Published in final edited form as:

J Am Geriatr Soc. 2011 October ; 59(10): 1847–1854. doi:10.1111/j.1532-5415.2011.03596.x.

Staging the Severity of Chronic Obstructive Pulmonary Disease in Older Persons Based on Spirometric z-Scores

Carlos A. Vaz Fragoso, MD^{1,2}, John Concato, MD^{1,2}, Gail McAvay, PhD², H. Klar Yaggi, MD^{1,2}, Peter H. Van Ness, PhD², and Thomas M. Gill, MD²

¹Veterans Affairs (VA) Clinical Epidemiology Research Center, West Haven, CT

²Yale University School of Medicine, Department of Internal Medicine, New Haven, CT

Abstract

Background/Objectives—Among older persons, the use of spirometric Z-scores as calculated by the Lambda-Mu-Sigma (LMS) method has a strong scientific rationale for establishing a diagnosis of chronic obstructive pulmonary disease (COPD), but its clinical validity in staging COPD severity is not known. We therefore evaluated the association between LMS-staged COPD and health outcomes, in two separate cohorts of older persons.

Design—Longitudinal cohort study.

Setting—The Cardiovascular Health Study (CHS, N=3,248) and the Third National Health and Nutrition Examination Survey (NHANES-III, N=1,354).

Participants—Community-living white participants aged 65–80 years.

Measurements—Using spirometric data, COPD was staged as mild, moderate, and severe based on LMS-derived Z-scores. Clinical validity was then evaluated according to all-cause mortality, respiratory symptoms (chronic bronchitis, dyspnea, or wheezing), and moderate-to-severe dyspnea (available in CHS only).

Results—In CHS, the LMS-staging of COPD as mild, moderate, and severe was associated with mortality—adjusted hazard ratio (HR) (95% confidence interval): 1.50 (1.15, 1.94), 1.31 (1.03, 1.67), and 2.00 (1.70, 2.36), as well as respiratory symptoms—adjusted odds ratio (OR): 1.69 (1.12, 2.56), 1.87 (1.28, 2.73), and 3.99 (2.91, 5.48), respectively. Also in CHS, moderate and severe, but not mild, LMS-staged COPD was associated with moderate-to-severe dyspnea—adjusted OR: 2.16 (1.24, 3.75), 3.98 (2.77, 5.74), and 0.84 (0.35, 2.01), respectively. Similar associations were found for mortality and respiratory symptoms in NHANES-III, except mild severity was not associated with mortality—adjusted HR: 0.93 (0.62, 1.40).

Conclusion—In white older persons, the spirometric staging of COPD severity based on LMS-derived Z-scores was associated with several clinically relevant health outcomes. These results support the use of the LMS method for staging the severity of COPD in older populations.

Address correspondence to: Carlos A. Vaz Fragoso, MD at the Clinical Epidemiology Research Center, VA Connecticut Healthcare System, 950 Campbell Ave., Mailcode 151B, West Haven, CT. USA. [Telephone (203) 688-9423; fax (203) 688-4209; carlos.fragoso@yale.edu].

Conflict of Interest

Sponsor's Role: The investigators retained full independence in the conduct of this research and report no conflicts of interest.

Author Contributions: The manuscript reflects the contributions of all six authors, including study concept and design, analysis and interpretation of data, and preparation of manuscript.

Keywords

COPD; spirometry; respiratory symptoms; mortality

INTRODUCTION

As a leading cause of disability and death worldwide, chronic obstructive pulmonary disease (COPD) is defined by airflow limitation, established spirometrically by a reduced ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC), with severity subsequently classified according to FEV1 alone.^{1,2} Current guidelines published by the two major bodies—Global Initiative for Obstructive Lung Disease (GOLD) and a combined task force from the American Thoracic and European Respiratory Societies (ATS/ERS)—recommend a multilevel staging system for COPD that is based on FEV1 cut-points expressed as percent predicted (%Pred): $[(\text{measured} \div \text{predicted}) \times 100]$.^{1,2}

Although well-established, the %Pred approach for staging the FEV1 is seriously flawed, for at least two reasons.^{3–9} First, it assumes incorrectly that a given value of FEV1 %Pred is equivalent for all persons, regardless of age, height, sex and ethnicity.^{3,4} To illustrate, at the 5th percentile of reference values, a white male of average height has a value for FEV1 of 74%Pred at age 30-years, but only 63%Pred at age 70-years.³ A second flaw underlying the use of FEV1 %Pred is that the staging cut-points recommended by GOLD and the ATS/ERS are arbitrary and not based on health outcomes, such as mortality and respiratory symptoms.^{1,2}

To address limitations in %Pred, some investigators have proposed that FEV1 should be expressed as a Z-score, calculated as a standardized residual (SR): $[(\text{measured} - \text{predicted}) / (\text{standard deviation of the residuals})]$.^{3,4} In this equation, the numerator is the “residual”, whereas the denominator quantifies the spread of the reference data (accounting for variability in age, sex, height, and ethnicity). A Z-score is thus a conversion of a raw measurement on a test to a standardized score in units of standard deviations, and has already been successfully incorporated into the diagnosis of osteopenia and osteoporosis.¹⁰ Importantly, in contrast to %Pred, prior work has shown that a given FEV1 SR value has a constant statistical meaning across the lifespan and that, among white and non-white older persons, FEV1 cut-points at the 5 and 10 percentile distribution of SR-derived Z-scores (SR-tiles) are associated with mortality and respiratory symptoms, respectively.^{3–7} Moreover, relative to these SR-tile cut-points, %Pred staging of FEV1 misclassifies the risk of death and likelihood of having respiratory symptoms.⁶

Nonetheless, the SR-tile approach also has limitations because it is based on conventional multiple regression techniques that may not adequately account for age-related differences in the variability of spirometric performance, as well as skewness in distributions.^{8,9} Consequently, an alternative method for calculating Z-scores has been proposed, termed Lambda-Mu-Sigma (LMS).^{8,9} This strategy uses the median (Mu), representing how spirometric variables change based on predictor variables; the coefficient of variation (Sigma), modeling the spread of reference values and adjusting for non-uniform dispersion; and skewness (Lambda), modeling a departure from normality (see Methods section).^{8,9} In addition to its strong mathematical rationale, prior work has shown that LMS-derived Z-scores for FEV1/FVC provide a valid means for establishing COPD in older persons, as determined by associations with health outcomes.¹¹ The use of LMS-derived Z-scores for FEV1 in staging the severity of COPD, however, has not yet been evaluated.

In the present study, which included data from two large cohorts of community-living older persons, we evaluated a 3-level staging system for COPD, based on percentile distributions of LMS-derived Z-scores for FEV1, with mortality and respiratory symptoms as the outcomes of interest. As a secondary aim, we evaluated the frequency distributions of COPD severity according to GOLD and ATS/ERS criteria, within strata of the new LMS-staging system.

METHODS

Study population

We used publicly-available data from the Cardiovascular Health Study (CHS) and the Third National Health and Nutrition Examination Survey (NHANES-III),^{12,13} with institutional review board approval obtained from our respective institutions. For the present study, eligible participants were white, aged 65–80 years, and had completed at least two ATS-acceptable spirometric maneuvers at the baseline initial examination. Our analyses were limited to whites aged 65–80 years because reference values for the LMS-method are currently not available for non-whites and those aged >80 years.^{8,9} To focus on “irreversible” airflow limitation as the principal comparison group, namely COPD, participants with self-reported asthma or spirometric restrictive-pattern were excluded (see spirometry section below). As per current convention, we did not exclude participants based on spirometric reproducibility criteria.¹⁴

CHS is a population-based, longitudinal study of older Americans, with an age range of 65–100 years (N=5,888).¹³ The cohort was assembled in 1989–90 as a random sample from Medicare eligibility lists in four U.S. communities and followed for mortality through 2002. Based on eligibility criteria, our CHS sample included 3,248 participants. NHANES-III used a complex design to generate a nationally representative sample of Americans, with an age range of 8–80 years (N=33,994).¹² The cohort was assembled in 1988–94 and followed for mortality through 2000. Based on eligibility criteria, our NHANES-III sample included 1,354 participants.

Spirometry

In both study samples, participants underwent spirometry during the baseline examination, according to contemporary ATS protocols.¹⁵ Spirometry was conducted using a water-sealed spirometer (Collins Survey II) in CHS, whereas a dry-rolling seal spirometer (Ohio Sensormed 827) was used in NHANES-III; both met ATS accuracy requirements.^{12,13,16,17} For each participant, the measured FEV1/FVC was calculated from the largest set of FEV1 and FVC values that were recorded in any of the spirometric maneuvers for which participant performance met ATS-acceptability criteria.^{2,14}

In both study samples, based on measured values for each participant, we calculated LMS-derived Z-scores for forced expiratory volume in 1-second (FEV1), forced vital capacity (FVC), and the ratio of FEV1/FVC, as previously recommended:^{8,9} $[(\text{measured} \div \text{predicted median})^{\text{Lambda}} - 1] \div (\text{Lambda} \times \text{Sigma})$. The LMS prediction equations were used to calculate predicted values for the median, lambda, and skewness.^{8,9} These equations were based on four pooled reference samples, with ages ranging from 4–80 years.^{8,9} A Z-score of -1.64 was then used to define the lower limit of normal (LLN), corresponding to the 5th percentile of distribution (5 LMS-tile). Using the 5 LMS-tile as the diagnostic threshold, we classified participants as having 1) normal pulmonary function (FEV1/FVC and FVC both ≥ 5 LMS-tile), 2) COPD (FEV1/FVC < 5 LMS-tile), or 3) restrictive-pattern (FEV1/FVC ≥ 5 LMS-tile but FVC < 5 LMS-tile).¹¹ As discussed earlier, participants who had a restrictive-pattern were excluded from the final study samples.

Among participants who had LMS-defined COPD, we then staged severity according to FEV1 cut-points, expressed as a percentile distribution of LMS-derived Z-scores (LMS-tile). Specifically, a 3-level range of severity was applied (mild, moderate, and severe), with FEV1 cut-points set at the 5 and 0.5 LMS-tile (Z-scores of -1.64 and -2.55 , respectively). The 5 LMS-tile was selected, as this corresponded to the statistical definition of “normal” (LLN).^{8,9} The 0.5 LMS-tile was selected empirically, in part, to ensure adequate sample size for subsequent analyses.

In both study samples, we also classified participants based on spirometric criteria from GOLD and the ATS/ERS.^{1,2} GOLD uses a fixed ratio threshold of 0.70 for FEV1/FVC and an 80%Pred threshold for FVC, with normal pulmonary function defined as FEV1/FVC ≥ 0.70 and FVC $\geq 80\%$ Pred, and COPD as FEV1/FVC < 0.70 .^{1,18} The %Pred for FVC was calculated as $(\text{measured} \div \text{predicted mean}) \times 100$, with predicted values derived from published multiple regression equations.^{1,18,19} The ATS/ERS uses a diagnostic threshold for FEV1/FVC and FVC calculated as the 5th percentile of the distribution of reference values (ATS/ERS-LLN₅), also derived from published multiple regression equations.¹⁹ Based on this threshold, the ATS/ERS defines normal pulmonary function as both FEV1/FVC and FVC $\geq$ ATS/ERS-LLN₅, and COPD as FEV1/FVC $<$ ATS/ERS-LLN_{5,2}.

Among participants who had GOLD and ATS/ERS defined COPD, we then staged severity according to FEV1 %Pred.^{1,2,18,19} A 3-level range of severity was applied (mild, moderate, and severe), corresponding to published cut-points of 80 and 50 %Pred for GOLD,¹ and 70 and 50 %Pred for the ATS/ERS.²

Demographic and clinical measures

The baseline characteristics of both study samples included age, sex, height, body mass index (BMI; weight divided by height-squared, kg/m²), self-reported chronic conditions, health status, and smoking history.^{12,13} Respiratory symptoms included at least one of the following: (1) chronic cough or sputum production, defined by a “yes” response to: “Do you usually cough on most days for 3 consecutive months or more during the year?” or “Do you bring up phlegm on most days for 3 consecutive months or more during the year?” (CHS and NHANES-III); (2) dyspnea-on-exertion, defined by a “yes” response to: “Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?” (CHS and NHANES-III); or (3) wheezing, defined by a “yes” response to: “Does your chest ever sound wheezy or whistling occasionally apart from colds?” (CHS), or “Have you had wheezing or whistling in your chest at any time in the past 12 months?” (NHANES-III).^{12,13}

In CHS, but not NHANES-III, dyspnea severity was “graded” based on an ATS-published 5-level scale (ATS-DLD-78-A).²⁰ Using this scale, moderate-to-severe dyspnea corresponded to an ATS grade of III or higher, defined as a “Yes” response to any of the following questions: “Do you ever have to stop for breath when walking at your own pace on the level?” (ATS grade III), or “Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level?” (ATS grade IV), or “Are you too breathless to leave the house or breathless on dressing or undressing?” (ATS grade V).

All-cause mortality was recorded in CHS based on reviews of obituaries, medical records, death certificates, and a hospitalization database, with a median follow-up of 13.2 years (IQR, 9.0–13.6).¹³ All-cause mortality in NHANES-III was obtained from the National Death Index,²¹ with a median follow-up of 7.6 years (interquartile range [IQR], 6.4–9.8).

Statistical analysis

The baseline characteristics of each study sample were summarized as means accompanied by standard deviations or as counts accompanied by percentages.

In each study sample, the associations between the 3-level staging of LMS-defined COPD and death were evaluated using Cox regression models adjusted for baseline characteristics, including age, height, sex, ethnicity, smoking history, BMI, number of chronic conditions, and health status. The 3 stages of LMS-defined COPD were treated as nominal categories, with the reference group including participants who had normal pulmonary function. Goodness-of-fit for each Cox regression model 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; the terms were retained if P was <0.05 after adjusting for the multiplicity of comparisons. Higher-order effects were tested for the continuous covariates and included in the final model if they met the forward selection criterion of $p < 0.20$.²² Similarly, the associations of the 3-level staging of LMS-defined COPD with the presence of respiratory symptoms (CHS and NHANES-III) and moderate-to-severe dyspnea (available in CHS only), respectively, were evaluated by calculating odds ratios using logistic regression models.

In CHS only (the larger study sample), the frequency distributions of normal pulmonary function and mild, moderate, and severe COPD were calculated according to GOLD and ATS/ERS criteria, respectively, within strata of the LMS-staging system.

SUDAAN version 10 and SAS version 9.2 software were used in the analyses, with a $P < 0.05$ (two-sided) denoting statistical significance.^{23,24}

RESULTS

Table 1 shows the characteristics of participants in CHS and NHANES-III, respectively. Overall, the two study samples were similar in age, BMI, and frequency of chronic conditions, but CHS had a larger proportion of females and lower rates of fair-to-poor health status and mortality.

Table 2 shows hazard ratios (HR) for all-cause mortality among participants who had LMS-defined COPD, according to LMS FEV1 stage and relative to participants with LMS-defined normal pulmonary function. In CHS, mild, moderate, and severe COPD were significantly associated with mortality for each FEV1 stage, with adjusted HR (95% confidence interval) of 1.50 (1.15, 1.94), 1.31 (1.03, 1.67), and 2.00 (1.70, 2.36), respectively. In contrast, mortality in NHANES-III was significantly increased for moderate and severe COPD, with adjusted HR of 1.55 (1.07, 2.25) and 2.57 (1.75, 3.78), respectively, but not mild COPD (adjusted HR, 0.93 [0.62, 1.40]).

Table 3 shows odds ratios (OR) for respiratory symptoms among participants who had LMS-defined COPD, according to LMS FEV1 stage and relative to participants with LMS-defined normal pulmonary function. In CHS, mild, moderate, and severe COPD were significantly associated with an increased likelihood of having respiratory symptoms, with adjusted OR of 1.69 (1.12, 2.56), 1.87 (1.28, 2.73), and 3.99 (2.91, 5.48), respectively. Similar results were observed in NHANES-III, with adjusted OR of 1.80 (1.04, 3.12), 2.56 (1.13, 5.81), and 5.80 (3.26, 10.32), respectively, for participants with mild, moderate, and severe COPD.

Table 4 shows odds ratios (OR) for moderate-to-severe dyspnea among CHS participants who had LMS-defined COPD, according to LMS FEV1 stage and relative to participants with LMS-defined normal pulmonary function. A significantly increased likelihood of having moderate-to-severe dyspnea was found for moderate and severe COPD, with adjusted OR of 2.16 (1.24, 3.75) and 3.98 (2.77, 5.74), respectively, but not for mild COPD (adjusted OR, 0.84 [0.35, 2.01]).

Table 5 shows the frequency distributions of CHS participants for normal pulmonary function and severity of COPD, calculated according to GOLD and ATS/ERS criteria, respectively, within strata of the LMS-staging system. Of the participants who had LMS-defined normal pulmonary function, 34.6% (946/2738) and 9.3% (256/2738) were classified as having mild or moderate COPD by GOLD and ATS/ERS criteria, respectively. Of the participants who had LMS-defined mild COPD, 40.2% (43/107) were classified as having moderate COPD by GOLD criteria, whereas all had the same mild designation by ATS/ERS criteria. Of the participants who had LMS-defined moderate COPD, all had the same moderate designation by GOLD criteria, whereas 28.8% (38/132) were classified as having mild COPD by ATS/ERS criteria. Lastly, of the participants who had LMS-defined severe COPD, 28.1% (71/253) were classified as having moderate COPD by both GOLD and ATS/ERS criteria.

DISCUSSION

Using data on white participants aged 65–80 years from two large epidemiologic studies, we found that staging COPD based on percentile distributions of LMS-derived Z-scores for FEV1 was associated with several clinically relevant health outcomes. Moreover, we found that current spirometric criteria by GOLD and the ATS/ERS, relative to LMS-staging, may misclassify mild and moderate COPD. These results support the use of the LMS method for staging the severity of COPD.^{1,2}

A strong mathematical and clinical rationale exists for staging the severity of COPD according to LMS-derived Z-scores.^{8–11} First, the LMS method accounts for age-related changes in pulmonary function, including variability and skewness in reference data.^{8,9} In contrast, the %Pred method does not account for variability or skewness, and applies a less appropriate measure of central tendency — the mean of the predicted value rather than the median. Second, LMS-derived Z-score thresholds for FEV1 as applied in this study were associated with clinically relevant health outcomes. All-cause mortality is an objective and definitive outcome that is resistant to miscoding and has been the primary endpoint in landmark studies of oxygen therapy.²⁵ Respiratory symptoms are the most distressing feature of chronic lung disease, and can lead to disability and increased healthcare utilization.^{25,26} Although lacking specificity, respiratory symptoms drive clinical decisions, as evident in practice guidelines published by GOLD, ATS, and the American College of Physicians.^{1,27,28} Finally, among respiratory symptoms, dyspnea is particularly important because it is now a recommended primary end point in clinical trials and outcomes research.^{29,30} In contrast, %Pred thresholds for FEV1 lack clinical validation, as discussed earlier.⁶

Our results provide an evidence-based strategy for staging severity in COPD. Namely, moderate-to-severe COPD may be established by an FEV1 <5 LMS-tile (i.e. below the LLN), because this threshold conferred a significant association with mortality and respiratory symptoms across both study populations, as well as with moderate-to-severe dyspnea in CHS. Severe COPD may be distinguished from moderate COPD based on the graded associations between FEV1 LMS-tile and health outcomes, with hazard ratios and odds ratios being substantially higher at FEV1 LMS-tile <0.5 (severe) versus 0.5-to-4.9 (moderate). In contrast, mild COPD may be established by an FEV1 ≥5 LMS-tile (i.e. at or above the LLN). This threshold yielded a significant association with respiratory symptoms across both study populations, with odds ratios less than those in the moderate or severe COPD groups, but did not yield a significant association with moderate-to-severe dyspnea and was associated with mortality in CHS, but not NHANES-III.

Our results (see Table 5) also suggest that, among older persons, spirometric criteria by GOLD and the ATS/ERS potentially misclassify the diagnosis and severity of COPD. This may arise for two reasons. First, with advancing age, COPD may be increasingly overdiagnosed because the GOLD and ATS/ERS thresholds for FEV1/FVC lie above the LMS-defined LLN.^{8,9,11,31} Second, COPD severity may be staged incorrectly by GOLD and the ATS/ERS because a given value of FEV1 %Pred is not equivalent for all persons, particularly with advancing age.^{3,4} If LMS thresholds for FEV1/FVC and FEV1 are deemed superior, our results thus show that GOLD may misclassify about one-third of participants with normal pulmonary function as having mild or moderate COPD, and about one-quarter of severe COPD participants as having moderate severity. Similarly, the ATS/ERS may misclassify nearly 10% of participants with normal pulmonary function as having mild or moderate COPD, and about one-quarter of severe COPD participants as having moderate severity.

We acknowledge, however, that because LMS-derived spirometric Z-scores have not yet been published for non-whites and because racial differences exist in pulmonary function, our results may not be generalizable to groups other than whites.^{8,9,32} Consequently, to broaden its applicability, LMS-derived Z-scores will need to be calculated for non-white populations. In the interim, we propose the use of FEV1 SR-tiles, for reasons already discussed.^{3–6} Other investigators recommend that the FEV1 should be standardized to height (FEV1/height² or FEV1/height³), potentially precluding the need for reference equations.^{33–35} Importantly, it is uncertain whether the SR-tile or “standardized height” approaches are appropriate for other spirometric measures, particularly FEV1/FVC (increasingly skewed with advancing age).^{5,7–9,11} Accordingly, in a clinical or epidemiological setting focused on COPD, because establishing a diagnosis and staging severity require the FEV1/FVC and FEV1, respectively, there is a substantial advantage to using an approach that is equally applicable to both spirometric measures and across the lifespan, which is the case with the LMS method.^{2,7–9,11}

We recognize other potential limitations to our study. First, spirometry in NHANES-III and CHS was not specifically obtained after a bronchodilator. Although persons with self-reported asthma were excluded from our study samples, the absence of information on “reversibility” may lead to misidentification of airflow limitation as COPD (participants may have underreported asthma).³⁶ Postbronchodilator values may have had a minimal effect on our results, however, because study participants had high rates of smoking (conferring less reversible airways’ pathology), and because reversibility is neither a sufficient criterion to exclude COPD nor an independent predictor of mortality.^{37,38} Second, participants who had a spirometric restrictive-pattern were excluded from our analysis, as the study objective was to compare airflow limitation (COPD) to normal pulmonary function. Although traditionally defined by airflow limitation,^{1,2} COPD may also lead to substantial air trapping and, in turn, a restrictive-pattern.³⁹ Hence, some participants who were excluded for a restrictive-pattern may have had COPD with air trapping, an assessment that would require body plethysmography, which is generally unavailable in large population-based studies, including CHS and NHANES-III.^{2,39} Third, the associations between LMS-defined FEV1 stage and mortality differed modestly across the two study samples, although these differences were less apparent at FEV1<5 LMS-tile and could be due to sampling issues and differences in follow-up time. Lastly, the study populations were assembled in the late 1980s and early 1990s and followed through 2000–2002, raising the issue of “timeliness” of data. Accordingly, to address the stated limitations, future work should evaluate the clinical validity of LMS-staged COPD in more contemporary cohorts (including a broad representation of racial and ethnic groups), using postbronchodilator spirometry and, if available, body plethysmography.

In conclusion, among white older persons, the LMS-staging of COPD severity was associated with several clinically relevant health outcomes. These results provide strong evidence to support the use of LMS-staging of COPD severity in older populations.

Acknowledgments

The Cardiovascular Health Study (CHS) was conducted and supported by the NHLBI in collaboration with the CHS Study Investigators, respectively. This manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the CHS or the NHLBI

Dr. Vaz Fragoso is currently a recipient of career development awards from the Department of Veterans Affairs and the Yale Pepper Center, and an R03 award from the National Institute on Aging (R03AG037051). Dr. Concato is supported by the Department of Veterans Affairs Cooperative Studies Program. Dr. Yaggi is supported by a Career Development Transition Award from the Department of Veterans Affairs Clinical Science Research and Development Service. Dr. Gill is the recipient of an NIA Midcareer Investigator Award in Patient-Oriented Research (K24AG021507).

The study was conducted at the Yale Claude D. Pepper Older Americans Independence Center (P30AG21342).

REFERENCES

1. GOLD executive summary. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007; 176:532–555. [PubMed: 17507545]
2. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005; 26:948–968. [PubMed: 16264058]
3. Miller MR, Pincock AC. Predicted values: how should we use them? *Thorax*. 1988; 43:265–267. [PubMed: 3406912]
4. Official statement of the European Respiratory Society. Lung volumes and forced ventilatory flows. *Eur Respir J*. 1993; 6:S5–S40.
5. Vaz Fragoso CA, Concato J, McAvay G, et al. Defining chronic obstructive pulmonary disease in older persons. *Respir Med*. 2009; 103:1468–1476. [PubMed: 19464159]
6. Vaz Fragoso CA, Concato J, McAvay G, et al. Chronic obstructive pulmonary disease in older persons: a comparison of two spirometric definitions. *Respir Med*. 2010; 104:1189–1196. [PubMed: 20199857]
7. Vaz Fragoso CA, Gill TM. Defining chronic obstructive pulmonary disease in an aging population. *J Am Geriatr Soc*. 2010; 58:2224–2226. (Editorial). [PubMed: 21054303]
8. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages. *Am J Respir Crit Care Med*. 2008; 177:253–260. [PubMed: 18006882]
9. [Accessed May 17, 2011] Spirometry (LMS). Available at: <http://www.lungfunction.org/growinglungs/all-age.html>
10. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: Scientific review. *JAMA*. 2002; 288:1889–1897. [PubMed: 12377088]
11. Vaz Fragoso CA, Concato J, McAvay G, et al. The ratio of the forced expiratory volume in 1-second to forced vital capacity in establishing chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010; 181:446–451. [PubMed: 20019341]
12. U.S. Department of Health and Human Services. National Center for Health Statistics. Hyattsville, Maryland: Centers for Disease Control and Prevention; 1996. Third National Health and Nutrition Examination Survey, 1988–94, NHANES-III Laboratory Data File (CD-ROM), Public Use Data File Documentation Number 76200. Available from National Technical Information Service, Springfield, VA
13. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol*. 1991; 1:263–276. [PubMed: 1669507]
14. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26:319–338. [PubMed: 16055882]

15. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis.* 1991; 144:1202–1218. [PubMed: 1952453]
16. [Accessed February 8, 2011] Spirometry Procedure Manual. NHANES-III. Available at: <http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/spiro.pdf>
17. Enright P, Kronmal RA, Higgins MW, et al. Prevalence and correlates of respiratory symptoms and disease in the elderly. *Chest.* 1994; 106:827–834. [PubMed: 8082366]
18. Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax.* 2007; 62:237–241. [PubMed: 17090573]
19. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999; 159:179–187. [PubMed: 9872837]
20. [Accessed February 8, 2011] ATS-DLD-78-A: Adult Dyspnea Questionnaire. Available at <http://www.cdc.gov/niosh/respire.html>
21. Wheatcroft, G.; Cox, CS.; Lochner, KA. National Center for Health Statistics. Hyattsville, Maryland: 2007. Comparative analysis of the NHANES-III public-use and restricted-use linked mortality files.
22. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol.* 1995; 48:1503–1510. [PubMed: 8543964]
23. Research Triangle Institute. SUDAAN Language Manual, Release 9.0. Research Triangle Park, NC: Research Triangle Institute; 2004.
24. SAS Institute Inc.. SAS/STAT 9.2 User's Guide. Cary, NC, USA.: 2008.
25. Gross NJ. Chronic obstructive pulmonary disease outcome measurements. *Proc Am Thorac Soc.* 2005; 2:267–271. [PubMed: 16267347]
26. Cherry DK, Burt CW, Woodwell DA. National ambulatory medical care survey: 1999 summary. *Advanced Data from Vital and Health Statistics.* (CDC). 2001; 322:1–36.
27. Qaseem A, Snow V, Shekelle P, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline from the American college of physicians. *Ann Intern Med.* 2007; 147:633–638. [PubMed: 17975186]
28. American Thoracic Society/European Respiratory Society. [Accessed February 8, 2011] Standards for the diagnosis and management of patients with COPD. Available at: <http://www.thoracic.org/clinical/copd-guidelines/index.php>
29. American Thoracic Society. Dyspnea: Mechanisms, assessment, and management. A consensus statement. *Am J Respir Crit Care Med.* 1999; 159:321–340. [PubMed: 9872857]
30. Curtis JR, Martin DP, Martin TR. Patient-assessed health outcomes in chronic lung disease. *Am J Respir Crit Care Med.* 1997; 156:1032–1039. [PubMed: 9351600]
31. Hansen JF, Sun X-G, Wasserman K. Spirometric criteria for airway obstruction. *Chest.* 2007; 131:349–355. [PubMed: 17296632]
32. Dransfield MT, Bailey WC. COPD: Racial disparities in susceptibility, treatment, and outcomes. *Clin Chest Med.* 2006; 27:463–471. [PubMed: 16880056]
33. Miller MR, Pedersen OF, Dirksen A. A new staging strategy for chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2007; 2:657–663. [PubMed: 18268941]
34. Chinna S, Gislason T, Aspelund T, et al. Optimum expression of adult lung function based on all-cause mortality: Results from the Reykjavik study. *Respir Med.* 2007; 101:601–609. [PubMed: 16889951]
35. Miller MR, Pedersen OF. New concepts for expressing forced expiratory volume in 1 s arising from survival analysis. *Eur Respir J.* 2010; 35:873–882. [PubMed: 19741033]
36. Enright PL, McClelland RL, Newman AB, et al. Underdiagnosis and undertreatment of asthma in the elderly. *Chest.* 1999; 116:603–613. [PubMed: 10492260]
37. Vestbo J, Hansen EF. Airway hyperresponsiveness and COPD mortality. *Thorax.* 2001; 56 Suppl 2:11–14.
38. Hansen EF, Vestbo J. Bronchodilator reversibility in COPD. *Eur Respir J.* 2005; 26:6–7. [PubMed: 15994382]

39. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment? *Chest*. 1999; 115:869–873. [PubMed: 10084506]

Table 1

Baseline characteristics and mortality rates for the two study samples

Characteristic	CHS N=3,248	NHANES-III N=1,354
Age (years), mean ($\pm$ SD)	71.5 ($\pm$ 4.1)	72.5 ($\pm$ 4.4)
Females, No. (%)	1,871 (57.6)	692 (51.1)
BMI (kg/m ²), mean ($\pm$ SD)	26.2 ($\pm$ 3.8)	26.7 ($\pm$ 4.7)
<i>Smoking status, No. (%)</i>		
Never	1,455 (44.8)	592 (43.7)
Former	1,425 (43.9)	595 (43.9)
Current	367 (11.3)	167 (12.3)
Chronic conditions, * mean ($\pm$ SD)	0.9 ($\pm$ 0.9)	0.9 ($\pm$ 1.0)
Fair-to-poor health status, No. (%)	637 (19.6)	324 (24.0)
<i>Health Outcomes</i>		
Respiratory symptoms, [†] No. (%)	1,377 (43.1)	609 (45.1)
Dyspnea-on-exertion, [‡] No. (%)	1,073 (33.4)	466 (34.5)
Moderate-to-severe dyspnea, [§] No. (%)	291 (9.1)	----
Deaths, [¶] No. (%)	1,446 (44.5)	448 (33.1)
Mortality rate (per 1,000 person-years)	39.3	42.6

Abbreviations: ATS, American Thoracic Society; BMI, body mass index; CHS, Cardiovascular Health Study; NHANES-III, Third National Health and Nutrition Examination Survey; SD, standard deviation.

* Number of self-reported, physician-diagnosed.

[†] Includes a composite of chronic cough or sputum production, dyspnea-on-exertion (ATS grade 1), or wheezing (see methods). Missing data: CHS, n=52 (1.6%); NHANES-III, n=4 (<1%).

[‡] ATS dyspnea grade 1: defined as a “Yes” response to: “Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?” — CHS and NHANES-III. Missing data: CHS, n=20 (<1%); NHANES-III, n=5 (<1%).

[§] ATS dyspnea grade 3 or higher (recorded only in CHS; see methods). Missing data: n = 20 (<1%).

[¶] Vital status was available on all participants.

Table 2

Hazard ratios for all-cause mortality among participants with mild, moderate, and severe LMS-defined COPD

LMS spirometric category [*]	No. (%) [†]	No. (%) [‡] of deaths	Hazard Ratio (95% CI) for Mortality [§]	
			Unadjusted	Adjusted
CHS (N = 3,230) [¶]				
Normal pulmonary function	2,738 (84.8)	1,121 (40.9)	1.00	
COPD: FEV1 LMS-tile				
Mild	107 (3.3)	61 (57.0)	1.59 (1.23, 2.06)	1.50 (1.15, 1.94)
Moderate	132 (4.1)	72 (54.6)	1.52 (1.20, 1.93)	1.31 (1.03, 1.67)
Severe	253 (7.8)	183 (72.3)	2.48 (2.12, 2.90)	2.00 (1.70, 2.36)
NHANES-III (N = 1,339) [#]				
Normal pulmonary function	1,143 (85.4)	341 (29.8)	1.00	
COPD: FEV1 LMS-tile				
Mild	67 (5.0)	19 (28.4)	0.89 (0.62, 1.30)	0.93 (0.62, 1.40)
Moderate	54 (4.0)	27 (50.0)	1.84 (1.32, 2.56)	1.55 (1.07, 2.25)
Severe	75 (5.6)	53 (70.7)	3.44 (2.45, 4.83)	2.57 (1.75, 3.78)

Abbreviations: CHS, Cardiovascular Health Study; NHANES-III, Third National Health and Nutrition Examination Survey; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LMS, Lambda-Mu-Sigma method; LMS-tile, percentile distribution of LMS derived Z-scores; 5 LMS-tile, the lower limit of normal (5th percentile of the distribution of LMS derived Z-scores).

* Normal pulmonary function was defined by FEV1/FVC and FVC, both ≥ 5 LMS-tile; COPD by FEV1/FVC < 5 LMS-tile, with mild as FEV1 ≥ 5 LMS-tile, moderate as FEV1 0.5-to-4.9 LMS-tile, and severe as FEV1 < 0.5 LMS-tile.

† Percent of study sample

‡ Row percent

§ Values were calculated using Cox regression models, in unadjusted and adjusted longitudinal analyses, with the reference group including participants who had LMS-defined normal pulmonary function.

¶ Exclusions: 18 participants ($< 1\%$) had missing covariates.

Exclusions: 15 participants (1.1%) had missing covariates.

Table 3

Odds ratios for respiratory symptoms among participants with mild, moderate, and severe LMS-defined COPD

LMS spirometric category *	No. (%) †	No. (%) ‡ with respiratory symptoms§	Odds Ratio (95% CI) for Respiratory Symptoms ¶	
			Unadjusted	Adjusted
CHS (N = 3,179) #				
Normal pulmonary function	2,694 (84.7)	1,055 (39.2)	1.00	
COPD: FEV1 LMS-tile				
Mild	105 (3.3)	53 (50.5)	1.58 (1.07, 2.34)	1.69 (1.12, 2.56)
Moderate	132 (4.2)	76 (57.6)	2.11 (1.48, 3.00)	1.87 (1.28, 2.73)
Severe	248 (7.8)	186 (75.0)	4.66 (3.46, 6.28)	3.99 (2.91, 5.48)
NHANES-III (N = 1,335) **				
Normal pulmonary function	1,139 (85.3)	472 (41.4)	1.00	
COPD: FEV1 LMS-tile				
Mild	67 (5.0)	34 (50.8)	1.46 (0.84, 2.51)	1.80 (1.04, 3.12)
Moderate	54 (4.0)	35 (64.8)	2.60 (1.22, 5.53)	2.56 (1.13, 5.81)
Severe	75 (5.6)	61 (81.3)	6.16 (3.36, 11.28)	5.80 (3.26, 10.32)

Abbreviations: CHS, Cardiovascular Health Study; NHANES-III, Third National Health and Nutrition Examination Survey; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LMS, Lambda-Mu-Sigma method; LMS-tile, percentile distribution of LMS derived Z-scores; 5 LMS-tile, the lower limit of normal (5th percentile of the distribution of LMS derived Z-scores).

* Normal pulmonary function was defined by FEV1/FVC and FVC, both ≥ 5 LMS-tile; COPD by FEV1/FVC < 5 LMS-tile, with mild as FEV1 ≥ 5 LMS-tile, moderate as FEV1 0.5-to-4.9 LMS-tile, and severe as FEV1 < 0.5 LMS-tile.

† Percent of study sample

‡ Row percent

§ Included chronic cough or sputum production, dyspnea-on-exertion, and wheezing (see methods).

¶ Values were calculated using logistic regression models, in unadjusted and adjusted cross-sectional analyses, using baseline data and with the reference group including participants who had LMS-defined normal pulmonary function.

Exclusions: 18 participants ($< 1\%$) had missing covariates and 51 (1.6%) were missing respiratory symptoms.

** Exclusions: 15 participants (1.1%) had missing covariates and 4 ($< 1\%$) were missing respiratory symptoms.

Table 4

Odds ratios for having moderate-to-severe dyspnea among CHS participants with mild, moderate, and severe LMS-defined COPD (N = 3,210) *

LMS spirometric category [†]	No. (%) [‡]	No. (%) [§] with moderate-to-severe dyspnea [¶]	Odds ratio (95% CI) for moderate-to-severe dyspnea [#]	
			Unadjusted	Adjusted
Normal pulmonary function	2,725 (84.9)	199 (7.3)	1.00	
COPD: FEV1 LMS-tile				
<i>Mild</i>	106 (3.3)	6 (5.7)	0.76 (0.33, 1.76)	0.84 (0.35, 2.01)
<i>Moderate</i>	131 (4.1)	20 (15.3)	2.29 (1.39, 3.76)	2.16 (1.24, 3.75)
<i>Severe</i>	248 (7.7)	66 (26.6)	4.60 (3.35, 6.32)	3.98 (2.77, 5.74)

Abbreviations: CHS, Cardiovascular Health Study; ATS, American Thoracic Society; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LMS, Lambda- Mu-Sigma method; LMS-tile, percentile distribution of LMS derived Z-scores; 5 LMS-tile, the lower limit of normal (5th percentile of the distribution of LMS derived Z-scores).

* Dyspnea severity was evaluated in CHS only (not available in Nanes III). In this analysis, 20 participants (<1%) were excluded because of missing data on dyspnea.

† Normal pulmonary function was defined by FEV1/FVC and FVC, both ≥5 LMS-tile; COPD by FEV1/FVC<5 LMS-tile, with mild as FEV1 ≥5 LMS-tile, moderate as FEV1 0.5-to-4.9 LMS-tile, and severe as FEV1 <0.5 LMS-tile.

‡ Percent of study sample

§ Row percent

¶ Moderate-to-severe dyspnea was defined by an ATS dyspnea grade 3 or higher (see methods).

Values were calculated using a logistic regression model, in unadjusted and adjusted cross-sectional analyses, using baseline data and with the reference group including participants who had LMS-defined normal pulmonary function. In these analyses, 18 participants (<1%) were excluded because of missing covariates.

Table 5

Frequency distributions of CHS participants for normal pulmonary function and severity of COPD, according to GOLD and ATS/ERS criteria, within strata of the LMS-staging system *

A. LMS versus GOLD (N=3,230)						
LMS spirometric category ‡	GOLD spirometric category †				LMS sample size	
	Normal pulmonary function	COPD: FEV1 %Pred			Severe: <50	
		Mild: ≥80	Moderate: 50-79			
		No. (%) §				
Normal pulmonary function	1,792 (65.4)	616 (22.5)	330 (12.1)	0	2738	
COPD: FEV1 LMS-tile						
Mild: ≥ 5	0	64 (59.8)	43 (40.2)	0	107	
Moderate: 0.5-to-4.9	0	0	132 (100)	0	132	
Severe: < 0.5	0	0	71 (28.1)	182 (71.9)	253	
B. LMS versus ATS/ERS (N=3,230)						
LMS spirometric category ‡	ATS/ERS spirometric category ¶				LMS sample size	
	Normal pulmonary function	COPD: FEV1 %Pred			Severe: <50	
		Mild: ≥70	Moderate: 50-69			
		No. (%) §				
Normal pulmonary function	2,482 (90.7)	214 (7.8)	42 (1.5)	0	2738	
COPD: FEV1 LMS-tile						
Mild: ≥ 5	0	107 (100)	0	0	107	
Moderate: 0.5-to-4.9	0	38 (28.8)	94 (71.2)	0	132	
Severe: < 0.5	0	0	71 (28.1)	182 (71.9)	253	

Abbreviations: CHS, Cardiovascular Health Study; ATS/ERS, American Thoracic Society/European Respiratory Society; ATS/ERS-LLN₅, lower limit of normal; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1-second; %Pred, percent predicted; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; LMS, Lambda-Mu-Sigma method; LMS-tile, percentile distribution of LMS derived Z-scores; 5 LMS-tile, the lower limit of normal (5th percentile of the distribution of LMS derived Z-scores).

* Concordant spirometric designations are shown by cells with bold borders.

† Normal pulmonary function was defined by FEV1/FVC≥0.70 and FVC≥80%Pred; COPD by an FEV1/FVC<0.70, with mild as FEV1 ≥80%Pred, moderate as FEV1 50–70%Pred, and severe as FEV1 <50%Pred.

† Normal pulmonary function was defined by FEV1/FVC and FVC, both ≥ 5 LMS-tile; COPD by FEV1/FVC <5 LMS-tile, with mild as FEV1 ≥ 5 LMS-tile, moderate as FEV1 0.5-to-4.9 LMS-tile, and severe as FEV1 <0.5 LMS-tile.

§ Row percent.

¶ Normal pulmonary function was defined by FEV1/FVC and FVC, both $\geq$ ATS/ERS-LLN₅; COPD by FEV1/FVC $<$ ATS/ERS-LLN₅, with mild as FEV1 $\geq 70\%$ Pred, moderate as FEV1 50–69%Pred, and severe as FEV1 $<50\%$ Pred.