI group. Our models demonstrated that FFM is a factor associated strongly with exercise capacity in underweight patients, whereas in the obese group, the amount of fat mass was associated independently and negatively with exercise capacity. In addition, the present study showed that HRQL is not associated with FFM after adjustment for lung function and pack-years of smoking and that higher amounts of fat mass are associated with higher plasma levels of CRP in normal weight and preobese patients with COPD.

Stratification Into BMI Groups

We found that stratification using BMI allowed discrimination of groups of patients with COPD who showed slight but significant differences in lung function, exercise capacity, HRQL, and systemic inflammation. In a recent systematic review, Souto-Miranda et al[28] demonstrated that from 32 studies reporting body composition as an outcome domain to evaluate the impact of pulmonary rehabilitation, 22 used BMI as an outcome measure. However, because BMI does not allow differentiation between FFM and fat mass, a strong association between this variable and patients' physical condition or health status is unexpected. The current evidence shows that, in more severe COPD stages, preobese and obese patients show improved survival compared with normal weight patients with COPD.[29,30] Recently, Betancourt-Peña et al[31] showed that patients with a diagnosis of COPD who were underweight and obese had lower 6MWD compared with healthy and preobese patients with COPD. However, the authors suggested that these findings should be confirmed in large studies.[31] Our findings demonstrated that being normal weight is associated with better exercise capacity and HRQL in comparison with patients who are on both extremities of BMI (ie, BMI of < 21 kg/m^2 or ≥ 30 kg/m^2). Importantly, when interpreting the clinical meaning of BMI values in patients with COPD, one also should consider other aspects, such as disease severity, frequency of exacerbations, cardiovascular risk factors, and body composition.

Stratification Into FFMI Groups

Although some information can be obtained by the stratification into BMI groups, FFMI is a more accurate and suitable parameter to express pulmonary and extrapulmonary characteristics, such as disease severity and exercise capacity.[14] Using BIA, we were able to stratify patients with COPD further into clinically significant FFMI groups. Previous studies also have shown that the frequency of low FFMI in patients with COPD decreases in higher BMI groups and is more common in male patients.[9,10] The stratification into normal and high FFMI showed subgroups of patients with better lung function, exercise capacity, physical activity, HRQL, and symptoms compared with their low FFMI counterparts. These differences were found mainly in the normal weight and preobese groups. In the underweight group, the absence of statistically significant differences may be explained partially by a lack of power in view of the low number of patients in the normal ($n = 32$) and high ($n = 14$) FFMI groups. In contrast, the absence of differences between patients with low, normal, and high FFMI in the obese group occurred despite a relatively uniform distribution of patients. This suggests that FFMI as assessed by BIA is not an informative variable in obese patients with COPD.

Different Association Between Body Composition, Exercise Capacity, HRQL, and Systemic Inflammation

Our findings regarding the association between body composition and exercise capacity, HRQL, and systemic inflammation corroborate and further extend results from previous studies. Regarding exercise capacity, Rodríguez et al[32] demonstrated that determinants of exercise capacity may differ between obese and nonobese patients with COPD. Interestingly, BMI was associated inversely with 6MWD only in obese patients with COPD,[32] and fat mass index already has been shown to be associated negatively with 6MWD in this population.[10] Recently, Gaynor-Sodeifi et al[33] showed that most scientific evidence supports the existence of a positive association between FFM and exercise capacity in people with COPD. Remarkably, the method of exercise testing (weight-bearing vs nonweight-bearing exercise) was

TABLE 2] Baseline Characteristics of the Patients With COPD Stratified Into Low, Normal, and High FFMI Within BMI Groups

BMI Group	Underweight (< 21 kg/m^2; n = 243)			Normal Weight (21-< 25 kg/m^2; n = 633)			Preobese (25-< 30 kg/m^2; n = 811)			Obese (30-< 35 kg/m^2; n = 343)		
FFMI Group	Low (n = 197)	Normal (n = 32)	High (n = 14)	Low (n = 337)	Normal (n = 194)	High (n = 102)	Low (n = 341)	Normal (n = 328)	High (n = 142)	Low (n = 132)	Normal (n = 119)	High (n = 92)
Male sex	77 (39)	8 (25)	6 (43)	208 (62)	101 (52)	61 (60)	253 (75)	217 (66)	76 (54)[a]	102 (77)	75 (63)[a]	55 (60)[a]
Age, y	63 ± 9	62 ± 9	65 ± 8	66 ± 8	65 ± 8	65 ± 9	65 ± 8	66 ± 8	66 ± 8	65 ± 9	65 ± 8	63 ± 8
FFMI, kg/m^2	14.1 ± 1.6	15.7 ± 1.3[b]	16.8 ± 1.6[b]	16.0 ± 1.4	17.1 ± 1.6[b]	19.0 ± 1.9[b]	17.8 ± 1.6	19.0 ± 1.7[b]	20.6 ± 2.3[b]	19.6 ± 1.7	20.6 ± 2.0[b]	22.9 ± 2.7[b]
FMI, kg/m^2	4.7 ± 1.5	3.7 ± 1.4[b]	2.0 ± 1.1[b]	6.9 ± 1.6	6.4 ± 1.6[b]	4.8 ± 1.8[b]	8.9 ± 1.7	8.5 ± 2.0[a]	7.5 ± 2.6[b]	11.7 ± 1.7	11.5 ± 2.2	9.9 ± 3.1[b]
FEV_1, % predicted	44.5 ± 19.4	49.0 ± 19.1	53.0 ± 21.3	47.9 ± 18.8	53.5 ± 18.8[b]	59.5 ± 20.7[b]	51.5 ± 18.6	56.2 ± 17.8[b]	56.2 ± 16.5[a]	52.4 ± 17.2	57.4 ± 16.6	56.6 ± 18.1
TLCO, % predicted	38.9 ± 18.4	43.3 ± 18.6	41.3 ± 13.5	46.6 ± 18.6	50.2 ± 18.5	58.5 ± 21.7[b]	51.5 ± 18.1	57.0 ± 21.6[b]	57.0 ± 18.1[a]	56.6 ± 19.6	57.5 ± 18.5	62.3 ± 21.7
Current smokers	67 (34)	12 (38)	5 (39)	90 (27)	50 (26)	26 (26)	73 (21)	58 (18)	31 (22)	27 (21)	31 (26)	29(32)
Smoking history, pack-years	34 (16-56)	38 (16-48)	43 (22-55)	37 (18-59)	40 (16-62)	36 (15-57)	42 (19-64)	42 (19-64)	42 (21-60)	46 (26-72)	46 (29-69)	40 (16-71)
Exacerbations ≥ 2	106 (54)	20 (62)	5 (36)	178 (53)	91 (47)	43 (42)	174 (51)	152 (46)	62 (44)	73 (55)	54 (45)	45 (49)
mMRC ≥ 2	99 (50)	14 (44)	8 (57)	161 (48)	76 (39)	28 (27)[b]	179 (53)	135 (41)[a]	63 (44)	70 (53)	59 (50)	46 (50)
IPAQ, MET min/wk	2,629 (859-5,554)	2,688 (815-5,379)	1,555 (834-3,864)	2,113 (700-5,224)	2,833 (1,281-6,377)	3,732[b] (1,386-7,391)	2,679 (648-5,343)	2,895 (834-6,399)	3,399[b] (1,440-8,106)	2182 (638-5729)	1,746 (495-5,490)	1,980 (678-4,279)
6MWD												. . .
Meters	409 ± 103	455 ± 80[a]	464 ± 93	415 ± 113	444 ± 99[a]	456 ± 104[b]	413 ± 111	437 ± 101[a]	416 ± 103	397 ± 101	408 ± 88	400 ± 111
% Predicted	61 ± 16	70 ± 14[a]	70 ± 18	63 ± 17	68 ± 15[b]	70 ± 16[b]	63 ± 16	69 ± 15[b]	68 ± 18[b]	63 ± 16	66 ± 14	65 ± 18
6MWW, kg/m	22,182 ± 6,826	24,321 ± 5,476	24,941 ± 5,483	28,028 ± 8,919	30,364 ± 8,219[b]	31,974 ± 8,735[b]	33,433 ± 10,448	35,389 ± 9,568[b]	33,527 ± 9,493	37,586 ± 10,434	39,060 ± 10,162	38,043 ± 11,623
Fibrinogen, g/L	2.4 (1.9-3.3)	2.1 (1.7-2.8)	1.8 (1.6-2.5)	2.5 (1.8-3.2)	2.7 (1.8-3.3)	2.3 (1.7-3.4)	2.6 (1.8-3.4)	2.4 (1.8-3.3)	2.5 (1.7-3.1)	2.3 (1.7-3.0)	2.2 (1.7-3.2)	2.4 (1.8-3.3)
CRP, mg/dL	0.3 (0.1-0.6)	0.2 (0.1-0.5)	0.3 (0.0-0.5)	0.4 (0.2-0.6)	0.3 (0.1-0.6)	0.3 (0.1-0.6)[a]	0.5 (0.2-0.8)	0.5 (0.2-0.7)	0.4 (0.2-0.6)	0.5 (0.3-1.0)	0.5 (0.2-0.7)	0.6 (0.3-1.1)
IL-6, pg/mL	2.2 (0.5-11.4)	2.3 (0.2-10.1)	1.8 (0.3-6.8)	3.3 (0.5-7.6)	2.3 (0.6-5.2)	2.0 (0.4-6.8)	3.2 (0.8-8.4)	2.9 (0.4-8.8)	2.5 (0.4-8.7)	3.6 (0.8-10.6)	3.9 (0.8-10.5)	3.2 (1.1-8.4)
IL-8, pg/mL	9.2 (5.9-14.0)	9.4 (7.3-17.7)	7.9 (4.9-9.6)	8.1 (5.6-12.4)	8.2 (5.3-10.7)	7.8 (4.8-11.8)	8.2 (5.5-12.7)	8.3 (5.5-11.2)	8.6 (5.5-12.3)	8.3 (5.5-13.1)	7.7 (5.6-11.8)	7.5 (5.1-10.8)
TNFα, pg/mL	7.3 (4.5-11.7)	7.0 (3.5-11.7)	4.0 (3.4-8.2)	7.8 (4.8-11.6)	7.6 (4.7-11.7)	8.5 (5.4-12.0)	8.7 (5.4-13.8)	8.5 (5.3-12.4)	8.9 (5.5-13.9)	7.6 (4.8-13.7)	8.2 (5.1-13.0)	7.6 (4.8-11.4)
WBC count, 10^9/mL	7.7 (6.5-9.2)	7.1 (6.3-9.8)	6.8 (5.5-7.7)	7.7 (6.4-9.2)	7.3 (6.2-9.0)	7.5 (6.4-8.6)	7.7 (6.3-9.2)	7.7 (6.5-9.1)	7.4 (6.3-8.5)	7.6 (6.7-9.0)	7.6 (6.3-9.0)	7.7 (6.7-9.4)
SGRQ, points												. . .
Symptoms	57 ± 20	56 ± 20	59 ± 18	55 ± 22	55 ± 21	52 ± 23	56 ± 21	55 ± 22	56 ± 22	56 ± 21	57 ± 20	58 ± 21

(Continued)

TABLE 2] *(Continued)*

BMI Group	Underweight (< 21 kg/m^2; n = 243)			Normal Weight (21-< 25 kg/m^2; n = 633)			Preobese (25-< 30 kg/m^2; n = 811)			Obese (30-< 35 kg/m^2; n = 343)		
FFMI Group	Low (n = 197)	Normal (n = 32)	High (n = 14)	Low (n = 337)	Normal (n = 194)	High (n = 102)	Low (n = 341)	Normal (n = 328)	High (n = 142)	Low (n = 132)	Normal (n = 119)	High (n = 92)
Activity	61 ± 25	55 ± 25	56 ± 24	60 ± 26	53 ± 26[a]	48 ± 29[b]	58 ± 25	53 ± 26	56 ± 26	65 ± 23	64 ± 25	62 ± 22
Impact	32 ± 21	28 ± 16	30 ± 16	30 ± 21	26 ± 19	25 ± 22	31 ± 20	28 ± 19	30 ± 21	35 ± 23	30 ± 20	34 ± 23
Total	46 ± 20	41 ± 17	43 ± 16	44 ± 20	40 ± 19	37 ± 22[a]	44 ± 19	40 ± 19	43 ± 20	48 ± 20	45 ± 19	47 ± 20
BODE index	4 (2-5)	3 (2-4)	4 (2-5)	2 (1-4)	2 (1-4)[b]	1 (0-2)[b]	2 (1-4)	2 (1-4)[b]	2 (1-3)	2 (1-4)	1 (1-3)	2 (1-4)

Data are presented as No. (%), mean ± SD, or median (interquartile range). 6MWD = 6-min walk distance; 6MWW = 6-min walk work; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity index; CRP = C-reactive protein; FFMI = fat-free mass index; FMI = fat mass index; IPAQ = International Physical Activity Questionnaire; MET = metabolic equivalent; mMRC = modified Medical Research Council dyspnea scale; SGRQ = St. George Respiratory Questionnaire; TNFα = tumor necrosis factor α; TLCO = lung transfer factor for CO.

[a]$P < .05$ vs low FFMI from the same BMI group.

[b]$P < .01$ vs low FFMI from the same BMI group.

Figure 2 – *Box-and-whisker plots showing comparisons of exercise capacity and health-related quality of life between patients with COPD with low, normal, or high FFMI within BMI groups. Estimate means and CIs from general linear model univariate regression analysis are presented for SGRQ (A) and 6MWD (B). 6MWD = 6-min walk distance; FFMI = fat-free mass index; Ref. = reference; SGRQ = Saint George's Respiratory Questionnaire for COPD.*

shown to affect the consistency of these associations. The reported associations were more heterogenous when weight-bearing exercise tests (eg, 6MWD, incremental shuttle walk test) were used. The authors raised the hypothesis that these discrepancies could be the result of a potentially confounding influence of BMI (or excess adiposity) on physiologic responses to weight-bearing exercise. Our findings support this hypothesis because our models demonstrated that the strength and significance of the association between FFM and 6MWD vary depending on the patient's BMI. Strikingly, in the obese group, although FFM was not associated with 6MWD, fat mass was associated negatively with 6MWD. Also, we demonstrated that dyspnea and lung function, and not body composition, are the main determinants of

TABLE 3] Associations of FFM and FM With Exercise Capacity, Quality of Life, and Systemic Inflammation in Patients With COPD Stratified Into BMI Groups

	Model 1		Model 2		Model 3		Model 4	
Variable	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
6MWD, m								
Underweight								
FFM, /kg	2.46 (0.64-4.28)	.008	6.49 (4.03-8.96)	< .001	3.83 (1.59-6.07)	< .001	3.68 (1.50-5.85)	< .001
FM, /kg	1.87 (−1.33 to 5.08)	.250	−0.33 (−3.51 to 2.84)	.836	-1.21 (−4.06 to 1.64)	.405	−0.98 (−3.30 to 1.94)	.558
Normal weight								
FFM, /kg	2.52 (1.50-3.57)	< .001	4.60 (3.01-6.19)	< .001	1.12 (−0.33 to 2.58)	.129	0.83 (−0.56 to 2.22)	.242
FM, /kg	−0.53 (−2.48 to 1.42)	.593	−0.92 (−2.85 to 1.00)	.347	−0.13 (−1.80 to 1.54)	.876	−0.15 (−1.47 to 1.78)	.852
Preobese								
FFM, /kg	1.88 (1.11-2.65)	< .001	1.60 (0.37-2.83)	.011	0.34 (−0.73 to 1.42)	.531	0.37 (−0.63 to 1.37)	.468
FM, /kg	−0.70 (−2.14 to 0.75)	.346	−1.34 (−2.78 to 0.11)	.070	−0.94 (−2.19 to 0.32)	.143	−0.56 (−1.73 to 0.60)	.342
Obese								
FFM, /kg	0.83 (−0.18 to 1.84)	.107	0.22 (−1.26 to 1.70)	.771	0.03 (−1.23 to 1.29)	.958	−0.14 (−1.29 to 1.01)	.810
FM, /kg	−1.96 (−3.69 to −0.23)	.027	−2.82 (−4.53 to -1.11)	< .001	−2.27 (−3.72 to −0.82)	.002	−2.08 (−3.40 to −0.75)	.002
SGRQ total, points								
Underweight								
FFM, /kg	−0.22 (−0.56 to 0.13)	.213	−0.73 (−1.21 to −0.25)	.003	−0.09 (−0.52 to 0.34)	.689	−0.07 (−0.43 to 0.30)	.722
FM, /kg	−0.36 (−0.96 to 0.25)	.249	−0.14 (−0.76 to 0.47)	.651	−0.03 (−0.57 to 0.51)	.915	−0.15 (−0.61 to 0.32)	.537
Normal weight								
FFM, /kg	−0.27 (−0.46 to −0.08)	.006	−0.82 (−1.12 to −0.52)	< .001	−0.14 (−0.42 to 0.14)	.322	−0.07 (−0.31 to 0.16)	.121
FM, /kg	−0.12 (−0.49 to 0.25)	.424	0.04 (−0.33 to 0.41)	.846	−0.10 (−0.43 to 0.23)	.553	−0.24 (−0.52 to 0.03)	.083
Preobese								
FFM, /kg	−0.21 (−0.35 to −0.06)	.005	−0.14 (−0.38 to 0.09)	.237	0.09 (−0.13 to 0.30)	.425	0.10 (−0.08 to 0.27)	.286
FM, /kg	0.05 (−0.23 to 0.32)	.739	0.03 (−0.25 to 0.32)	.816	0.04 (−0.22 to 0.29)	.771	−0.07 (−0.28 to 0.13)	.477

(Continued)

TABLE 3] *(Continued)*

Variable	Model 1		Model 2		Model 3		Model 4	
	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
Obese								
FFM, /kg	0.00 (−0.19 to 0.20)	.976	0.01 (−0.29 to 0.31)	.949	0.02 (−0.26 to 0.30)	.871	0.08 (−0.15 to 0.31)	.507
FM, /kg	0.25 (−0.09 to 0.59)	.142	0.27 (−0.08 to 0.61)	.132	0.08 (−0.25 to 0.40)	.646	0.03 (−0.24 to 0.29)	.837
CRP, $\log_{10}$								
Underweight								
FFM, /kg	0.005 (−0.004 to 0.015)	.270	−0.003 (−0.017 to 0.010)	.618	−0.003 (−0.017 to 0.012)	.731	−0.002 (−0.017 to 0.013)	.794
FM, /kg	−0.003 (−0.019 to 0.014)	.766	0.003 (−0.014 to 0.020)	.713	0.003 (−0.011 to 0.026)	.411	0.007 (−0.012 to 0.025)	.477
Normal weight								
FFM, /kg	0.001 (−0.004 to 0.006)	.620	−0.008 (−0.015 to −0.002)	.055	−0.003 (−0.011 to 0.005)	.485	−0.002 (−0.011 to 0.006)	.599
FM, /kg	0.016 (0.006-0.025)	.001	0.018 (0.009-0.028)	< .001	0.018 (0.008-0.027)	< .001	0.017 (0.007-0.027)	.001
Preobese								
FFM, /kg	0.001 (−0.003 to 0.004)	.695	−0.002 (−0.008 to 0.004)	.523	0.001 (−0.005 to 0.007)	.830	0.001 (−0.005 to 0.007)	.834
FM, /kg	0.007 (0.000-0.014)	.038	0.008 (0.001-0.015)	.034	0.008 (0.001-0.015)	.033	0.008 (0.001-0.015)	.036
Obese								
FFM, /kg	−0.003 (−0.008 to 0.001)	.190	0.000 (−0.008 to 0.007)	.945	0.001 (−0.007 to 0.008)	.908	0.001 (−0.007 to 0.008)	.902
FM, /kg	0.002 (−0.006 to 0.011)	.577	0.002 (−0.007 to 0.011)	.638	−0.001 (−0.08 to 0.009)	.994	−0.001 (−0.009 to 0.009)	.989

Data were obtained from multiple linear regression models: model 1, crude; model 2, adjusted for age and sex; model 3, additionally adjusted for lung function (FEV_1 and TLCO % predicted) and pack-years of smoking; and model 4, additionally adjusted for dyspnea (modified Medical Research Council dyspnea scale). 6MWD = 6-min walk distance; CRP = C-reactive protein; FFM = fat-free mass; FM = fat mass; SGRQ = St. George Respiratory Questionnaire.

SGRQ total score. In relationship to systemic inflammation, Rutten et al[15] showed that fat mass was associated with plasma levels of CRP independent of sex and age in a group of patients with moderate to severe COPD. In the current study, the amount of fat mass was associated independently with plasma levels of CRP exclusively in normal weight and preobese patients with COPD. Previous studies suggest that increases in plasma levels of IL-6 and tumor necrosis factor α may be related more strongly to markers of abdominal fat distribution, such as visceral adipose tissue and waist to hip ratio, than to total body fat mass.[34,35] Although Byun et al[36] found weak correlations among IL-6, tumor necrosis factor α, and BIA-derived markers of muscle mass in patients with COPD, no significant differences were found among markers of systemic inflammation when comparing patients with different FFMI in the current study.

Limitations of the Study

First, the use of BIA to assess body composition may be considered a limitation because it provides a measure of whole body composition that may be affected by the hydration and fed conditions. The use of other methods that allow quantification of muscle and fat mass at regional levels, such as dual-energy X-ray absorptiometry and MRI could be more appropriate. However, the use of these methods may be limited by equipment costs and the need for trained operating personnel, which could hamper their use in large cohorts. Second, the reference values were derived from a sample of the general population 45 to 69 years of age. Approximately 33% of the patients included were older than 70 years; thus for these patients, the FFMI cutoff values may be more rigorous because they were derived from younger people. Third, this study presents cross-sectional analysis and can report only associations, but not causal relationships. We highlight that the findings regarding the associations among body composition, exercise capacity, HRQL, and systemic inflammation are plausible and more than mere correlations, considering that we explored different models with the addition of important potential confounders. Finally, although this study focused on muscle quantity, future studies should investigate whether differences in markers of muscle quality can be observed in patients with COPD with similar BMI and body composition characteristics.

Interpretation

Using a large data set from a cohort of patients with COPD, we demonstrated that depending on BMI, body composition is associated differently with exercise capacity, HRQL, and systemic inflammation. Low FFMI is associated with lower exercise capacity in underweight and normal weight patients with COPD. In contrast, in preobese and obese patients, the benefits of increasing FFMI are hampered by influences of excessive fat mass. The group of obese patients was the most impaired in terms of exercise capacity and HRQL regardless of FFMI. In these patients, weight loss with preservation of FFMI may be the first and most important therapeutic aim. Considering lung function, physical condition, and health status, we demonstrated that normal weight with high FFMI is the favorable combination within the broad spectrum of body weight and body composition in patients with COPD.

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None declared.

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Author contributions: F. V. C. M. had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. F. V. C. M. was involved in the conception of the study, analyzing and interpreting the data, statistical analysis, and conceptualizing and drafting of the manuscript. C. F. V., R. A. J., H. W., R. B., T. W., and M. A. S. contributed to the design of the study, to the interpretation of the data, to the development, and to critical revision of the manuscript; approved the final submitted version; and agreed to be accountable for all aspects of the work. P. A. and F. M. E. F. contributed to the drafting of the manuscript, to the design of the study, to the interpretation of the data, to the development and critical revision of the manuscript; approved the final submitted version; and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Data sharing statement: The basic data are part of the German COPD cohort COSYCONET (www.asconet.net) and are available on request. The website of the network provides a detailed procedure for respective applications. The data can be obtained after submission of a proposal that is evaluated by the steering committee. All results to which the manuscript refers are documented appropriately in the text, figures, or tables.

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