Body composition and mortality in chronic obstructive pulmonary disease¹,²

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ABSTRACT
Background: Survival studies have consistently shown significantly greater mortality rates in underweight and normal-weight patients with chronic obstructive pulmonary disease (COPD) than in overweight and obese COPD patients.

Objective: To compare the contributions of low fat-free mass and low fat mass to mortality, we assessed the association between body composition and mortality in COPD.

Design: We studied 412 patients with moderate-to-severe COPD (Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) stages II–IV, forced expiratory volume in 1 s of 36 ± 14% of predicted (range: 19–70%). Body composition was assessed by using single-frequency bioelectrical impedance. Body mass index, fat-free mass index, fat mass index, and skeletal muscle index were calculated and related to recently developed reference values. COPD patients were stratified into defined categories of tissue-depletion patterns. Overall mortality was assessed at the end of follow-up.

Results: Semistarvation and muscle atrophy were equally distributed among disease stages, but the highest prevalence of cachexia was seen in GOLD stage IV. Forty-six percent of the patients (n = 189) died during a maximum follow-up of 5 y. Cox regression models, with and without adjustment for disease severity, showed that fat-free mass index (relative risk: 0.90; 95% CI: 0.84, 0.96; P = 0.003) was an independent predictor of survival, but fat mass index was not. Kaplan-Meier and Cox regression plots for cachexia and muscle atrophy did not differ significantly.

Conclusions: Fat-free mass is an independent predictor of mortality irrespective of fat mass. This study supports the inclusion of body-composition assessment as a systemic marker of disease severity in COPD staging. Am J Clin Nutr 2005;82:53–9.

KEY WORDS Mortality, chronic obstructive pulmonary disease, COPD, body composition, muscle mass, lung function

INTRODUCTION
Survival studies in selected groups of patients with chronic obstructive pulmonary obstruction (COPD) and in population-based studies have consistently shown higher COPD-related mortality rates in underweight and normal-weight patients than in overweight and even obese patients (1–3). This relation is different from the U-shaped survival curve that is commonly seen for body mass index (BMI) in large population studies (reviewed in 4). We hypothesized that this discrepancy might be explained by specific adverse effects of an excess loss of metabolically and functionally active fat-free mass (FFM) on mortality in chronic disease that are not seen with BMI. This increased mortality risk in COPD might be due to direct effects on lung function (5) or adverse effects of the loss of FFM on skeletal muscle strength (6), exercise capacity (7, 8), and health status (9) that may increase the frequency or severity of acute exacerbations of the disease. Furthermore, a recent study showed that a small midtigh cross-sectional area, as measured with computed tomography scan, was associated with increased mortality risk during a 3-y follow-up (10). In the same study, midtigh cross-sectional area could not be estimated by using anthropometric measurements. Bioelectrical impedance analysis (BIA) is an easy, safe, noninvasive, and convenient method of measuring the lean and fat body compartments (11). In addition, it has been validated extensively in COPD and other chronic wasting conditions, which have shown high correlations between FFM measured by BIA and that measured by reference methods such as magnetic resonance imaging (12) or deuterium dilution (13). The objective of this study was to compare the effects of low FFM and low fat mass (FM) assessed by BIA on mortality in COPD patients.

SUBJECTS AND METHODS
Subjects
Data were collected from 412 clinically stable COPD patients [Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) stages II–IV] who were screened for admission to a clinical pulmonary rehabilitation program between 1 January 1988 and 30 December 1991. This group was selected because it was a homogeneous group of clinically stable patients from the southern part of the Netherlands and because none of the patients had undergone interventions that might modulate body composition, eg, nutritional intervention, intensive exercise training, or muscle strength training, before screening and during the total follow-up of 5 y. Such interventions currently are common in the Netherlands as part of an integrated COPD management approach. Patients with unstable disease or other confounding conditions such as type 1 diabetes, cardiovascular disease, thyroid

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disease, or chronic inflammatory bowel disease were excluded. All baseline measurements were taken within 1 wk of admission to the rehabilitation center.

**Lung function**

Lung function testing included spirometry and resting arterial blood gases. Forced expiratory volume in 1 s (FEV₁) and inspiratory vital capacity (IVC) were measured with a wet spirometer by using the highest value of ≥3 acceptable spirometric maneuvers. Prebronchodilation and postbronchodilation FEV₁ and IVC were expressed as a percentage of the reference values (14). Arterial blood gases were drawn by puncture of the at-rest brachial artery while the subjects breathed room air. Arterial oxygen tension (PaO₂) and arterial carbon dioxide tension (PaCO₂) were analyzed with the use of a blood gas analyzer (ABL 330; Radiometer, Copenhagen, Denmark).

**Body composition**

Body height was measured to the nearest 0.5 cm while the subjects were barefoot and standing (WM 715; Lameris, Breukelen, Netherlands). Body weight was measured on a calibrated beam scale (model 708; Seca, Hamburg, Germany). Body composition was assessed by using single-frequency BIA (50 Hz; Xitron Technologies, San Diego, CA). All measurements were performed by the same trained dietitian at a standardized time after breakfast. FFM was calculated by using disease-specific equations (13). FM was calculated as total body weight minus FFM. A prerequisite of the use of BIA is that the equations used to transform the measured resistance into FFM or total body water are adapted to the individuals measured and have been tested for validity in the populations for which they are intended. In these conditions, BIA measurements are accurate and comparable to other techniques used to assess body composition. BIA has been extensively validated and evaluated in patients with COPD. The equations used were validated against deuterium dilution as the reference method, whereas other studies showed good association with dual-exposure X-ray absorptiometry (15, 16). The skeletal muscle index (SMI) was determined according to the equations used by Janssen et al (12).

**Follow-up**

Mortality was assessed on 31 January 1993. Patients were followed for 2–5 y or until death, whichever came first. Mortality was assessed as overall mortality due to all causes.

**Statistical analysis**

BMI, FFM index (FFMI), and FM index (FMI) were calculated by dividing body weight (in kg), FFM, and FM, respectively, by height (in m) squared to adjust for body surface area. Patients were stratified by body composition into 4 categories, as follows. Patients in category 1 (cachexia) had BMI <21 and FFMI <16 (men) or <15 (women); patients in category 2 (semi-starvation) had BMI <21 and FFMI ≥16 (men) or ≥15 (women); patients in category 3 (muscle atrophy) had BMI ≥21 and FFMI <16 (men) or <15 (women); and patients in category 4 (no impairment) had BMI ≥21 and FFMI ≥16 (men) or ≥15 (women).

The cutoff for FFMI is based on the linear association between FFM and body weight in normal-weight to overweight COPD patients as described by Baarends et al (8). In earlier publications, our group showed that these cutoffs are discriminative for exercise capacity (7) and health status (17). FFMI and FMI were compared with the sex-specific percentiles reported by Schutz et al (18). As an additional characterization, the SMI was measured, as proposed by Janssen et al, for a comparison of the total study population as well as the subgroups with results from the third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 (19). The percentage of patients theoretically at risk for physical disability was assessed by using the cutoffs for physical disability risk set by Janssen et al. Subjects from NHANES III were classified as physically disabled (ie, having difficulty performing activities of daily living) if they answered “yes” to either or both of the following questions: 1) “Because of any impairment or health problem, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around at home?” and 2) “Because of any impairment or health problem, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?”

In the study by Janssen et al (19), the cutoffs for severe physical disability risk were set at SMI ≤5.75 (men) or ≤5.80 (women), and for moderate physical disability risk were set at SMI ≤6.75 and >5.75 (women) or ≤10.75 and >8.50 (men). Results are presented as mean (±SD) for all variables that were normally distributed. Univariate analysis was performed by using the Kaplan-Meier method. A log-rank chi-square test for comparing survival between groups was used to analyze the association between depletion pattern and survival. The Cox proportional hazards model was used to quantify the relation between mortality and body composition (ie, FFMI and FMI), age, sex (0 = women, 1 = men), disease severity [PaO₂, PaCO₂, and FEV₁ (% of predicted) as continuous variables], and GOLD classification (as a categorized variable). Lung function criteria that defined the GOLD stages were normal lung function, GOLD 0 (at risk); the ratio of FEV₁ to IVC <70% and FEV₁ ≥80%, GOLD I (mild); FEV₁/IVC <70% and FEV₁ <80% and ≥50%, GOLD II (moderate); FEV₁/IVC <70% and FEV₁ ≤50% and ≥30%, GOLD III (severe); and FEV₁/IVC ≤70% and FEV₁ <30% or FEV₁ <50% and PaO₂ <8.0 kPa, GOLD IV (very severe).

The relative risk (RR) corresponding to a risk factor in this model is the exponential of the regression coefficient. The differences in distribution of body composition categories in GOLD stages II–IV were tested by using the chi-square test.

We performed all analyses with and without inclusion of the variable smoking (0 = no smoking or former smoking, 1 = current smoking). However, the cumulative pack-year exposure was high in all patients, and status as a former smoker was not objectively verified (eg, by cotinine measurements in saliva). Therefore, smoking was not associated with mortality in these subjects, and we decided to report only the results without this variable in the model.

A two-sided value of P < 0.05 was considered significant. Baseline comparisons between groups stratified by disease severity or body composition were performed by using an unpaired Student’s t test with Bonferroni correction for multiple comparisons. Data were analyzed by using SPSS for WINDOWS statistical software (version 11.0; SPSS Inc, Chicago, IL).
RESULTS

Patient characteristics are shown in Table 1. The mean age of the study group was 64 ± 9 years, 77% were male, and mean FEV₁ was 36 ± 14% of predicted (range: 19–70%). Because there was a significant difference between men and women in BMI, FFMI, and FMI (all: *P* < 0.05), we stratified mean values for FFMI, FMI, and SMI of the 4 body-composition categories by sex in Table 2 and related them separately to the sex-specific reference values reported by Schutz et al (18) and Janssen et al (19). The proportions of men to women did not differ significantly between the 4 body-composition categories. In categories 1 and 3, mean FFMI was below the 10th or even the 5th percentile in both male and female patients. Mean FFMI in categories 2 and 4 was within median range (<50th percentile) except for male patients in category 2, whose values were below the 10th percentile. FMI did not differ significantly between categories 1 and 2 or between categories 3 and 4 in either men or women. Although female patients with a low BMI had an FMI below the 10th percentile, male patients had an FMI within the median range. This indicates a sex-specific shift in body composition. When we applied the criteria for SMI and related physical disability that Janssen et al (19) used, a high proportion of the total patient population was characterized as being at moderate (51%) or high (31%) risk. In line with that study, male patients in the current study were at higher risk of physical disability than were female patients. On univariate Cox regression analysis, however, the association between BMI and survival in the current study did not differ significantly between the men (RR: 0.75; 95% CI: 0.65, 0.86) and the women (RR: 0.75; 95% CI: 0.51, 0.99). Furthermore, classification of the patients in the 4 categories clearly showed that, independent of sex, significantly (*P* < 0.001) more patients were at moderate to high risk of disability in the cachexia and muscle atrophy categories (ie, 1 and 3) than in semistarvation and no-impairment categories (ie, 2 and 4) (Table 2).

In Figure 1, body-composition categories are linked to GOLD stage of disease severity. Most of the patients had advanced COPD (GOLD II, *n* = 71; GOLD III, *n* = 134; and GOLD IV, SMI and related physical disability that Janssen et al (19) used, a high proportion of the total patient population was characterized as being at moderate (51%) or high (31%) risk. In line with that study, male patients in the current study were at higher risk of physical disability than were female patients. On univariate Cox regression analysis, however, the association between BMI and survival in the current study did not differ significantly between the men (RR: 0.75; 95% CI: 0.65, 0.86) and the women (RR: 0.75; 95% CI: 0.51, 0.99). Furthermore, classification of the patients in the 4 categories clearly showed that, independent of sex, significantly (*P* < 0.001) more patients were at moderate to high risk of disability in the cachexia and muscle atrophy categories (ie, 1 and 3) than in semistarvation and no-impairment categories (ie, 2 and 4) (Table 2).

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Cachexia was significantly \((P = 0.001)\) more prevalent in GOLD stage IV than in GOLD stages II and III. The mean duration of follow-up was 48 ± 20 mo, during which time 46% of the patients died. Univariate analysis showed that low BMI, FFMI, and FMI were significantly associated with increased mortality risk (Table 3). In addition, Cox stepwise regression analysis showed that FFMI was selected when BMI was no longer significant (data not shown) when entered as either an absolute value or as dichotomized BMI (≥21 or <21); this indicates that FFMI is a stronger predictor for mortality than is BMI. After multivariate analysis, adjusted only for age (\(P = 0.001\)) and sex (0 = women, 1 = men) (model 2), FFMI was an independent predictor of mortality (\(P = 0.001\) and 0.003 for model 1 and model 2, respectively), but FMI was not (Table 3). Although only a few patients were in the semistarvation category, the Kaplan-Meier plots for all the body-composition categories are shown in Figure 2. Survival was significantly \((P < 0.001)\) less in patients with cachexia (26 mo; 21, 31 mo) and muscle atrophy (24 mo; 15, 33 mo) than in patients with semistarvation (36 mo; 28, 44 mo) or no impairment (47 mo; 37, 57 mo). The survival plot of the semistarvation category did not differ significantly from that of the no-impairment category during the first 3 y.

### TABLE 3

Univariate and multivariate analysis of predictors of mortality

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate</th>
<th>Model 1</th>
<th>Model 2</th>
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<tr>
<td>Age</td>
<td>RR 1.04 CI</td>
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<td></td>
<td>1.02, 1.06</td>
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<td>0.001</td>
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<td>0.49, 1.06</td>
<td>0.94, 1.06</td>
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<td>0.071</td>
<td>0.100</td>
<td>0.100</td>
</tr>
<tr>
<td>BMI</td>
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<td>RR 0.88 CI</td>
<td>RR 0.88 CI</td>
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<td></td>
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<td>0.82, 0.94</td>
<td>0.82, 0.94</td>
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<tr>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
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<tr>
<td>FFMI</td>
<td>RR 0.88 CI</td>
<td>RR 1.01 CI</td>
<td>RR 1.01 CI</td>
</tr>
<tr>
<td></td>
<td>0.83, 0.94</td>
<td>0.94, 1.08</td>
<td>0.94, 1.08</td>
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<tr>
<td></td>
<td>0.001</td>
<td>0.843</td>
<td>0.843</td>
</tr>
<tr>
<td>FMI</td>
<td>RR 0.93 CI</td>
<td>RR 0.98 CI</td>
<td>RR 0.98 CI</td>
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<td>0.88, 0.99</td>
<td>0.97, 0.99</td>
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<td>0.009</td>
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<td>FEV\textsubscript{1}</td>
<td>RR 0.98 CI</td>
<td>RR 0.99 CI</td>
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<tr>
<td></td>
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<tr>
<td>IVC</td>
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<td>0.016</td>
<td>0.843</td>
<td>0.843</td>
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<tr>
<td>PaCO\textsubscript{2}</td>
<td>RR 1.17 CI</td>
<td>RR 0.98 CI</td>
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<td>0.047</td>
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<td>PaO\textsubscript{2}</td>
<td>RR 0.84 CI</td>
<td>RR 0.98 CI</td>
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<tr>
<td></td>
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\(^1\) RR, relative risk; FFMI, fat-free mass index; FMI, fat mass index; FEV\textsubscript{1}, forced expiratory volume in 1 s; IVC, inspiratory vital capacity; PaCO\textsubscript{2}, arterial carbon dioxide tension; PaO\textsubscript{2}, arterial oxygen tension.

\(^2\) FFMI, FMI, age, and sex (0 = women, 1 = men).

\(^3\) FFMI, FMI, age, sex (0 = women, 1 = men), FEV\textsubscript{1}, IVC, PaCO\textsubscript{2}, and PaO\textsubscript{2}.

\(^4\) Variable not included in the model.
The RRs (95% CIs) of patients in the 3 tissue-depletion categories compared with those of patients in the no-impairment category were 1.91 (1.37, 2.67; \( P = 0.006 \)), 1.23 (1.68, 2.24; NS), and 1.96 (1.21, 3.17; \( P < 0.001 \)) for categories 1 (cachexia), 2 (semistarvation), and 3 (muscle atrophy), respectively. Therefore, patients in both categories with low FFMI have a greater mortality risk than do patients with normal fat-free mass index [category 2 (semistarvation; \( n = 40 \), dashed gray line) had a significantly greater risk of mortality than did patients with normal fat-free mass index [category 2 (semistarvation; \( n = 40 \), dashed gray line, and category 4 (no impairment; \( n = 232 \), dashed black line).]

The Cox regression plots for the 4 categories, adjusted for age, sex, FMI, and disease severity markers, are shown in Figure 3. The RRs (95% CIs) of patients in the 3 tissue-depletion categories compared with those of patients in the no-impairment category were 1.91 (1.37, 2.67; \( P = 0.006 \)), 1.23 (1.68, 2.24; NS), and 1.96 (1.21, 3.17; \( P < 0.001 \)) for categories 1 (cachexia), 2 (semistarvation), and 3 (muscle atrophy), respectively. Therefore, patients in both categories with low FFMI have a greater mortality risk than do patients with no impairment, and, thus, low BMI does not increase mortality risk beyond the increase due to low FFMI.

**DISCUSSION**

This study shows that FFMI is an independent predictor of mortality in COPD irrespective of FM and provides further support for the use of body-composition assessment as a systemic marker of disease severity in COPD staging. It also confirms previous studies of COPD that showed an independent association between lower-limb cross-sectional area and mortality, particularly in patients with FEV_{1} <50\% (10). In the current study, however, BIA was used, which is an easier method of estimating FFMI in these patients without needing expensive apparatus or highly skilled technicians. Recently, Janssen et al (12) developed and crossvalidated BIA equations against magnetic resonance imaging in a sample of 388 men and women who varied widely in age and BMI. In that study, the correlation between BIA- and magnetic resonance imaging–measured muscle mass was 0.86. Gosker et al (20) showed in patients with COPD that FFMI assessed by BIA was significantly related to muscle fiber cross-sectional area taken from a biopsy of muscle tissue from the vastus lateralis, which indicated that whole-body FFM also reflects lower-limb muscle atrophy in chronic disease. FFMI estimation via BIA was also used in a recent analysis of NHANES III that identified skeletal muscle cutoffs associated with a high likelihood of physical disability (19). With the use of these criteria, the current study group was characterized as being at moderate to high risk of physical disability. These studies all indicate that BIA may be a useful clinical screening instrument for characterization of the tissue-depletion pattern in chronic lung disease.

The findings of this study differ from those of previous studies showing that an abundance of FM is particularly associated with increased cardiovascular disease–related mortality risk in overweight to obese subjects (reviewed in 21). The current study indicates that, in COPD patients, the association between FFMI and survival is independent of the amount of FM and that FFMI provides information to assist prognosis beyond that provided by BMI. Strikingly similar physical disability and mortality risks were seen in the cachexia and muscle atrophy categories, which indicated that a critical loss of muscle mass, not reflected in BMI, may be responsible for physical disability and greater mortality risk. In previous studies, we also showed significant differences in functional impairment such as exercise capacity measured by a 12-min walking test (7) or incremental cycle ergometry between patients in the cachexia and muscle atrophy categories relative to those in the semistarvation and no-impairment categories. Remarkably, the survival plot of the semistarvation category did not differ significantly from that of the no-impairment category during the first 3 y, whereas, thereafter, mortality was clearly higher in the semistarvation category. One could speculate that these patients initially have less mortality risk because of (relative) preservation of FFM but that, in due course, they are at greater risk of a critical loss of FFMI. This hypothesis, however, should be confirmed in a longitudinal study using repeated measurements of body composition. The current study also showed remarkable sex-specific differences in body composition and disability risk from the reference values, and those differences warrant further investigation. As compared with the data of Schutz et al (18), the shift in body composition toward less FFM and more FM was more striking in men than in women. One could argue that the male patients in the semistarvation category were not truly starving according to the external standards of Schutz et al (18). However, those patients clearly had lower FM than did patients in categories 3 and 4. Furthermore, in both the men and the women, comparison with the reference values of Janssen et al (19) showed that physical disability risk was clearly lower in categories 3 and 4, which confirmed previous studies relating those tissue-depletion categories to objective measures of skeletal function and exercise capacity (6–8). As was also indicated by Janssen et al (19), the SMI cutoffs were a significantly stronger predictor of physical disability in men than in women. This observation could indicate that SMI cutoffs should be adjusted. However, it might also be possible that the association between FFMI and physical disability risk, as judged by a questionnaire, really differs between males and females. This could reflect a different relation of body composition and functional capacity between males and females. It could also reflect a different coping strategy between males and females toward the functional limitations consequent to their chronic disease.
The relative preservation of FFM in COPD patients could result from inactivity as a consequence of the progressive disability due to the disease. It could also be a consequence of biological factors such as a derangement in (fat) oxidative metabolism, as indicated by impaired β-adrenoceptor-mediated lipolysis, which reduced fat mobilization (22). That, in turn, could lead to an increase in glucose turnover and protein utilization, as was reflected in an increased whole-body protein turnover (23). The abovementioned shift in body composition could therefore be an indication of either accelerated sarcopenia or an early phase of cachexia. Because cachexia was seen mostly in GOLD IV COPD patients (characterized not only by severe airflow obstruction but also by PaO2 <8.0 kPa), the loss of FM as well as of FFM might be related to specific effects of hypoxia on energy balance.

FFMI was associated with mortality with and without adjustment for static lung volumes and resting arterial blood gases. These markers are traditionally used to define disease severity and are included in the recent GOLD stages, but that does not exclude the possibility that other lung function markers might affect FFMI or the relation between FFMI and mortality. In particular, adjustment for the degree of emphysema would have been interesting, because previous studies showed that FFMI correlated with the diffusing capacity for carbon monoxide as a hallmark of emphysema (6). Furthermore, weight loss and low FFMI were significantly more common in patients with emphysema, as assessed by high-resolution computed tomography scanning, than in patients with chronic bronchitis (24). The process of emphysema might induce weight loss or loss of FFM, but weight loss or loss of FFMI also may induce emphysema. Post-mortem studies of persons who died in the Warsaw Ghetto during World War II suggested that death due to starvation was associated with pulmonary emphysema (25). In line with this observation but using advanced techniques to assess emphysema, an elegant study recently showed the presence of emphysema-like changes in the lungs of chronically malnourished anorexia nervosa patients (5).

On the basis of numerous reports showing an association between BMI and mortality risk in COPD, Celli at al (26) recently proposed that clinical staging for COPD should be based not only on spirometry and resting arterial blood gases, eg, the recent GOLD criteria, but also on BMI, exercise capacity, and dyspnea score. The results of the current study indicate that FFMI could be an even better independent predictor of systemic disease severity than is BMI.

The current study was limited by a skewed distribution of the study population toward more males and the more severe GOLD stages III and IV. In addition, categories 2 and 3 (semistarvation and muscle atrophy) were relatively small. Longitudinal studies with repeated assessments of body composition are needed to increase our knowledge of the sequence of body-composition changes so that we can better target therapeutic interventions. In advanced stages of disease, low FFM has already been clearly identified as a primary determinant of perceived disability, handicap, and health care costs, and it is therefore considered an important target for therapy (7, 17, 19, 27). Several studies specifically aimed therapeutic interventions at the accretion of muscle mass in patients with advanced COPD to improve functional capacity (28–33). The current study indicates that therapeutic strategies should depend not on BMI but on body composition. Although the studies by our group (28, 29, 31, 34) indicated that current therapeutic modalities can increase FFMI, the extent to which improvement in FFMI per se is reflected in other relevant outcome measures, including mortality, and the minimal clinically effective increase in FFMI remain to be investigated.

AMS and EFM set up the study. With the aid of RB, AMS analyzed the data and wrote the manuscript. CAW performed all body composition measurements. All authors read, commented on, and contributed to the manuscript. None of the authors had any personal or financial conflict of interest.

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