Published in final edited form as:

J Investig Med. 2011 October ; 59(7): 1089–1095. doi:10.231/JIM.0b013e31822bb213.

RESPIRATORY IMPAIRMENT AND MORTALITY IN OLDER PERSONS: A NOVEL SPIROMETRIC APPROACH

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

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

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

Abstract

Background—The Lambda-Mu-Sigma (LMS) method calculates the lower limit of normal for spirometric measures of pulmonary function as the 5th percentile of the distribution of Z-scores, suitably accounting for age-related changes in pulmonary function. Extending prior work, and to assess whether the LMS method is clinically valid when evaluating respiratory impairment in the elderly, our current objective was to evaluate the association of LMS-defined respiratory impairment (airflow limitation and restrictive-pattern) with all-cause mortality and respiratory symptoms (chronic bronchitis, dyspnea, or wheezing) in older persons.

Methods—Spirometric data and outcome data on white participants aged 65 to 80 years were obtained from the Third National Health and Nutrition Examination Survey (NHANES-III, N=1497) and the Cardiovascular Health Study (CHS, N=3583). Multivariable analyses determined the corresponding associations, adjusting for important covariates.

Results—In the NHANES-III and CHS populations, respectively, LMS-defined airflow limitation had adjusted hazard ratios (95% confidence interval) of 1.64 (1.28–2.11) and 1.69 (1.48–1.92) for mortality; adjusted odds ratios for respiratory symptoms were 2.71 (1.92–3.83) and 2.63 (2.11–3.27). LMS-defined restrictive-pattern was also significantly associated with mortality (adjusted hazard ratios of 1.98 [1.54–2.53] and 1.68 [1.44–1.95], as well as with respiratory symptoms (adjusted odds ratios of 1.55 [1.03–2.34] and 1.37 [1.07–1.75], in NHANES-III and CHS, respectively.

Conclusion—LMS-defined airflow limitation and restrictive-pattern confers a significantly increased risk of death and likelihood of having respiratory symptoms. These results support the use of LMS-derived spirometric Z-scores as a basis for evaluating respiratory impairment in older persons.

INTRODUCTION

The combination of host factors, along with exposures to tobacco smoke, respiratory infections, occupational dusts, and air pollution that occur across the lifespan, can lead to respiratory impairment, respiratory symptoms, and increased mortality.^{1–5} Controversy exists, however, regarding the spirometric evaluation of respiratory impairment, including

Address correspondence to: Carlos A. Vaz Fragoso, MD, 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].

Author Contributions: Dr. Vaz Fragoso had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to study concept and design, to data acquisition, analysis and interpretation, and to drafting the submitted article.

airflow limitation and restrictive-pattern.^{5,6} In particular, current spirometric criteria differ in the diagnostic thresholds for the ratio of forced expiratory volume in 1-second to forced vital capacity (FEV1/FVC), and for FVC alone. For example, the Global Initiative for Obstructive Lung Disease (GOLD) advocates a fixed-ratio of 0.70 for FEV1/FVC and an 80% predicted cut-point for FVC, whereas the American Thoracic and European Respiratory Societies (ATS/ERS) recommend a lower limit of normal (LLN), calculated as the 5th percentile of the distribution of reference values (ATS/ERS-LLN₅), for both FEV1/FVC and FVC.⁵⁻⁷

Among older persons, establishing respiratory impairment based on GOLD thresholds has potential problems, for at least two reasons.⁸⁻¹³ First, normal aging is associated with increased rigidity of the chest wall and loss of elastic recoil of the lung, factors that often lead to an FEV1/FVC <0.70 for individuals 65-years or older, including those who are otherwise never-smokers and healthy.⁸⁻¹⁴ Second, spirometric performance among older persons, including those who are otherwise never-smokers and healthy, is associated with increased variability (coefficient of variation), thereby increasing the disparity between the 80% predicted cut-point for FVC and lower values of observed FVC, including lower limits of normal.^{8,9} Applying official GOLD thresholds in a large cohort of community-living older persons, prior work has shown that 55% (2743/4965) of participants are classified as having a respiratory impairment (airflow limitation or restrictive-pattern).¹⁵ For these reasons, it is possible that a substantial proportion of GOLD-defined respiratory impairment simply represents typical age-related changes, rather than “clinical disease” (e.g., asthma or chronic obstructive pulmonary disease in the case of airflow limitation).⁸⁻¹³

The ATS/ERS-LLN₅ threshold also has potential limitations, because its calculation has been traditionally based on multiple regression equations that assume a linear relationship between predictor variables (age and height) and spirometric measures, and because it also assumes that reference values are distributed normally and have constant variability across the lifespan.^{8,9} This approach is especially problematic for a ratio of two spirometric measures, as with the FEV1/FVC. As evidence of the problem, published reports have shown that conventional multiple regression techniques for the FEV1/FVC have limited explanatory ability when applied to an elderly population, with R² values ranging from 0.01 to 0.15.^{11,16,17}

To address the concerns described above, a diagnostic threshold for spirometric measures based on the Lambda-Mu-Sigma (LMS) method has been advocated. As an approach widely used to construct growth charts,^{8,9} the LMS method calculates the LLN as the 5th percentile of the distribution of Z-scores (LMS-LLN₅), analogous to the reporting of bone mineral density.^{8,9,18} Mathematically, LMS-derived Z-scores include 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.^{8,9,19} By using this approach, the LMS method is also an improvement on prior methods of determining spirometric Z-scores calculated from “standardized residuals” (relevant measurements obtained from multiple regression equations).^{11,12}

Beyond a strong mathematical rationale, we have previously evaluated the clinical validity of different Z-score thresholds for FEV1/FVC, based on associations with health outcomes, and found that the upper limit of this ratio that conferred a significantly increased risk occurred at the LMS-LLN₅.¹³ Our prior work assessing the FEV1/FVC ratio was based on a single study population, however, and did not specifically evaluate the clinical validity of LMS-defined airflow limitation and restrictive-pattern relative to normal spirometric function—a diagnostic process that requires simultaneous consideration of FEV1/FVC and

FVC (see Methods section).^{5,6} Thus, it remains to be seen whether the LMS method is appropriate when evaluating respiratory impairment, especially in older persons.

In the present study, using LMS-derived Z-scores for spirometric values and data from two large cohorts of community-living older persons, we evaluated the association of respiratory impairment with mortality and respiratory symptoms. As a secondary aim, we calculated the frequency of the potential misclassification of respiratory impairment when using current spirometric criteria, relative to LMS designations.

METHODS

Study Population

We used deidentified, publicly-available data from the Third National Health and Nutrition Examination Survey (NHANES-III) and the Cardiovascular Health Study (CHS), with approval obtained from the VA Connecticut and Yale University institutional review boards.^{20,21} For the present study, eligible participants were white, aged 65–80 years, and at baseline (initial examination) had completed at least two ATS-acceptable spirometric maneuvers. Our analyses were limited to whites aged 65–80 years, because reference values for the LMS-method are currently unavailable for non-whites and for those >80 years.^{8,9} As per current convention, we did not exclude participants based on spirometric reproducibility criteria.²² Lastly, to focus on “irreversible” pathology, participants with self-reported asthma were excluded.

The NHANES-III population, assembled in 1988–1994 and followed through 2000, used a complex design to generate a nationally representative sample, with an age range of 8-to-80 years (N=33,994).²⁰ Based on the eligibility criteria above (including available spirometry), our study sample within NHANES-III included 1,497 participants. The CHS population was assembled in 1989–1990 as a random sample from Medicare eligibility lists in four U.S. communities and followed through 2002, with an age range of 65-to-100 years (N=5,888).²¹ Based on the same eligibility criteria, our study sample within CHS included 3,583 participants.

Spirometry

In both NHANES-III and CHS, participants who underwent spirometry did so during their baseline examination, according to contemporary ATS protocols.²³ Spirometry was conducted using a dry-rolling seal spirometer in NHANES-III, whereas a water-sealed spirometer was used in CHS; both met ATS accuracy requirements.^{20,21,24,25} For each study 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 which met ATS-acceptability criteria.^{6,22}

In our study samples, we calculated LMS-derived Z-scores for FEV1/FVC and FVC, as recommended;^{8,9} see Appendix. Using the LMS-LLN₅ as the diagnostic threshold, we then defined: a) normal spirometric function as FEV1/FVC and FVC both $\geq$ LMS-LLN₅; b) airflow limitation as FEV1/FVC < LMS-LLN₅; and c) restrictive-pattern as FEV1/FVC $\geq$ LMS-LLN₅ and FVC < LMS-LLN₅.^{6,13}

In our study samples, we also classified respiratory status based on GOLD and ATS/ERS criteria. GOLD defined normal spirometric function as FEV1/FVC $\geq$ 0.70 and FVC $\geq$ 80% predicted, airflow limitation as FEV1/FVC < 0.70, and restrictive-pattern as FEV1/FVC $\geq$ 0.70 and FVC < 80% predicted.^{5,15} In this context, percent predicted was calculated as $([\text{measured} \div \text{predicted mean}] \times 100)$, with predicted values derived from published regression equations.^{5,7} ATS/ERS defined normal spirometric function as both FEV1/FVC

and $FVC \geq \text{ATS/ERS-LLN}_5$, airflow limitation as $FEV1/FVC < \text{ATS/ERS-LLN}_5$, and restrictive-pattern as $FEV1/FVC \geq \text{ATS/ERS-LLN}_5$ as well as $FVC < \text{ATS/ERS-LLN}_5$ ⁶; the ATS/ERS-LLN_5 was calculated from published regression equations.⁷

Clinical Measures

Baseline clinical characteristics of each study sample (NHANES-III and CHS) included age, sex, height, body mass index (BMI; weight divided by height-squared, expressed as kg/m^2), self-reported chronic conditions, health status, and smoking history.^{20,21} Respiratory symptoms were also evaluated as a composite measure that included: a) chronic cough or sputum production ("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?" for both NHANES-III and CHS); b) dyspnea-on-exertion ("yes" response to "Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?" for both NHANES-III and CHS) or c) wheezing ("yes" response to "Have you had wheezing or whistling in your chest at any time in the past 12 months?" for NHANES-III, and "Does your chest ever sound wheezy or whistling occasionally apart from colds?" for CHS).^{20,21}

All-cause mortality was recorded in NHANES-III based on the National Death Index,²⁶ with a median follow-up of 7.6 years (interquartile range [IQR], 6.4–9.8). CHS also recorded all-cause mortality, based on reviews of obituaries, medical records, death certificates, and a hospitalization database,²¹ with a median follow-up of 13.2 years (IQR, 9.0–13.6).

Statistical Analysis

Baseline characteristics of each study sample (NHANES-III and CHS) were first summarized as means accompanied by standard deviations or as counts accompanied by percentages.

Next, in each study sample, the association between LMS-defined respiratory impairment and death was evaluated using Cox regression models, adjusting for baseline clinical characteristics (age, height, sex, ethnicity, smoking history, BMI, number of chronic conditions, and health status). LMS-defined airflow limitation and restrictive-pattern were treated as nominal categories, with the reference group including participants with normal spirometric function. Each Cox regression model's 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; the terms were retained if $p < 0.05$ 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 $p < 0.20$.²⁷ Similarly, the association between LMS-defined respiratory impairment and the presence of respiratory symptoms was evaluated by calculating odds ratios using logistic regression models.

Lastly, as a descriptive and exploratory analysis, the prevalence of respiratory impairment was calculated in each study sample, as defined by GOLD, ATS/ERS, and LMS criteria. For these analyses, the frequencies of discordant designations of respiratory impairment by GOLD and ATS/ERS criteria were also evaluated relative to LMS criteria.

SUDAAN version 10 and SAS version 9.2 software were used in the analyses, with a $p < 0.05$ (two-sided) denoting statistical significance.^{28,29}

RESULTS

Table 1 shows the characteristics of participants in each study sample (NHANES-III and CHS). Overall, the two study samples were similar in age, BMI, and frequency of chronic conditions; CHS had more female representation and also had slightly lower rates of current smoking, fair-to-poor health status, and mortality.

Table 2 shows hazard ratios (HR) for all-cause mortality in each study sample, based on LMS-defined respiratory impairment. In contrast to normal function, LMS-defined airflow limitation had an adjusted HR (95% confidence interval [CI]) for mortality of 1.64 (1.28–2.11) and 1.69 (1.48–1.92) in NHANES-III and CHS, respectively. Similarly, LMS-defined restrictive-pattern had an adjusted HR for mortality of 1.98 (1.54–2.53) and 1.68 (1.44–1.95) in NHANES-III and CHS, respectively.

Table 3 shows odds ratios (OR) for having respiratory symptoms in each study sample, according to LMS-defined respiratory impairment. Relative to normal function, LMS-defined airflow limitation had an adjusted OR for respiratory symptoms of 2.71 (1.92–3.83) and 2.63 (2.11–3.27) in NHANES-III and CHS, respectively. Similarly, LMS-defined restrictive-pattern had an elevated adjusted OR for respiratory symptoms of 1.55 (1.03–2.34) and 1.37 (1.07–1.75) in NHANES-III and CHS, respectively.

Table 4 compares the prevalence of respiratory impairment based on GOLD, ATS/ERS, and LMS-LLN₅ criteria. GOLD yielded the highest frequency of airflow limitation at 37.7% (558/1,481) and 38.4% (1,370/3,563) in the NHANES-III and CHS study populations, respectively, whereas the ATS/ERS yielded the second highest frequency of airflow limitation at 19.1% (283/1,481) and 19.2% (683/3,563), respectively. In contrast, the LMS-LLN₅ yielded the lowest frequency of airflow limitation at 13.2% (196/1,481) and 13.8% (492/3,563), in NHANES-III and CHS, respectively. For restrictive-pattern, similar frequencies of impairment were found across the various spirometric thresholds and study samples, ranging from 9.4% to 11.2%.

Table 5 shows the percentages of discordant designations of respiratory impairment in each study sample when using GOLD and ATS/ERS criteria, relative to LMS criteria. As can be seen, GOLD frequently over-classified respiratory impairment, with discordance of 58.4% (326/558) and 57.0% (781/1,370) for airflow limitation, and 34.6% (56/162) and 41.2% (165/401) for restrictive-pattern, in NHANES-III and CHS, respectively. Similarly, the ATS/ERS frequently over-classified respiratory impairment, with discordance of 27.6% (78/283) and 24.3% (166/683) for airflow limitation, and 16.0% (24/150) and 23.3% (90/387) for restrictive-pattern, in NHANES-III and CHS, respectively. Potential under-classification of respiratory impairment was also found but was limited to restrictive-pattern, with discordance of 25.4% (36/142) and 29.1% (97/333) when using GOLD criteria, and 11.3% (16/142) and 10.8% (36/333) when using ATS/ERS criteria, in NHANES-III and CHS, respectively.

DISCUSSION

Using spirometric data on white participants aged 65–80 years from NHANES-III and CHS, we found that LMS-defined airflow limitation and restrictive-pattern were associated with a statistically significant increased risk of death and likelihood of respiratory symptoms. These results validate the use of LMS-derived Z-scores as a basis for evaluating respiratory impairment in older persons. In addition, relative to LMS designations, our findings suggest that current spirometric criteria published by GOLD and the ATS/ERS can potentially over-classify airflow limitation and under-classify restrictive-pattern.

Evaluating respiratory impairment based on the LMS-method has a strong mathematical and clinical rationale,^{8,9} by accounting for age-related changes in pulmonary function, including the increased variability and skewness in spirometric reference data.^{8,9} In the current context, Z-score based diagnostic thresholds for respiratory impairment were also associated with important clinical outcomes. All-cause mortality is an objective and definitive clinical outcome that is resistant to miscoding, and has been the primary endpoint in landmark studies of oxygen therapy.³⁰ In addition, respiratory symptoms are the most distressing feature of chronic respiratory disease and can lead to disability and increased healthcare utilization.^{30,31} Although somewhat subjective, our use of respiratory symptoms recognizes their importance in clinical decisions, as is evident in guidelines published by GOLD, ATS/ERS, and the American College of Physicians.^{5,32,33}

Our use of LMS-derived Z-scores also has precedence in clinical practice, including the use of Z-scores in bone mineral density testing and the common application of the LMS method to construct growth charts.^{8,9,18} Regarding spirometric measures, diagnostic interpretation is based on a single threshold set at the LLN, corresponding to an LMS-derived Z-score of -1.64. Using this threshold, a reduced FEV1/FVC establishes airflow limitation, because the impairment indicates a greater decline in timed lung volume (FEV1) than untimed lung volume (FVC). Conversely, the combination of a normal FEV1/FVC but reduced FVC establishes restrictive-pattern, because the impairment indicates similar declines in both the FEV1 and FVC.

Our results also quantify the frequency of discordant designations of respiratory impairment in older persons by current spirometric criteria relative to the LMS approach. For example, based on LMS criteria, GOLD and the ATS/ERS identify substantially more cases of airflow limitation and restrictive-pattern; GOLD also identifies substantially fewer cases of restrictive-pattern; see Table 5. The potential misclassification of respiratory impairment by current spirometric criteria is arguably attributable to methodological limitations.⁸⁻¹³ In particular, GOLD thresholds do not account for age-related changes in pulmonary function, and the calculation of the ATS/ERS-LLN₅ does not adequately account for age-related variability and skewness in spirometric reference data.⁸⁻¹³

In the present study, because self-reported asthma was an exclusion criterion and rates of smoking (former and current) were high (56.1% in NHANES-III and 55.9% in CHS), participants who had airflow limitation likely had COPD. Consequently, our results may have clinical implications for the evaluation and management of COPD in older persons.^{5,32,33} Specifically, because LMS-defined airflow limitation may be less likely to misclassify “disease,” future work should evaluate prospectively whether this new approach accurately predicts health care utilization related to COPD, including medication use and hospitalizations.

The LMS classification of restrictive respiratory impairment also has clinical implications. For example, the current standard of practice is to initially evaluate lung function based on spirometry.⁶ If a restrictive-pattern is present (see Methods section), the results are then confirmed by a reduced total lung capacity (TLC), as measured by plethysmography or helium dilution.⁶ A dilemma arises, however, in that spirometric definitions of a restrictive-pattern when based on GOLD or the ATS/ERS do not accurately predict a reduced TLC.⁶ For example, one study suggested that a reduced TLC can occur at an FEV1/FVC well below the GOLD-defined threshold of 0.70 (as low as 0.55), whereas another study has shown that only 58% of participants who have an ATS-defined spirometric restrictive-pattern also had a reduced TLC.^{34,35} Future work should evaluate whether LMS-defined spirometric restrictive-pattern predicts a reduced TLC more accurately, representing a

potential new clinical and epidemiological strategy for the initial evaluation of restrictive respiratory diseases.

We recognize potential limitations to our study. First, spirometry in NHANES-III and CHS was not obtained specifically after a bronchodilator. Although persons with self-reported asthma were excluded from our study samples, the absence of information on “reversibility” may have led to misclassification of airflow limitation as COPD (i.e. study participants may have underreported asthma).³⁶ Yet, postbronchodilator values may have had a minimal effect on our results, 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, NHANES-III and CHS used spirometers that may have differed in accuracy.³⁹ Nonetheless, differences in accuracy were likely small, as the spirometers met ATS accuracy requirements.^{24,25} Third, our results were generated for older white persons, using the only available data, but nonetheless limiting generalizability. Prior work has demonstrated racial differences in pulmonary function,⁴⁰ and the variability and skewness in reference data is less pronounced in younger versus older adults.⁸ 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—yet pulmonary function physiology is unlikely to change over the intervening time period. In view of these issues, future work should confirm the clinical validity of LMS-defined respiratory impairment in other racial, ethnic, and (younger) age groups, as well as in more contemporary cohorts or when using postbronchodilator spirometry.

In conclusion, among white older persons, LMS-defined airflow limitation and restrictive-pattern were significantly associated with mortality and respiratory symptoms. These results suggest that an approach based on LMS-derived spirometric Z-scores has the potential to provide an age-appropriate and clinically valid basis evaluating respiratory impairment.

Acknowledgments

This study was conducted at the Yale Claude D. Pepper Older Americans Independence Center (P30AG21342) and the Veterans Affairs Clinical Epidemiology Research Center.

Role of Sponsors: The investigators retained full independence in the conduct of this research.

Other: 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.

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

References

1. Thorne SL, Malarcher A, Maurice E, Caraballo R. Cigarette Smoking Among Adults—United States, 2007. *MMWR*. 2008; 57(45):1221–1226. [PubMed: 19008790]
2. Schindler C, Kunzli N, Bongard JP, et al. Short-term variation in air pollution and in average lung function among never-smoker: The Swiss study on air pollution and lung diseases in adults (SALPADIA). *Am J Respir Crit Care Med*. 2001; 163(2):356–61. [PubMed: 11179106]
3. Raheerison C, Girodet PO. Epidemiology of COPD. *Eur Respir Rev*. 2009; 18(114):213–221. [PubMed: 20956146]

4. Murray CJL, Lopez AD. Evidence-based health policy. Lessons from the global burden of disease study. *Science*. 1996; 274(5288):740–743. [PubMed: 8966556]
5. 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]
6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005; 26:948–968. [PubMed: 16264058]
7. 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; 159:179–87. [PubMed: 9872837]
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. Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. *Eur Respir J*. 2010; 36(1):12–19. [PubMed: 20595163]
10. Hansen JF, Sun X-G, Wasserman K. Spirometric criteria for airway obstruction. *Chest*. 2007; 131:349–355. [PubMed: 17296632]
11. Vaz Fragoso CA, Concato J, McAvay G, et al. Defining chronic obstructive pulmonary disease in older persons. *Resp Med*. 2009; 103:1468–1476.
12. Vaz Fragoso CA, Concato J, McAvay G, et al. Chronic obstructive pulmonary disease in older persons: a comparison of two spirometric definitions. *Resp Med*. 2010; 104:1189–96.
13. 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]
14. Meyer KC. Aging. *Proc Am Thorac Soc*. 2005; 2:433–9. [PubMed: 16322596]
15. 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]
16. Garcia-Rio F, Pino JM, Dorgham A, Alonso A, Villamor J. Spirometric reference equation for European females and males aged 65–85 years. *Eur Respir J*. 2004; 24:397–405. [PubMed: 15358698]
17. Enright PL, Kronmal RA, Higgins M, et al. Spirometry reference values for women and men 65–85 years of age: cardiovascular health study. *Am Rev Respir Dis*. 1993; 147:125–133. [PubMed: 8420405]
18. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. *JAMA*. 2002; 288:1889–97. [PubMed: 12377088]
19. Cole TL. Fitting smoothed centile curves to reference data. *J R Statist Soc A*. 1988; 151:385–418.
20. U.S. Department of Health and Human Services. National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988–94, NHANES-III Laboratory Data File (CD-ROM), Public Use Data File Documentation Number 76200. Hyattsville, Maryland: Centers for Disease Control and Prevention; National Technical Information Service; Springfield, VA: 1996.
21. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, et al. The Cardiovascular Health Study: Design and rationale. *Annals Epidemiol*. 1991; 1(3):263–276.
22. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26:319–338. [PubMed: 16055882]
23. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991; 144:1202–1218. [PubMed: 1952453]
24. Spirometry Procedure Manual. [Accessed June 9, 2011] NHANES-III. Available at: <http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/spiro.pdf>
25. Enright P, Kronmal RA, Higgins MW, et al. Prevalence and correlates of respiratory symptoms and disease in the elderly. *Chest*. 1994; 106:827–34. [PubMed: 8082366]
26. Wheatcroft, G.; Cox, CS.; Lochner, KA. Comparative analysis of the NHANES-III public-use and restricted-use linked mortality files. National Center for Health Statistics; Hyattsville, Maryland: 2007.

27. Peduzzi P, Concato J, Feinstein AR, Holford TR. 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]
28. Research Triangle Institute. SUDAAN Language Manual, Release 9.0. Research Triangle Park, NC: Research Triangle Institute; 2004.
29. SAS Institute Inc. SAS/STAT 9.2 User's Guide. Cary; NC, USA: 2008.
30. Gross NJ. Chronic obstructive pulmonary disease outcome measurements. *Proc Am Thorac Soc.* 2005; 2:267–271. [PubMed: 16267347]
31. Cherry DK, Burt CW, Woodwell DA. National ambulatory medical care survey: 1999 summary. *Advanced Data from Vital and Health Statistics.* 2001 July 17.322:1–36.
32. 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; 147:633–8. [PubMed: 17975186]
33. Celli BR, MacNee W. for the American Thoracic Society and European Respiratory Society Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004; 23(6):932–946. [PubMed: 15219010]
34. Gladly CA, Aaron SD, Lunau M, Clinch J, Dales R. Spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. *Chest.* 2003; 123:1939–1946. [PubMed: 12796171]
35. Aaron SD, Dales RE, Cardinal PC. How Accurate Is Spirometry at Predicting Restrictive Pulmonary Impairment? *Chest.* 1999; 115:869–873. [PubMed: 10084506]
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. Nelson SB, Gardner RM, Crapo RO, Jensen RL. Performance evaluation of contemporary spirometers. *Chest.* 1990; 97:288–297. [PubMed: 2298052]
40. Dransfield MT, Bailey WC. COPD: Racial disparities in susceptibility, treatment, and outcomes. *Clin Chest Med.* 2006; 27:463–471. [PubMed: 16880056]

APPENDIX

LMS Z-scores are calculated as: $[(\text{measured} \div \text{predicted median})^{\text{Lambda}} \text{ minus } 1] \div (\text{Lambda} \times \text{Sigma})$, with a Z-score of -1.64 corresponding to the 5th percentile of the distribution of Z-scores (LMS-LLN₅).^{8,9} The LMS prediction equations were used to calculate values for the median, lambda, and skewness; cubic splines for age were obtained from tables based on four pooled reference samples, with ages ranging from 4 to 80 years.^{8,9}

Table 1

Baseline clinical characteristics and mortality rates, stratified by study sample.

Characteristic	NHANES-III N=1,497	CHS N=3,583
Age (years), mean (SD)	72.5 (4.5)	71.5 (4.1)
Females, No. (%)	776 (51.8)	2,066 (57.7)
BMI (kg/m ²), mean (SD)	26.9 (4.8)	26.3 (3.9)
Smoking status, No. (%)		
Never	657 (43.9)	1,580 (44.1)
Former	644 (43.0)	1,576 (44.0)
Current	196 (13.1)	42 (11.9)
Chronic conditions, ^a mean (SD)	0.9 (1.0)	1.0 (0.9)
Self-reported COPD, No. (%)	159 (10.6)	367 (10.2) ^d
Fair-to-poor health status, No. (%)	370 (24.8)	732 (20.5)
Outcomes		
Respiratory symptoms, ^b No. (%)	694 (46.5)	1,561 (44.3)
Deaths, ^c No. (%)	520 (34.7)	1,652 (46.1)
Mortality rate (per 1,000 person-years)	45.5	41.8

Abbreviations: NHANES-III, Third National Health and Nutrition Examination Survey; CHS, Cardiovascular Health Study; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

^aNumber of self-reported, physician-diagnosed.

^bSee methods for details. Missing data: NHANES-III, n=5 (<1%); CHS, n=56 (1.6%).

^cVital status was available on all participants.

^dIncluded self-reported asthma.

Table 2

Hazard ratios for all-cause mortality, stratified by study sample and LMS-defined respiratory impairment.

LMS-defined spirometric category ^a	No. (%) of participants ^b	No. (%) of deaths among participants ^c	Hazard ratio for all-cause mortality (95% CI) ^d	
			Unadjusted	Adjusted
NHANES-III (N=1,481) ^e				
Normal function	1,143 (77.2)	341 (29.8)		1.00
Airflow limitation	196 (13.2)	99 (50.5)	1.92 (1.51–2.45)	1.64 (1.28–2.11)
Restrictive-pattern	142 (9.6)	71 (50.0)	2.15 (1.67–2.77)	1.98 (1.54–2.53)
CHS (N=3,563) ^f				
Normal function	2,738 (76.8)	1,121 (40.9)		1.00
Airflow limitation	492 (13.8)	316 (64.2)	1.98 (1.74–2.24)	1.69 (1.48–1.92)
Restrictive-pattern	333 (9.4)	204 (61.3)	1.90 (1.63–2.20)	1.68 (1.44–1.95)

Abbreviations: See Table 1; and LMS-LLN5, Lambda-Mu-Sigma defined lower limit of normal; FEV1/FVC, forced expiratory volume in 1-second to forced vital capacity.

^aNormal function was defined by FEV1/FVC and FVC both $\geq$ LMS-LLN5; airflow limitation by FEV1/FVC $<$ LMS-LLN5; and restrictive-pattern by FEV1/FVC $\geq$ LMS-LLN5 and FVC $<$ LMS-LLN5.

^bPercent of study sample: N of 1,481 for NHANES-III, and N of 3,563 for CHS.

^cPercent of row.

^dValues were calculated using Cox regression models, adjusted for multiple potential confounders (see methods).

^eNHANES-III missing data: 16 (1.1 %) participants were excluded because of missing data on covariates.

^fCHS missing data: 20 (0.6%) participants were excluded because of missing data on covariates.

Table 3
Odds ratios for having respiratory symptoms, stratified by study sample and LMS-defined respiratory impairment.

LMS-defined spirometric category ^a	No. (%) of participants ^b	No. (%) of participants with respiratory symptoms ^c	Odds ratio for respiratory symptoms (95% CI) ^d	
			Unadjusted	Adjusted
NHANES-III (N=1,476) ^e				
Normal function	1,139 (77.2)	472 (41.4)		1.00
Airflow limitation	196 (13.3)	130 (66.3)	2.78 (2.08–3.73)	2.71 (1.92–3.83)
Restrictive-pattern	111 (7.2)	70 (63.1)	2.08 (1.43–3.02)	1.55 (1.03–2.34)
CHS (N=3,508) ^f				
Normal function	2,694 (76.8)	1,055 (39.2)		1.00
Airflow limitation	485 (13.8)	315 (65.0)	2.88 (2.35–3.52)	2.63 (2.11–3.27)
Restrictive-pattern	329 (9.4)	182 (55.3)	1.92 (1.53–2.42)	1.37 (1.07–1.75)

Abbreviations: See Tables 1 and 2.

^aNormal function was defined by FEV1/FVC and FVC both $\geq$ LMS-LLN₅; airflow limitation by FEV1/FVC <LMS-LLN₅; and restrictive-pattern by FEV1/FVC $\geq$ LMS-LLN₅ and FVC <LMS-LLN₅.

^bPercent of study sample: N of 1,476 for NHANES-III, and N of 3,508 for CHS.

^cPercent of row.

^dValues were calculated using logistic regression models, adjusted for multiple potential confounders (see methods).

^eNHANES-III missing data: 16 (1.1%) participants were excluded because of missing data on covariates.

^fCHS missing data: 19 (0.5%) participants were excluded because of missing data on covariates.

Table 4

Prevalence of respiratory impairment, stratified by study sample and GOLD, ATS/ERS, LMS criteria.

Spirometric Threshold	Airflow Limitation		Restrictive-pattern	
	NHANES-III	CHS	NHANES-III	CHS
	N=1,481	N=3,563	N=1,548	N=3,508
GOLD ^a	558 (37.7)	1,370 (38.4)	162 (10.9)	401 (11.2)
ATS/ERS ^b	283 (19.1)	683 (19.2)	150 (10.1)	387 (10.9)
LMS ^c	196 (13.2)	492 (13.8)	142 (9.6)	333 (9.4)

Abbreviations: See Tables 1 and 2; ATS/ERS-LLN₅, ATS/ERS defined lower limit of normal; LMS-LLN₅, LMS defined lower limit of normal; FEV₁/FVC, forced expiratory volume in 1-second to forced vital capacity.

^a Based on a fixed-ratio threshold, with airflow limitation defined by a FEV₁/FVC <0.70, while restrictive-pattern is defined by a FEV₁/FVC ≥0.70 and FVC <80% predicted. Percent predicted is calculated as [(measured ÷ predicted) × 100].

^b Based on a threshold of ATS/ERS-LLN₅, with airflow limitation defined by a FEV₁/FVC <ATS/ERS-LLN₅, whereas restrictive-pattern is defined by a FEV₁/FVC ≥ATS/ERS-LLN₅ and FVC <ATS/ERS-LLN₅.

^c Based on a threshold of LMS-LLN₅, with airflow limitation defined by a FEV₁/FVC <LMS-LLN₅, whereas restrictive-pattern is defined by a FEV₁/FVC ≥LMS-LLN₅ and a FVC <LMS-LLN₅.

Table 5

The prevalence of discordant designations (misclassification) of respiratory impairment by GOLD and ATS/ERS criteria relative to LMS criteria, stratified by study sample.

Spirometric thresholds	No. (%)			
	Over-classified airflow limitation ^a		Over-classified restrictive-pattern ^b	
	NHANES-III	CHS	NHANES-III	CHS
GOLD	326/558 (58.4)	781/1370 (57.0)	56/162 (34.6)	165/401 (41.2)
ATS/ERS	78/283 (27.6)	166/683 (24.3)	24/150 (16.0)	90/387 (23.3)
	Under-classified airflow limitation ^c		Under-classified restrictive-pattern ^d	
	NHANES-III	CHS	NHANES-III	CHS
GOLD	0/196 (0)	0/492 (0)	36/142 (25.4)	97/333 (29.1)
ATS/ERS	0/196 (0)	0/492 (0)	16/142 (11.3)	36/333 (10.8)

Abbreviations: See Tables 1 and 2.

^a Airflow limitation by GOLD or ATS/ERS (denominator), but not by LMS (numerator).

^b Restrictive-pattern by GOLD or ATS/ERS (denominator), but not by LMS (numerator).

^c Airflow limitation by LMS (denominator), but not by GOLD or ATS/ERS (numerator).

^d Restrictive-pattern by LMS (denominator), but not by GOLD or ATS/ERS (numerator).