The Ratio of FEV_1 to FVC as a Basis for Establishing Chronic Obstructive Pulmonary Disease

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Rationale: **The lambda-mu-sigma (LMS) method is a novel approach that defines the lower limit of normal (LLN) for the ratio of FEV_1/FVC as the fifth percentile of the distribution of Z scores. The clinical validity of this threshold as a basis for establishing chronic obstructive pulmonary disease is unknown.**

Objective: **To evaluate the association between the LMS method of determining the LLN for the FEV_1/FVC, set at successively higher thresholds, and clinically meaningful outcomes.**

Methods: **Using data from a nationally representative sample of 3,502 white Americans aged 40–80 years, we stratified the FEV_1/FVC according to the LMS-LLN, with thresholds set at the 5th, 10th, 15th, 20th, and 25th percentiles (i.e., LMS-LLN_5, LMS-LLN_{10}, etc.). We then evaluated whether these thresholds were associated with an increased risk of death or prevalence of respiratory symptoms. Spirometry was not specifically completed after a bronchodilator.**

Measurements and Main Results: **Relative to an FEV_1/FVC greater than or equal to LMS-LLN_{25} (reference group), the risk of death and the odds of having respiratory symptoms were elevated only in participants who had an FEV_1/FVC less than LMS-LLN_5, with an adjusted hazard ratio of 1.68 (95% confidence interval, 1.34–2.12) and an adjusted odds ratio of 2.46 (95% confidence interval, 2.01–3.02), respectively, representing 13.8% of the cohort. Results were similar for persons aged 40–64 years and those aged 65–80 years.**

Conclusions: **In white persons aged 40–80 years, an FEV_1/FVC less than LMS-LLN_5 identifies persons with an increased risk of death and prevalence of respiratory symptoms. These results support the use of the LMS-LLN_5 threshold for establishing chronic obstructive pulmonary disease.**

Keywords: chronic obstructive pulmonary disease; FEV_1/FVC; lower limit of normal; mortality; respiratory symptoms

The threshold of the ratio of FEV_1/FVC that establishes chronic obstructive pulmonary disease (COPD) is uncertain (1–5). The Global Initiative for Obstructive Lung Disease (GOLD), for example, recommends a threshold based on a fixed ratio of 0.70, whereas the American Thoracic Society (ATS) and European Respiratory Society (ERS) advocate a threshold based on a lower limit of normal (LLN) (1, 3).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The lambda-mu-sigma (LMS) method is a novel approach that defines the lower limit of normal (LLN) for the ratio of FEV_1/FVC as the fifth percentile of the distribution of Z scores. The clinical validity of this threshold as a basis for establishing chronic obstructive pulmonary disease (COPD) is unknown.

What This Study Adds to the Field

In persons aged 40–80 years, an FEV_1/FVC less than LMS-LLN at the fifth percentile (LMS-LLN_5) identifies those with an increased risk of death and prevalence of respiratory symptoms.

Establishing COPD based solely on an FEV_1/FVC of less than 0.70 is seriously flawed (1, 2, 4). Because a fixed ratio does not account for normal age-related changes in airflow limitation, GOLD guidelines are likely to misdiagnose COPD, particularly in older persons (1, 2, 4). Likewise, establishing COPD based on the ATS/ERS-defined LLN can be problematic (2). Specifically, ATS/ERS guidelines define the LLN as the fifth percentile of the frequency distribution of reference values (ATS/ERS-LLN_5), as derived by multiple regression in "healthy" never-smokers (6). However, multiple regression assumes that the relationship between the predictor variables (e.g., age, height, sex, and ethnicity) and spirometric measures is linear, and that reference values are normally distributed and have constant variability (2). These assumptions are incorrect, especially among older persons, because reference values for the FEV_1/FVC range widely and are increasingly skewed at the extremes of age (2, 7).

Recently, Stanojevic and colleagues (2, 7) have proposed that the LLN should be calculated using the lambda-mu-sigma (LMS) method, an approach widely used to construct growth charts. These investigators have shown that the LMS method more accurately describes the relationship between spirometric lung function and anthropometric predictor variables across the lifespan (2, 7). Based on their results, the LMS-derived LLN for the FEV_1/FVC is defined as the fifth percentile of the distribution of Z scores (LMS-LLN_5) (2, 7). In the LMS method, the Z score accounts for: (*1*) the median (mu), representing how the spirometric variable changes with a predictor variable; (*2*) the coefficient of variation (sigma), which models the spread of spirometric reference values and adjusts for nonuniform dispersion; and (*3*) skewness (lambda), which models the departure of variables from normality using a box-Cox transformation (2, 7).

Although promising, because the LMS-LLN_5 is based only on a statistical definition of "normal," its clinical validity is uncertain, particularly in populations with a high prevalence of

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risk factors for COPD. For example, if a reference population of healthy never-smokers includes persons with a high frequency of exposures to air pollution, environmental tobacco smoke, or high-risk occupation, the LMS-LLN_5 may be lower than the threshold that defines "biologically normal." (8–10) We therefore propose that the LMS-LLN should be assessed empirically by evaluating the associations between successively higher thresholds and clinically meaningful outcomes, such as mortality and respiratory symptoms (5, 11–13).

In the present study, using data from a nationally representative sample of persons aged 40–80 years, we stratified the FEV_1/FVC according to the LLN, set at successively higher thresholds, and calculated on the basis of LMS-derived Z scores (2, 7). We then evaluated whether these LMS-derived thresholds identified persons at an increased risk of death and prevalence of respiratory symptoms. As a secondary aim, we also compared prevalence rates for COPD, based on GOLD, ATS/ERS, and LMS-derived thresholds.

METHODS

Study Population

We used data from the Third National Health and Nutrition Examination Survey (NHANES) III, a nationally representative sample of community-living Americans assembled in 1988–1994, with mortality surveillance through December 31, 2000 (14, 15). For the present study, our source population included 3,502 participants, aged 40–80 years, who were white, had no self-reported asthma, and completed at least two ATS-acceptable spirometric maneuvers (14). As per current ATS recommendations, we did not exclude participants based on spirometric reproducibility criteria (16). We selected an age range of 40 years or older because COPD and its related mortality are unusual in younger persons (17). Our study population was limited to whites, as spirometric reference values for the LMS method are currently unavailable for minority groups (2, 7).

Clinical Measures

As described elsewhere, NHANES III recorded the presence of respiratory symptoms in the prior 12 months, defined as chronic cough or sputum production lasting for at least 3 consecutive months (i.e., "chronic bronchitis"), dyspnea on exertion, or wheezing or "whistling in the chest." (14) Other clinical data included age, sex, ethnicity, height, body mass index (BMI; weight divided by height-squared, expressed as kg/cm^2), self-reported chronic conditions and health status, as well as COPD risk factors, such as smoking history, urban residence (i.e., surrogate for air pollution), and high-risk occupation (i.e., based on exposure to airborne dust) (10, 14).

NHANES III also recorded all-cause mortality, which was ascertained from a public-use–linked mortality file that contains information based on the National Death Index, with follow-up through December 31, 2000 (15). Vital status was available on all participants (15).

Spirometry

NHANES III used a customized dry-rolling seal spirometer (14). After calibration, each participant performed five to eight FVC maneuvers, with the goal of meeting ATS criteria (14). For each study participant, as per current guidelines, the measured FEV_1/FVC was calculated from the largest set of FEV_1 and FVC values that were recorded in any of the spirometric maneuvers meeting ATS acceptability criteria (8, 16).

Based on the measured value, an LMS-derived Z score for the FEV_1/FVC was then calculated for each participant as follows (2, 7): $([\text{measured } FEV_1/FVC \div \text{median } FEV_1/FVC]^{\text{lambda}} - 1) \div (\text{lambda} \times \text{sigma})$. The prediction equations from Stanojevic and colleagues (2, 7) were used to calculate values for the median, lambda, and skewness, and the cubic splines for age were retrieved from tables at www.growinglungs.org.uk (7). These tables are based on four pooled reference samples, with ages ranging from 4 to 80 years. For the age group of 40–80 years, the focus of our study population, the reference sample was exclusively drawn from NHANES III (2, 7). In the United States, NHANES III is preferred for establishing the reference range, because it is the only available, nationally representative sample of the U.S. population that included spirometry (1, 2, 14). Based on Z scores, we then stratified our study population to successively higher thresholds for the LMS-derived LLN, namely at the 5th, 10th, 15th, 20th, and 25th percentiles (LLN_5, LLN_{10}, etc.). For example, Z scores that were less than −1.64 corresponded to an FEV_1/FVC less than LMS-LLN_5 (2, 7). We increased the criterion for "abnormal" to as high as the 25th percentile, identifying nearly 40% of our study participants, because prior work has shown that the prevalence of COPD among older NHANES III participants may be as high as 34.5% when using a GOLD fixed ratio of 0.70 (5).

Statistical Analysis

We first summarized baseline characteristics as means of values accompanied by standard deviations or as counts accompanied by percentages, and we stratified the results according to age: 40–64 years and 65–80 years, denoting middle age and older age, respectively. Differences between middle age and older age were evaluated, using Chi-square for categorical variables or a (two-tailed) *t* test for continuous variables, with a *P* value less than 0.05 (two-sided) denoting statistical significance.

We next evaluated the association between the LMS-defined FEV_1/FVC strata and death, using a single Cox regression model adjusted for age, height, sex, ethnicity, smoking history, BMI, number of chronic conditions, and health status. The LMS-defined FEV_1/FVC strata were treated as nominal categories, with the reference group including participants with an FEV_1/FVC of at least LMS-LLN_{25}. Goodness of fit was assessed by model-fitting procedures and by the analysis of residuals. The proportional hazards assumption was tested by using interaction terms for the time-to-event outcome and each variable in the multivariable model. If significant at the *P* less than 0.05 level, after adjusting for the multiplicity of comparisons, these interaction terms were retained in the final model. Higher-order effects were tested for the continuous covariates, and were included in the final model if they met the forward selection criterion of *P* less than 0.20 (18). Scaled score residuals for each variable were calculated and plotted. In sensitivity analyses, observations with large residuals were removed from the data set; their removal made little change in reported results.

Similarly, we evaluated the associations between the LMS-defined FEV_1/FVC strata and the presence of respiratory symptoms by calculating odds ratios (ORs) using a single logistic regression model. We subsequently stratified the results according to middle age and older age, respectively. To enhance clinical interpretability, we also evaluated the associations between the LMS-defined FEV_1/FVC strata and the presence of respiratory symptoms limited to chronic bronchitis or exertional dyspnea. These symptoms represent the most frequent indications for therapeutic interventions in COPD (3).

Finally, we compared prevalence rates for COPD according to ATS/ERS, GOLD, and LMS-derived thresholds (1–3). This included determining prevalence rates for "misidentified" COPD that, based on the above risk analysis, was ultimately defined as participants who had an FEV_1/FVC less than ATS/ERS-LLN_5 or less than 0.70, but also had an FEV_1/FVC of at least the value of LMS-LLN_5.

SUDAAN version 10 (Research Triangle Institute, Research Triangle Park, NC) was used to estimate hazard ratios (HR; from Cox proportional hazards regression) and ORs (from logistic regression), with a *P* value less than 0.05 (two-sided) denoting statistical significance (19).

RESULTS

Table 1 shows the baseline characteristics of the study population, stratified by age. Overall, participants had a mean age of nearly 61 years, with about half being females. Compared with participants who were middle aged (40–64 yr), those who were older aged (65–80 yr) had less education and were less likely to be current smokers, but more likely to have fair-to-poor health status, chronic conditions, or respiratory symptoms. Over a follow-up period ranging between 6 and 12 years, 663 (18.9%) participants died, yielding an overall mortality rate of 22.5 per

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS, ACCORDING TO AGE

Characteristic	All, 40–80 Yr (*n = 3,502*)	Middle Age, 40–64 Yr (*n = 2,005*)	Older Age, 65–80 Yr (*n = 1,497*)
Age, mean (SD), yr	60.7 (12.0)	51.9 (7.4)	72.5 (4.5)*
Females, *n* (%)	1,827 (52.2)	1,051 (52.4)	776 (51.8)
Education, mean (SD), yr	12.2 (3.1)	12.7 (2.8)	11.4 (3.2)*
Urban residence†, *n* (%)	1,325 (37.8)	801 (40.0)	524 (35.0)
High-risk occupation‡, *n* (%)	491 (14.5)	267 (13.7)	224 (15.7)
Fair-to-poor health status, *n* (%)	671 (19.2)	301 (15.0)	370 (24.8)*
Smoking status, *n* (%) *			
Never	1,429 (40.8)	772 (38.5)	657 (43.9)
Former	1,337 (38.2)	693 (34.6)	644 (43.0)
Current	736 (21.0)	540 (26.9)	196 (13.1)
Chronic conditions§, mean (SD), *n*	0.69 (0.90)	0.50 (0.75)	0.94 (1.00)*
Respiratory symptoms¶, *n* (%)	1,451 (41.5)	757 (37.8)	694 (46.5)*

* $P < 0.05$; middle-age versus older-age.
† Surrogate for air pollution.
‡ Based on exposure to airborne dust.
§ Self-reported, physician diagnosed.
¶ In the prior 12 months, including chronic cough or sputum production lasting at least 3 consecutive months, dyspnea on exertion, and wheezing or "whistling in the chest."

1,000 person-years (95% confidence interval [CI], 20.8–24.2). For the middle-aged and older-aged groups, the mortality rates were 7.9 per 1,000 person-years (95% CI, 6.7–9.3) and 45.5 per 1,000 person-years (95% CI, 41.7–49.6), respectively.

Table 2 shows the HR for all-cause mortality and ORs for having respiratory symptoms, stratified according to the LMS-LLN for the FEV_1/FVC, among participants aged 40–80 years. In comparison to the reference group (i.e., $FEV_1/FVC \geqslant$ LMS-LLN_{25}), the risk of death was significantly elevated only among participants who had an FEV_1/FVC of less than LMS-LLN_5, with an adjusted HR of 1.68 (95% CI, 1.34–2.12). Similarly, the prevalence of respiratory symptoms was significantly elevated only among participants with an FEV_1/FVC of less than LMS-LLN_5, with an adjusted OR of 2.46 (95% CI, 2.01–3.02). These results did not change appreciably when respiratory symptoms were defined only as chronic bronchitis or exertional dyspnea (data available upon request). Comparable associations of FEV_1/FVC strata with all-cause mortality and respiratory symptoms were also observed for participants aged 40–64 years (Table 3) and those aged 65–80 years (Table 4). In addition, the distribution of participants across the FEV_1/FVC strata was comparable in each of the two age groups (Tables 3 and 4).

Table 5 shows the prevalence of COPD, as defined by the ATS/ERS-LLN_5, GOLD, and LMS-LLN_5 thresholds for the FEV_1/FVC. The percentage of participants aged 40–80 years who had ATS/ERS-defined COPD was 17.1%, including 15.6% in the middle-aged and 19.2% in the older-aged groups, while the percentage of participants aged 40–80 years who had

TABLE 2. HAZARD RATIOS FOR ALL-CAUSE MORTALITY AND ODDS RATIOS FOR RESPIRATORY SYMPTOMS, ACCORDING TO THE LAMBDA-MU-SIGMA–LOWER LIMIT OF NORMAL FOR THE FEV_1/FVC SET AT SUCCESSIVELY HIGHER PERCENTILES, AMONG PARTICIPANTS AGED 40–80 YEARS

Measured FEV_1/FVC	No. of Participants *n* (%)	No. of Deaths among Participants *n* (%)	No. of Participants with Respiratory Symptoms *n* (%)	HR for Mortality (95% CI)		OR for Respiratory Symptoms (95% CI)	
				Unadjusted	Adjusted*	Unadjusted	Adjusted†
All-cause mortality risk‡							
$\geqslant$LMS-LLN_{25}	2,123 (61.4)	335 (15.8)	—	1.00		—	—
LMS-$LLN_{20} \leqslant$ to $<$ LLN_{25}	191 (5.5)	38 (19.9)	—	1.26 (0.85–1.88)	1.24 (0.85–1.83)	—	—
LMS-$LLN_{15} \leqslant$ to $<$ LLN_{20}	210 (6.1)	43 (20.5)	—	1.28 (0.97–1.70)	1.24 (0.92–1.66)	—	—
LMS-$LLN_{10} \leqslant$ to $<$ LLN_{15}	210 (6.1)	34 (16.2)	—	0.99 (0.76–1.29)	1.13 (0.85–1.49)	—	—
LMS-$LLN_5 \leqslant$ to $<$ LLN_{10}	248 (7.2)	63 (25.4)	—	1.59 (1.22–2.08)	1.26 (0.95–1.66)	—	—
$<$LMS-LLN_5	477 (13.8)	138 (28.9)	—	1.92 (1.52–2.42)	1.68 (1.34–2.12)	—	—
Respiratory symptoms§							
$\geqslant$LMS-LLN_{25}	2,117 (61.3)	—	801 (37.8)	—	—	1.00	
LMS-$LLN_{20} \leqslant$ to $<$ LLN_{25}	191 (5.5)	—	66 (34.6)	—	—	0.87 (0.62–1.21)	0.92 (0.64–1.32)
LMS-$LLN_{15} \leqslant$ to $<$ LLN_{20}	210 (6.1)	—	84 (40.0)	—	—	1.10 (0.83–1.44)	1.20 (0.88–1.64)
LMS-$LLN_{10} \leqslant$ to $<$ LLN_{15}	210 (6.1)	—	78 (37.1)	—	—	0.97 (0.74–1.28)	1.02 (0.74–1.39)
LMS-$LLN_5 \leqslant$ to $<$ LLN_{10}	248 (7.2)	—	111 (44.8)	—	—	1.33 (1.05–1.69)	1.12 (0.85–1.47)
$<$LMS-LLN_5	477 (13.8)	—	295 (61.8)	—	—	2.66 (2.18–3.26)	2.46 (2.01–3.02)

Definition of abbreviations: CI = confidence interval; LMS = lambda-mu-sigma; LMS-LLN = LMS-defined lower limit of normal, with strata defined by the 5th, 10th, 15th, 20th, and 25th percentile (e.g. LMS-$LLN_{20} \leqslant$ to $<$ LLN_{25} denotes a range greater than or equal to the 20th percentile but less than the 25th percentile); OR = odds ratio.
Total *n* = 3,502.
* Values were calculated using a single Cox regression mortality model that was adjusted for age, age^2, height, sex, smoking history, body mass index (BMI), BMI^2, BMI^3, self-reported health status, and number of chronic conditions. The reference group was defined by an $FEV_1/FVC \geqslant$ LMS-LLN_{25}.
† Values were calculated using a single logistic regression model that was adjusted for age, height, sex, smoking history, BMI, self-reported health status, and number of chronic conditions. The reference group was defined by an $FEV_1/FVC \geqslant$ LMS-LLN_{25}.
‡ A total of 43 participants (1.2%) were excluded because of missing data on covariates.
§ A total of 49 participants (1.3%) were excluded because of missing data on covariates or respiratory symptoms.

TABLE 3. HAZARD RATIOS FOR ALL-CAUSE MORTALITY AND ODDS RATIOS FOR RESPIRATORY SYMPTOMS, ACCORDING TO THE LAMBDA-MU-SIGMA–LOWER LIMIT OF NORMAL FOR THE FEV_1/FVC SET AT SUCCESSIVELY HIGHER PERCENTILES, AMONG PARTICIPANTS AGED 40–64 YEARS

Measured FEV_1/FVC	No. of Participants *n* (%)	No. of Deaths among Participants *n* (%)	No. of Participants with Respiratory Symptoms *n* (%)	HR for Mortality (95% CI)		OR for Respiratory Symptoms (95% CI)	
				Unadjusted	Adjusted*	Unadjusted	Adjusted†
All-cause mortality risk‡							
⩾LMS-LLN_{25}	1,216 (61.5)	65 (5.4)	—	1.00		—	—
LMS-LLN_{20} ⩽ to < LLN_{25}	100 (5.1)	5 (5.0)	—	0.91 (0.32–2.65)	0.80 (0.28–2.36)	—	—
LMS-LLN_{15} ⩽ to < LLN_{20}	113 (5.7)	10 (8.8)	—	1.67 (0.94–2.96)	1.43 (0.74–2.75)	—	—
LMS-LLN_{10} ⩽ to < LLN_{15}	137 (6.9)	10 (7.3)	—	1.34 (0.75–2.38)	1.15 (0.68–1.96)	—	—
LMS-LLN_5 ⩽ to < LLN_{10}	131 (6.6)	11 (8.4)	—	1.51 (0.90–2.53)	1.34 (0.82–2.16)	—	—
<LMS-LLN_5	281 (14.2)	39 (13.9)	—	2.66 (1.88–3.75)	1.85 (1.30–2.63)	—	—
Respiratory symptoms§							
⩾LMS-LLN_{25}	1,215 (61.5)	—	412 (33.9)	—	—	1.00	
LMS-LLN_{20} ⩽ to < LLN_{25}	100 (5.1)	—	32 (32.0)	—	—	0.92 (0.59–1.42)	0.98 (0.61–1.57)
LMS-LLN_{15} ⩽ to < LLN_{20}	113 (5.7)	—	40 (35.4)	—	—	1.07 (0.68–1.67)	1.01 (0.60–1.69)
LMS-LLN_{10} ⩽ to < LLN_{15}	137 (6.9)	—	47 (34.3)	—	—	1.02 (0.67–1.54)	0.92 (0.60–1.41)
LMS-LLN_5 ⩽ to < LLN_{10}	131 (6.6)	—	53 (40.5)	—	—	1.32 (0.95–1.84)	1.12 (0.79–1.58)
<LMS-LLN_5	281 (14.2)	—	165 (58.7)	—	—	2.77 (2.00–3.84)	2.22 (1.54–3.21)

For definition of abbreviations *see* Table 2. Total n = 2,005.

* Values were calculated using a single Cox regression mortality model that was adjusted for age, height, sex, smoking history, body mass index (BMI), self-reported health status, and number of chronic conditions. The reference group was defined by an FEV_1/FVC ⩾ LMS-LLN_{25}.

† Values were calculated using a single logistic regression model that was adjusted for age, age^2, height, sex, smoking history, BMI, BMI^2, BMI^3, self-reported health status, and number of chronic conditions. The reference group was defined by an FEV_1/FVC ⩾ LMS-LLN_{25}.

‡ A total of 27 participants (1.3%) were excluded because of missing data on covariates.

§ A total of 28 participants (1.4%) were excluded because of missing data on covariates or respiratory symptoms.

GOLD-defined COPD was 27.0%, including 19.1% in the middle-aged and 37.7% in the older-aged groups. In contrast, the percentage of participants aged 40–80 years who had LMS-defined COPD was 13.8%, including 14.3% in the middle-age and 13.2% in the older-age groups.

Table 6 shows the prevalence of misidentified COPD based on an FEV_1/FVC of at least LMS-LLN_5. ATS/ERS and GOLD thresholds "misidentified" COPD in 19.2 and 48.9% of participants aged 40–80 years, respectively, 8.3 and 25.1% of participants in the middle-aged group, respectively, and 31.0 and 63.2% of participants in the older-aged group, respectively.

DISCUSSION

Among persons aged 40–80 years, we found that an FEV_1/FVC threshold for establishing COPD based on the LMS-LLN_5 is associated with a statistically significant increase in the risk of death and likelihood of having respiratory symptoms. These results support a definition of COPD that is based on an LMS-LLN_5 threshold for the FEV_1/FVC.

The LMS method for calculating the LLN has a strong statistical rationale, because it accounts for normal age-related increases in airflow limitation, as well as the variability of the

TABLE 4. HAZARD RATIOS FOR ALL-CAUSE MORTALITY AND ODDS RATIOS FOR RESPIRATORY SYMPTOMS, ACCORDING TO THE LAMBDA-MU-SIGMA–LOWER LIMIT OF NORMAL FOR THE FEV_1/FVC SET AT SUCCESSIVELY HIGHER PERCENTILES, AMONG PARTICIPANTS AGED 65–80 YEARS

Measured FEV_1/FVC	No. of Participants *n* (%)	No. of Deaths among Participants *n* (%)	No. of Participants with Respiratory Symptoms *n* (%)	HR for Mortality (95% CI)		OR for Respiratory Symptoms (95% CI)	
				Unadjusted	Adjusted*	Unadjusted	Adjusted†
All-cause mortality risk‡							
⩾LMS-LLN_{25}	907 (61.2)	270 (29.8)	—	1.00		—	—
LMS-LLN_{20} ⩽ to < LLN_{25}	91 (6.1)	33 (36.3)	—	1.24 (0.84–1.84)	1.33 (0.88–2.00)	—	—
LMS-LLN_{15} ⩽ to < LLN_{20}	97 (6.6)	33 (34.0)	—	1.08 (0.80–1.46)	1.15 (0.85–1.55)	—	—
LMS-LLN_{10} ⩽ to < LLN_{15}	73 (4.9)	24 (32.9)	—	1.08 (0.74–1.56)	1.13 (0.76–1.68)	—	—
LMS-LLN_5 ⩽ to < LLN_{10}	117 (7.9)	52 (44.4)	—	1.48 (1.14–1.94)	1.24 (0.90–1.70)	—	—
<LMS-LLN_5	196 (13.2)	99 (50.5)	—	1.87 (1.42–2.45)	1.63 (1.22–2.17)	—	—
Respiratory symptoms§							
⩾LMS-LLN_{25}	902 (61.1)	—	389 (43.1)	—	—	1.00	
LMS-LLN_{20} ⩽ to < LLN_{25}	91 (6.2)	—	34 (37.4)	—	—	0.79 (0.48–1.29)	0.89 (0.51–1.58)
LMS-LLN_{15} ⩽ to < LLN_{20}	97 (6.6)	—	44 (45.4)	—	—	1.10 (0.73–1.63)	1.43 (0.94–2.19)
LMS-LLN_{10} ⩽ to < LLN_{15}	73 (5.0)	—	31 (42.5)	—	—	0.97 (0.65–1.46)	1.15 (0.77–1.72)
LMS-LLN_5 ⩽ to < LLN_{10}	117 (7.9)	—	58 (49.6)	—	—	1.30 (0.82–2.04)	1.14 (0.74–1.76)
<LMS-LLN_5	196 (13.3)	—	130 (66.3)	—	—	2.60 (1.92–3.52)	2.72 (1.91–3.89)

For definition of abbreviations *see* Table 2. Total n = 1,497.

* Values were calculated using a single Cox regression mortality model that was adjusted for age, height, sex, smoking history, body mass index (BMI), BMI^2, BMI^3, number of chronic conditions and self-reported health by time interaction. The reference group was defined by an FEV_1/FVC ⩾ LMS-LLN_{25}.

† Values were calculated using a single logistic regression model that was adjusted for age, height, sex, smoking history, BMI, self-reported health status, and number of chronic conditions. The reference group was defined by an FEV_1/FVC ⩾ LMS-LLN_{25}.

‡ A total of 16 participants (1.1%) were excluded because of missing data on covariates.

§ A total of 21 participants (1.4%) were excluded because of missing data on covariates or respiratory symptoms.

TABLE 5. PREVALENCE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AS DEFINED BY THE AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY–DEFINED LOWER LIMIT OF NORMAL AT THE FIFTH PERCENTILE, GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE, AND LAMBDA-MU-SIGMA–LOWER LIMIT OF NORMAL AT THE FIFTH PERCENTILE THRESHOLDS FOR FEV_1/FVC

	No. (%) of Participants		
FEV_1/FVC Threshold	All, 40–80 Yr (*n = 3,502*)	Middle Age, 40–64 Yr (*n = 2,005*)	Older-Age, 65–80 Yr (*n = 1,497*)
<ATS/ERS-LLN_5	599 (17.1)	312 (15.6)	287 (19.2)
<0.70 (GOLD)	947 (27.0)	382 (19.1)	565 (37.7)
<LMS-LLN_5	484 (13.8)	286 (14.3)	198 (13.2)

Definition of abbreviations: ATS/ERS-LLN_5= American Thoracic Society/European Respiratory Society–defined lower limit of normal at the fifth percentile; GOLD = Global Initiative for Obstructive Lung Disease, with a fixed-ratio threshold of 0.70; LMS = lambda-mu-sigma; LMS-LLN_5 = LMS-defined LLN_5.

reference data and its departure from normality (2, 7). In support of the LMS method, we found that the distributions of NHANES III participants across the FEV_1/FVC strata were comparable for the middle-aged and older-aged groups (Tables 3 and 4).

The results of our study also provide a strong clinical rationale for using an LMS-LLN threshold for the FEV_1/FVC at the fifth percentile of the distribution of Z scores (i.e., LMS-LLN_5) as a basis for establishing COPD in middle age and older age. In both age groups, only individuals with an FEV_1/FVC less than LMS-LLN_5 had an increased risk of all-cause mortality and prevalence of respiratory symptoms. All-cause mortality is an objective and definitive health outcome that is resistant to miscoding and has been the primary endpoint in landmark studies of oxygen therapy in COPD (11). In addition, respiratory symptoms are the most distressing feature of COPD, and can lead to disability and increased healthcare use (11, 12).

Our results suggest that diagnostic thresholds published by the ATS/ERS and GOLD commonly "misidentify" COPD, especially in older age. Specifically, we found that 31.0 and 63.2% of study participants aged 65–80 years were misidentified as having COPD, because they had an FEV_1/FVC less than ATS/ERS-LLN_5 or less than 0.70, respectively, but also a "normal" FEV_1/FVC of at least LMS-LLN_5. In comparison, participants aged 40–64 years had misidentification rates for COPD of 8.3 and 25.1% for the ATS/ERS and GOLD thresholds, respectively. These high rates of misidentification are likely due to methodological limitations of the ATS/ERS and GOLD approaches. For example, because the ATS/ERS threshold does not account for the variability of the reference data, including departure from normality (especially at the extremes of age) (2), it will overestimate the prevalence of COPD with advancing age. Similarly, because the GOLD threshold cannot distinguish normal age-related increases in airflow limitation from clinically significant pathology (1, 2), it will also overestimate the prevalence of COPD with advancing age.

Our results have important implications for clinical practice. Because a threshold based on the LMS-LLN_5 is less likely to overdiagnose COPD, it could lead to a more targeted use of COPD-specific pharmacotherapies and, hence, a reduced frequency of medication-related adverse events (20, 21). Nonetheless, because pulmonary function, like many clinical phenomena, occurs along a continuum, we would suggest that the LMS-LLN_5 should serve as a guide rather than a rigid "yes/no" threshold for the diagnosis of COPD (22). Individuals with an FEV_1/FVC that lies just above the LMS-LLN_5, for example, may still have COPD, particularly if they have significant risk factors for COPD and the likelihood of an alternative diagnosis is low. Importantly, our results may also be applicable to other respiratory diseases that are characterized by airflow limitation, such as asthma, although this will need to be formally evaluated in future studies.

We recognize potential limitations to our study. First, because cause of death in NHANES III was based only on information from death certificates (14, 15), we evaluated all-cause mortality as an outcome rather than COPD-specific mortality. Prior work has demonstrated that COPD is commonly underreported as a cause of death, even among patients with symptomatic COPD (23). Furthermore, COPD increases the risk of death from cardiovascular disease and lung cancer, and the number of deaths from these causes is much greater than those from respiratory disease among patients with COPD (23–25). In the Lung Health Study, for example, 81.8% of deaths in participants with COPD were due to cardiovascular disease or lung cancer (26). Nonetheless, our findings should be validated in cohorts that include adjudicated data on cause of death.

Second, we evaluated a diagnostic threshold based on the presence of respiratory symptoms, which are not necessarily specific to COPD (11, 12). Nonetheless, respiratory symptoms in COPD can be highly disabling and resource intensive (11, 12). For these reasons, and because there was a threshold relationship between the LMS-defined FEV_1/FVC strata and

TABLE 6. PREVALENCE OF MISIDENTIFIED CHRONIC OBSTRUCTIVE PULMONARY DISEASE, AS DEFINED BY AN FEV_1/FVC GREATER THAN OR EQUAL TO LAMBDA-MU-SIGMA–DEFINED LOWER LIMIT OF NORMAL AT THE FIFTH PERCENTILE

	No. (%) of Participants*		
	All, 40–80 Yr	Middle Age, 40–64 Yr	Older Age, 65–80 Yr
<ATS/ERS-LLN_5 and ⩾LMS-LLN_5	115/599 (19.2)	26/312 (8.3)	89/287 (31.0)
<0.70 (GOLD) and ⩾LMS-LLN_5	463/947 (48.9)	96/382 (25.1)	357/565 (63.2)

Definition of abbreviations: ATS/ERS-LLN_5= American Thoracic Society/European Respiratory Society–defined lower limit of normal at the fifth percentile; GOLD = Global Initiative for Obstructive Lung Disease, with a fixed-ratio threshold of 0.70; LMS-LLN_5= lambda-mu-sigma–defined LLN_5.

* The denominator for the percent calculations included all participants in the corresponding age-group who had an FEV/FVC less than ATS/ERS-LLN_5 or less than 0.70 (GOLD), respectively.

respiratory symptoms, including those specific to chronic bronchitis and dyspnea, we conclude that it is valid to base a spirometric definition of COPD on these clinical features.

Third, because spirometry in NHANES III was not specifically obtained after a bronchodilator, we could not assess reversibility in airflow limitation, a recommended criterion for defining COPD (1). It is unlikely, however, that the absence of information on "reversibility" had a meaningful effect on our results, because persons with self-reported asthma were excluded from our analytical sample, and because prior work has shown that bronchodilator reversibility is neither a sufficient criterion to exclude COPD nor an independent predictor of mortality (27, 28). Nonetheless, we acknowledge that our study population may have included participants with asthma, either as a sole form of obstructive airways disease or concurrent with COPD.

Fourth, because specific LMS-derived Z scores for the FEV_1/FVC have not yet been published for minorities (i.e., African Americans and Mexican Americans) (2, 7), our results are limited to a white population. Prior work has demonstrated racial differences in pulmonary function, in general, and COPD-related risk factors and susceptibility, in particular (29).

Fifth, because the sample size for each of the LMS-derived FEV_1/FVC strata was modest, our analysis may have been underpowered to detect clinically meaningful effects at strata above the LLN_5.

Finally, because a separate validation set was not included in the current analysis, our results will need to be replicated in other, ideally larger, cohorts that include population groups other than whites, so that the validity and generalizability of the LMS-LLN_5 as a diagnostic threshold for COPD can be more firmly established.

In conclusion, among white persons aged 40–80 years, an FEV_1/FVC threshold at the LMS-LLN_5 conferred both an increase in the risk of death and likelihood of having respiratory symptoms. Although further validation is needed in other population groups, including minority representation, these results nonetheless provide strong support for the use of the LMS-LLN_5 as a threshold for the diagnosis of COPD.

Conflict of Interest Statement: C.A.V.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; P.H.V.N. holds $10,001–$50,000 in stock ownership or options in Vanguard Health Care Mutual Fund; C.L.R. received $1,001–$5,000 from GlaxoSmithKline and $1,001–$5,000 from Novartis for the COPD Advisory Board, $50,001–$100,000 from GlaxoSmithKline as an ECLIPSE study participant, and $50,001–$100,001 from Boehringer Ingelheim as an UPLIFT study participant; H.K.Y. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.M.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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