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Longitudinal Association Between Muscle Loss and Mortality in Ever Smokers

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BACKGROUND: Body composition measures, specifically low weight or reduced muscle mass, are associated with mortality in COPD, but the effect of longitudinal body composition changes is undefined.

RESEARCH QUESTION: Is the longitudinal loss of fat-free mass (FFM) associated with increased mortality, including in those with initially normal or elevated body composition metrics?

STUDY DESIGN AND METHODS: Participants with complete data for at least one visit in the COPDGene study (n = 9,268) and the ECLIPSE study (n = 1,760) were included and monitored for 12 and 8 years, respectively. Pectoralis muscle area (PMA) was derived from thoracic CT scans and used as a proxy for FFM. A longitudinal mixed submodel for PMA and a Cox proportional hazards submodel for survival were fitted on a joint distribution, using a shared random intercept parameter and Markov chain Monte Carlo parameter estimation.

RESULTS: Both cohorts demonstrated a left-shifted distribution of baseline FFM, not reflected in BMI, and an increase in all-cause mortality risk associated with longitudinal loss of PMA. For each 1-cm^2 PMA loss, mortality increased 3.1% (95% CI, 2.4%-3.7%; $P < .001$) in COPDGene, and 2.4% (95% CI, 0.9%-4.0%; $P < .001$) in ECLIPSE. Increased mortality risk was independent of enrollment values for BMI and disease severity [BODE (body mass, airflow obstruction, dyspnea, and exercise capacity) index quartiles] and was significant even in participants with initially greater than average PMA.

INTERPRETATION: Longitudinal loss of PMA is associated with increased all-cause mortality, regardless of BMI or initial muscle mass. Consideration of novel screening tests and further research into mechanisms contributing to muscle decline may improve risk stratification and identify novel therapeutic targets in ever smokers. CHEST 2022; 161(4):960-970

KEY WORDS: COPD; mortality; muscle wasting; sarcopenia

FOR EDITORIAL COMMENT, SEE PAGE 867

ABBREVIATIONS: BODE = body mass, airflow obstruction, dyspnea, and exercise capacity; COPDGene = Genetic Epidemiology of COPD; COTE = COPD-specific comorbidity test; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FFM = fat-free mass; FFMI = fat-free mass index; IQR = interquartile range; PMA = pectoralis muscle area

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Take-home Points

Study Question: Is the loss of muscle mass over time associated with increased mortality in those with normal or elevated body composition metrics?

Results: Loss of muscle mass was associated with increased risk of all-cause mortality regardless of BMI and muscle mass at study enrollment.

Interpretation: Accurately identifying patients who are losing muscle mass may have implications for risk stratification and therapy selection.

Derangements of body composition, specifically low weight or reduced muscle mass, have been associated with mortality in COPD. Few data exist, however, on the effect of changes in body composition over time. The most easily obtained measure, BMI, is calculated as a person's weight divided by their height squared. Low BMI values are consistently associated with increased mortality,[1,2] resulting in its dichotomous inclusion in the body mass, airflow obstruction, dyspnea, and exercise capacity (BODE) index, a predictor of COPD mortality.[3]

Low fat-free mass (FFM) or fat-free mass index (FFMI; FFM divided by height squared), most commonly defined as values below the fifth percentile for age and sex, contribute to the definition of sarcopenia, a syndrome of accelerated loss of muscle mass and strength.[4] Sarcopenia is observed across all COPD severity classes and BMI categories and has been associated with an increased risk of death in smokers, regardless of airflow obstruction.[5-7] There remains a paucity of data describing the consequences of FFM above the sarcopenic threshold or the impact of changes in FFM over time. Because sarcopenia may be treatable or preventable through exercise training and dietary modification, these are clinically relevant questions.[8]

Using longitudinal data from the COPDGene (Genetic Epidemiology of COPD) study and the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, we sought to investigate whether loss of FFM, even in those who are not frankly sarcopenic, was associated with increased all-cause mortality in ever smokers. We hypothesized that loss of FFM would be associated with increased risk of death even in those with normal or high BMI or FFM at enrollment.

Study Design and Methods

Study Population

The analysis was performed using two previously described multicenter, longitudinal, observational cohort studies. The primary analysis was conducted using baseline and 5-year follow-up data from the COPDGene study,[9] which enrolled 10,198 non-Hispanic White or Black people with and without COPD, aged 45 to 80 years, with at least a 10-pack-year smoking history.[10] Enrollment occurred at 21 centers in the United States with assessments every 5 years; the 10-year follow-up visits are currently ongoing. Vital status was assessed by querying the Social Security Death Index in December 2016 as well the longitudinal follow-up program through August 2020.[11]

The analyses were replicated using data from the ECLIPSE study[12]; complete results are available in the online article. ECLIPSE enrolled 2,164 people with COPD and 337 people without COPD, who were aged 45 to 75 years, with a smoking history of at least 10 pack-years.[13] Participants were enrolled from 26 centers across 12 countries and actively monitored for a total of 3 years with assessments completed at baseline, 12 months, and 36 months. Five years after initial study completion, participants were contacted and their medical records reviewed to ascertain their vital status.

Written informed consent was obtained from all participants, and both studies were approved by the institutional review boards of all participating centers.

Comorbidities

The COPD-specific comorbidity test (COTE) was calculated for each participant, based on their self-reported medical history from study questionnaires.[14] The index assigns points based on the 12 comorbidities that have the strongest association with increased risk of death in people with COPD.

Lung Function

Spirometry was done at baseline and at each follow-up visit in both studies, before and after the administration of an inhaled short-acting β-agonist. Postbronchodilator values were used to determine the presence and severity of obstruction. Six-minute walk testing was completed according to international guidelines at study visits for all participants in COPDGene and in participants diagnosed with COPD in ECLIPSE.[15] Disease severity was calculated for each study

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visit using the BODE index, with further classification into four classes: 1 (score, 0-2), 2 (score, 3-4), 3 (score, 5-6), and 4 (score, 7-10).[3]

Imaging

The use of CT imaging to quantify muscle area as a proxy for FFM has been endorsed in international guidelines.[16] Pectoralis muscle area (PMA), unlike lumbar, psoas, or thigh muscle area, can be derived from routine chest CT imaging. In patients with COPD, PMA correlates well with FFM derived by direct methods ($R^2 = 0.92$).[17-21] Participants in both studies underwent repeated noncontrast CT scanning of the chest at full inflation with a 5-year interval in COPDGene and a 3-year interval in ECLIPSE.[10,13] PMA was quantified from a single axial slice of the CT scan above the aortic arch, as described previously.[22,23] Each resulting image was reviewed for quality control, visually identifying and excluding segmentation failures (eg, malposition of the arm, distortion from an implanted device). The calculated PMA represents the aggregate cross-sectional area of the right and left pectoralis major and minor muscles, expressed in centimeters squared.

The models described below used PMA as a covariate; however, normative population data do not exist for PMA. To facilitate comparison, FFMI was calculated from PMA, using a formula previously derived in the ECLIPSE cohort.[17] Because of the composition of the ECLIPSE cohort, only non-Hispanic White participants were compared with published normative values of FFMI and BMI for people aged 45 to 69 years.[24,25]

Statistical Analyses

For the primary analysis, a longitudinal mixed model for PMA and a Cox proportional hazards model for survival were fitted on a joint distribution with a shared parameter, current value association structure, and Markov chain Monte Carlo parameter estimation.[26,27] Compared with time-dependent Cox models, joint models have been demonstrated to more precisely estimate repeated measures that display biological variation or are measured with error (endogenous variables). Because endogenous variables are related to a subject-specific stochastic process, they inherently violate the assumptions of the Cox framework. In addition, joint models allow for valid inferences in the setting of missing data, such as those participants who completed only their initial enrollment or interval follow-up examination, even when the missingness depends on the unobserved data points.[28]

Model covariates were chosen a priori, based on the literature. The longitudinal submodel included covariates for time, age, race, height, weight, sex, pack-years, oral steroid use, and smoking status. A random intercept (the shared parameter) was included to account for repeated measures. The survival submodel included covariates for time, age, race, sex, pack-years, smoking status, COTE index, and BODE score. Age, weight, smoking status, COTE index, and BODE score were allowed to vary with time in all models. In addition, in the COPDGene analyses, pack-years was also allowed to vary with time. Data were right-censored and the proportional hazards assumption was tested using the nonzero slope method.[29] Kaplan-Meier curves were constructed, using the subset of patients with two visits.

Summary statistics are presented as mean and SD or as number and percentage, as appropriate. Differences between two groups were evaluated with *t* tests and differences between multiple groups by one-way analysis of variance. An α of .05 was used, and all statistical tests were two-sided. All the analyses were performed with R version 3.6.3 (R Foundation for Statistical Computing) and the JMbayes package.[30]

Results

Complete data for at least one visit were available for 9,268 participants from COPDGene and for 1,760 participants from ECLIPSE (e-Fig 1). Their baseline characteristics are shown in Table 1. The COPDGene cohort was 53.9% male, 66.8% non-Hispanic White, and had a median follow-up time of 3,454 [interquartile range (IQR), 1,767-3,899] days. The ECLIPSE cohort was 64.5% male, 97.7% non-Hispanic White, and had a median follow-up duration of 2,395 (IQR, 1,095-2,921) days. At the time of censoring, 20.7% of the COPDGene cohort and 29.0% of the ECLIPSE cohort were confirmed as deceased.

Baseline Body Composition

Women had significantly less PMA than men ($P < .001$ in both cohorts). At COPDGene enrollment, women had a median PMA of 30.1 cm^2 (IQR, 25.4-36.0 cm^2) and men had a median PMA of 48.6 cm^2 (IQR, 40.1-58.9 cm^2). In ECLIPSE, women had a median PMA of 26.1 cm^2 (IQR, 22.6-29.7 cm^2) and men had a median PMA of 38.4 cm^2 (IQR, 32.6-44.6 cm^2) at enrollment.

The FFMI at enrollment was calculated from the PMA for the 4,872 COPDGene participants and 1,306 ECLIPSE participants for whom normative data were available: non-Hispanic White people between 45 and 70 years of age. Compared with healthy populations, participants in both cohorts were overrepresented in FFMI percentiles below the mean despite a BMI distribution that closely mirrors the general population (Fig 1). BMI as a proxy for FFMI, in this cohort, tends to overestimate muscle mass in normal-weight or obese people. Low FFMI percentiles were similar across all BODE severity classes (e-Fig 2).

Association Between Mortality and Muscle Loss

Data for two visits were available for 4,333 COPDGene participants and 941 ECLIPSE participants; their characteristics are shown in e-Table 1. The median change in PMA for women in COPDGene was −1.8 cm^2 (IQR, 1.2 to −5.2 cm^2) or −6.0% (IQR, 4.2% to −16.4%) and for men was −2.8 cm^2 (IQR, 2.0 to −8.0 cm^2) or −6.0% (IQR, 4.4% to −15.2%) over 5 years. In ECLIPSE, the median change in PMA for women was −1.0 cm^2 (IQR, 1.0 to −3.1 cm^2) or −4.0% (IQR, 3.6% to −11.5%) and for men was −1.9 cm^2 (IQR, 1.5 to −5.0 cm^2) or −5.2% (IQR, 3.6% to −13.0%) over 3 years (e-Fig 3).

Age, sex, smoking status (current or former), BODE score, COTE index, and PMA were significantly associated with mortality in both COPDGene and

TABLE 1] Characteristics of Study Participants at Enrollment

Characteristic	ECLIPSE	COPDGene
Sample size	1,760	9,268
Age, mean (SD), y	63.7 (7.1)	59.7 (9.0)
Male, No. (%)	1,136 (64.5)	4,991 (53.9)
Non-Hispanic White, No. (%)	1,719 (97.7)	6,188 (66.8)
Current smoker, No. (%)	630 (35.8)	4,859 (52.4)
Pack-years on study entry, median (IQR)	44.0 (30.0-60.0)	39.2 (27.1-54.4)
BMI, mean (SD)	26.5 (5.5)	28.8 (6.16)
Chronic oral steroid use, No. (%)	25 (1.4)	224 (2.4)
COTE index, median (IQR)	0 (0-1)	0 (0-1)
BODE index, mean (SD)	3.2 (2.2)	1.8 (2.3)
Pectoral muscle area, median (IQR), cm^2		
Men	38.37 (32.63-44.64)	48.55 (40.12-58.86)
Women	26.10 (22.55-29.74)	30.13 (25.36-36.01)
6-Min walk distance, mean (SD), m	367.2 (122.3)	412.2 (121.5)
FEV_1 percent predicted, mean (SD), %	48.0 (15.7)	76.8 (25.3)
Days monitored, median (IQR)	2,395 (1,095-2,921)	3,454 (1,767-3,899)
Deaths, No. (%)	510 (29.0)	1,922 (20.7)

BODE = body mass, airflow obstruction, dyspnea, and exercise capacity; COPDGene = Genetic Epidemiology of COPD study; COTE = COPD-specific comorbidity test; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; IQR = interquartile range.

ECLIPSE. Pack-years and race were, in addition, significant predictors in COPDGene. In both cohorts, longitudinal loss of PMA was associated with increased mortality. In COPDGene, there was a 3.1% (95% CI, 2.4%-3.7%; $P < .001$) increase in mortality for each 1-cm^2 loss of PMA and in ECLIPSE, there was a 2.4% (95% CI, 0.9%-4.0%; $P < .001$) increase in mortality for each 1-cm^2 loss of PMA.

Mortality Risk Stratified by Baseline Body Composition Metrics

Because normative data are not available for all people in COPDGene, participants were dichotomized on the basis of whether their baseline PMA was above or below the cohort mean (adjusted for sex and height). Participants who entered the study with an above-average PMA for the cohort had a

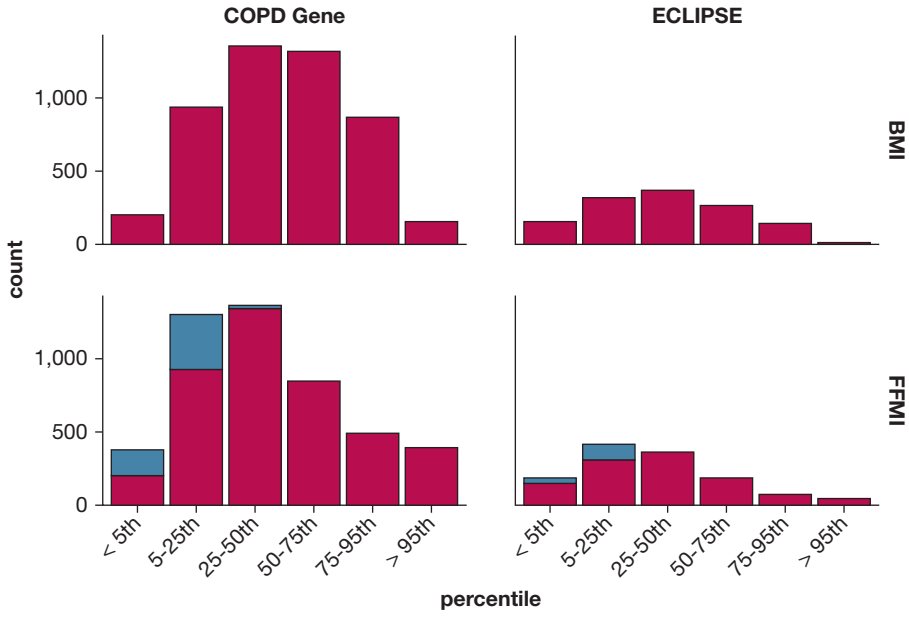

Figure 1 – *The population percentiles of fat-free mass index (FFMI) and BMI for non-Hispanic White participants between 45 and 70 years of age in COPDGene and ECLIPSE, compared with healthy population data. In the upper panels, participant BMI reflects that of the general population, as demonstrated by the normal distribution. In contrast, in the lower panels the FFMI distributions are right-skewed, with the blue-shaded portions representing participants overrepresented in the lower percentiles of FFMI compared with their BMI. COPDGene = Genetic Epidemiology of COPD Study; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints.*

2.2% (95% CI, 1.0%-3.6%; $P \leq .001$) increased risk of death for each 1 cm^2 of PMA loss, whereas those who entered the study with a below-average PMA had a 6.1% (95% CI, 5.0%-7.3%; $P < .001$) increased risk of death per 1-cm^2 decrease in PMA (Fig 2). Results for ECLIPSE are reported in the online article. Similarly, as healthy people are estimated to lose 0.64% to 0.98% of their peak muscle mass annually,[31,32] participants who lost 5% or less of their baseline PMA were classified as stable compared with those who lost more than 5%. Strikingly, those with above-average PMA who lost muscle had similar survival to those with below-average, but stable, PMA (Fig 3).

Higher BMI did not ameliorate the association between longitudinal loss of PMA and mortality (Fig 2). Participants in COPDGene with a BMI below 21 kg/m^2 had a 3.5% (95% CI, 1.2%-5.8%; $P < .001$) increased risk of death for each 1-cm^2 loss of PMA. For those with a BMI between 21 and 30 kg/m^2, the risk of death increased by 3.0% (95% CI, 2.2%-4.0%; $P < .001$), and for those with a BMI greater than 30 kg/m^2, the risk increased by 2.8% (95% CI, 1.5%-4.1%; $P < .001$) for each 1-cm^2 loss of PMA. Results for ECLIPSE and cohort characteristics by BMI category (e-Table 2, e-Fig 4) are reported in the online article.

Mortality Risk Stratified by Biologic Sex and Race

There was a significant interaction between biologic sex and PMA in COPDGene ($P < .001$). The risk of death increased by 5.4% (95% CI, 3.7%-6.7%; $P < .001$) for women and 2.9% (95% CI, 2.1%-3.6%; $P < .001$) for men for each 1-cm^2 loss of PMA (Fig 2). Results for ECLIPSE are reported in the online article (e-Fig 4).

Black participants in COPDGene had significantly higher initial PMA values than non-Hispanic White participants ($P < .001$). At enrollment, Black participants had a median PMA of 47.9 cm^2 (IQR, 37.3-61.2 cm^2) and non-Hispanic White participants had a median PMA of 35.3 cm^2 (IQR, 27.8-45.7 cm^2). Each 1-cm^2 loss of PMA was associated with a 2.7% (95% CI, 1.7%-3.8%; $P < .001$) increased risk of death for Black participants and a 3.4% (95% CI, 2.4%-4.3%; $P < .001$) increased risk of death for non-Hispanic White participants (Fig 2). Because of cohort demographics, a similar analysis was not feasible in ECLIPSE.

Mortality Risk Stratified by Disease Severity Metrics

Mean PMA at COPDGene enrollment was significantly different across BODE classes for both men and women ($P < .001$), with higher BODE class associated with

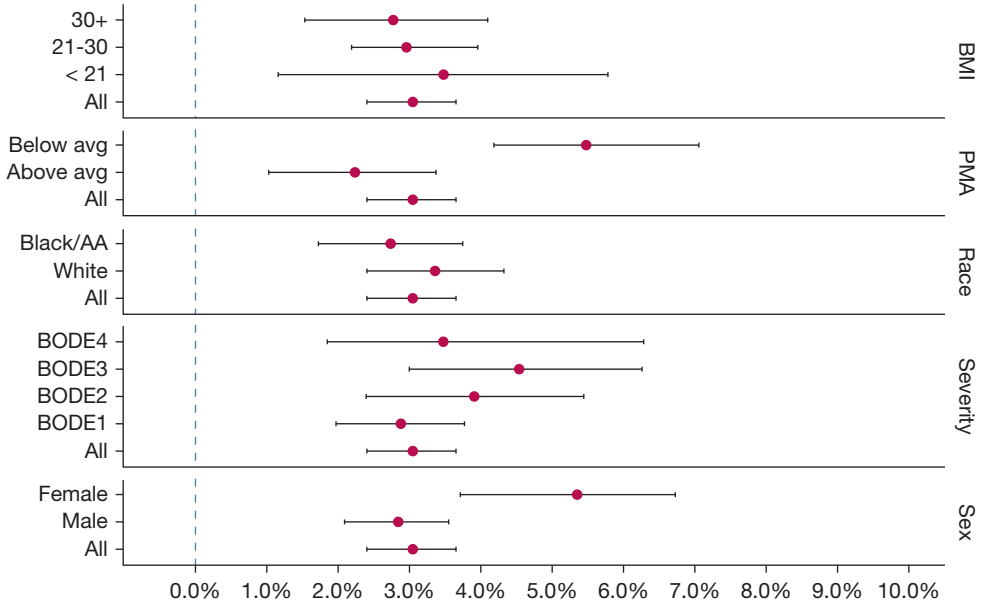

Figure 2 – *Effect sizes from stratified analyses in the COPDGene cohort. Stratification was based on the value of the variable (listed in the gray boxes on the right) at the time of study enrollment. Each dot represents the point estimate for the increased risk of mortality per 1-cm^2 loss of pectoral muscle area, and horizontal lines depict the CI. avg = average; Black/AA = Black/African American; BODE = body mass, airflow obstruction, dyspnea, and exercise capacity; COPDGene = Genetic Epidemiology of COPD Study; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; PMA = pectoral muscle area.*

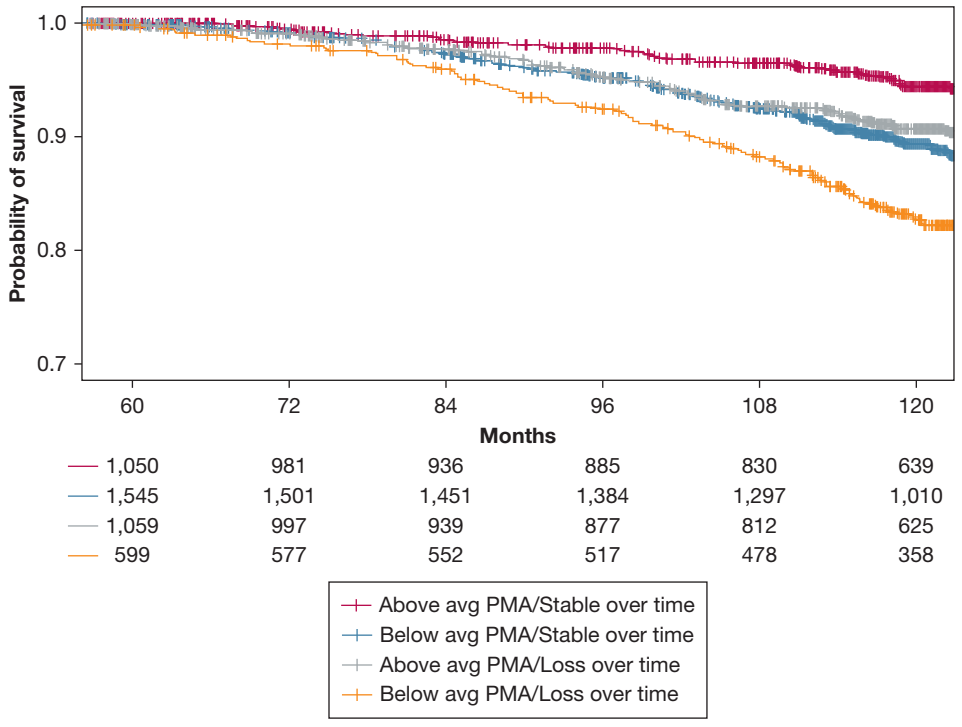

Figure 3 – *Kaplan-Meier survival curves for participants in COPDGene with more than one pectoral muscle area (PMA) measurement. Patients were dichotomized on the basis of whether their PMA was above or below the cohort mean at enrollment (adjusted for sex and height) as well as whether they lost more than the expected age-related muscle area. avg = average; COPDGene = Genetic Epidemiology of COPD Study.*

lower mean PMA. The association between PMA loss and mortality, however, was not significantly different across BODE classes (Fig 2). For each 1-cm^2 loss of PMA, the risk of death increased by 2.9% (95% CI, 2.0%-3.8%; $P < .001$), 3.9% (95% CI, 2.4%-5.5%; $P < .001$), 4.5% (95% CI, 3.0%-6.3%; $P < .001$), and 3.5% (95% CI, 1.9%-6.3%; $P < .001$) for BODE classes 1 through 4, respectively. Results by BODE score for the ECLIPSE cohort (e-Fig 4) as well as the use of percent emphysema for severity stratification (e-Fig 5) are reported in the online article.

Discussion

Using PMA derived from chest CT imaging in two sizable, observational, longitudinal cohorts of ever smokers, we demonstrated an increased risk of all-cause mortality in those with interval PMA loss. Notably, the increased mortality risk was independent of BMI and disease severity, as measured by BODE classes, and was significant even in participants with average or above-average PMA at enrollment compared with cohort peers. We found a significant interaction between sex and PMA loss; by contrast, no similar interaction was seen between PMA loss and race. Because measurement of PMA by chest CT imaging is a validated proxy for total body FFM, our findings have significant implications for risk stratification of ever smokers and interventions to reduce mortality.

The first such implication is to emphasize the inadequacy of BMI to capture the mortality risk associated with body composition. A normal or elevated BMI does not exclude low FFM, nor does BMI stability exclude FFM loss, which is currently underrecognized in routine clinical practice. Our work extends the literature demonstrating that ever smokers have a higher prevalence of sarcopenia[33-35] by showing that even above sarcopenic thresholds, ever smokers are overrepresented in lower percentiles of FFMI compared with population norms, despite a BMI distribution that mimics the general population. Our data also extend results from Schols and colleagues,[6] who demonstrated that people with COPD with low FFMI had worse 3-year survival than those with low BMI. By showing that muscle loss, even in the absence of sarcopenia, is associated with mortality risk, we highlight the need to incorporate muscle mass assessment into clinical care.

Second, loss of PMA occurred in participants across the full range of body composition, and in neither cohort was average or above-average PMA at enrollment protective against the mortality risk associated with PMA loss. These data support the hypothesis that muscle loss, rather than absolute bulk, underpins the risk of death. Muscle loss not only has implications for mortality, but for morbidity and quality of life. Loss of muscle bulk results in increased risk for falls leading to fractures, dysphagia resulting in increased risk of pulmonary infection, and reduced respiratory muscle function leading to gas exchange abnormalities.[36-38] There is increasing evidence that sarcopenia also contributes to immune function deterioration, potentially leading to a positive feedback loop with immunosenescence and inflamm-aging.[39,40]

Third, because our data indicate the mortality risk accompanying loss of muscle was independent of disease severity, they imply that referral to therapies targeted at maintenance or improvement of muscle mass should not be deferred until obstructive disease is severe. Exercise programs, such as pulmonary rehabilitation, have been demonstrated to improve muscle mass and mortality in the short term in patients with COPD,[41-44] and resistance training carries a strong recommendation in international guidelines.[16] Although these guidelines do not currently recommend protein, calorie, or vitamin D supplementation, anabolic hormone therapy, or other pharmacologics such as ghrelin agonists, this may more accurately reflect a paucity of research rather than a true lack of efficacy. Further research into the mechanisms underlying muscle loss is needed to optimize screening and treatment regimens. To date, cigarette smoke, physical inactivity, corticosteroid use, and respiratory exacerbations are each hypothesized as potential contributors to muscle mass loss.[45-48]

Strengths of our analysis include the use of longitudinal measurement of muscle mass over time, replication in a second cohort, comparison with normative FFMI data, and a long follow-up duration. Repeated measures in both cohorts allowed us to investigate change in muscle mass and therefore the full range of PMA values, rather than only those at the extremes.

Our study also has several limitations, particularly our use of PMA expressed as centimeters squared as the covariate unit. The strikingly higher risk per centimeter squared of PMA loss for women compared with men is reduced when recast in relative terms. In this cohort, the mortality risk per 1 cm^2 for women was 1.9 times higher than for men, but women lost a median of only 63% as much muscle area as men, suggesting that the risk per percent muscle loss is likely more comparable than the absolute numbers suggest. Similarly, those with higher BMI or lower BODE score had slightly higher mean PMA than their counterparts and thus a 1-cm^2 loss is a relatively smaller percent change. A survival model using percent change in PMA would improve interpretability; however, it would introduce bias and reduce power by necessitating exclusion of all participants with only one measurement before death or censorship. Furthermore, PMA is an endogenous variable and, as discussed in the Study Design and Methods section, not optimally represented as traditional Cox covariate.

An additional limitation is that not all of the results in our replication cohort attained statistical significance, although many of the same trends were observed (e-Fig 4). This disparity is likely due to the smaller cohort size, causing a reduction in power, as well as the shorter interval between measurements.

Lastly, muscle mass or muscle area is not a readily available clinical metric. Few patients undergo dual x-ray absorptiometry or bioelectrical impedance analysis measurements for FFM, and although CT imaging-derived measures could be obtained from routine clinical scans, such algorithms have not yet been implemented in the clinical context. Our results support the implementation of such algorithms, as the early identification and amelioration of muscle loss may improve survival.

Interpretation

Ever smokers are overrepresented in lower percentiles of FFMI compared with the general population. FFM loss, assessed by PMA on chest CT scan, is associated with an increased risk of all-cause mortality, regardless of an individual's body composition or obstructive disease severity, and this loss is not necessarily reflected in the BMI. Implementation of screening tests for muscle decline and further research into risk factors contributing to muscle loss may facilitate timely referrals to exercise programs such as pulmonary rehabilitation.

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Author contributions: S. E. M. is the guarantor of the manuscript and wrote the manuscript. S. E. M., G. R. W., and M. J. S. were responsible for study design and statistical analysis. R. M.-M., Ru. S. J. E., and Ra. S. J. E. contributed to the computational imaging methodology. R. M.-M., W. W. L., M. J. S., E. A. R., J. B., R. C., M.-L. McD., H. B. R., B. M., M. T. D., M.L. K. H., K. Y., G. K., J. E. H., Ra. S. J. E., J. L. C., K. S., and G. R. W. revised the manuscript for critical intellectual content.

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