Published in final edited form as:

Am J Med. 2013 January ; 126(1): 49–57. doi:10.1016/j.amjmed.2012.07.016.

RESPIRATORY IMPAIRMENT IN OLDER PERSONS: WHEN LESS MEANS MORE

Carlos A. Vaz Fragoso, MD^{1,2}, Thomas M. Gill, MD², Gail McAvay, PhD², Philip H. Quanjer, MD, PhD³, Peter H. Van Ness, PhD, MPH², and John Concato, MD.^{1,2}

¹Veterans Affairs (VA) Clinical Epidemiology Research Center, West Haven, CT, USA ²Yale University School of Medicine, Department of Internal Medicine, New Haven, CT, USA ³Erasmus Medical Centre, Erasmus University, Department of Pulmonary Diseases and Sophia Children's Hospital, Rotterdam, The Netherlands

Abstract

Background—Among older persons, within the clinical context of respiratory symptoms and mobility, evidence suggests that improvements are warranted regarding the current approach for identifying respiratory impairment (i.e., a reduction in pulmonary function).

Methods—Among 3,583 white participants aged 65–80 (Cardiovascular Health Study), we calculated the prevalence of respiratory impairment using the current spirometric standard from the Global Initiative for Obstructive Lung Disease (GOLD) and an alternative spirometric approach termed Lambda-Mu-Sigma (LMS). Results for GOLD- and LMS-defined respiratory impairment were evaluated for their (cross-sectional) association with respiratory symptoms and gait speed, and also for the 5-year cumulative incidence probability of mobility disability.

Results—The prevalence of respiratory impairment was 49.7% (1,780/3,583) when using GOLD and 23.2% (831/3,583) when using LMS. Differences in prevalence were most evident among participants who had no respiratory symptoms, with respiratory impairment classified more often by GOLD (38.1% [326/855]) than LMS (12.3% [105/855]); as well as among participants who had normal gait speed, with respiratory impairment classified more often by GOLD (46.4% [1,003/2,164]) than LMS (19.3% [417/2,164]). Conversely, the 5-year cumulative incidence probability of mobility disability for respiratory impairment was higher for LMS than GOLD (0.313 and 0.249 for never-smokers, and 0.352 and 0.289 for ever-smokers, respectively), but was similar for normal spirometry by LMS or GOLD (0.193 and 0.185 for never-smokers, and 0.219 and 0.216 for ever-smokers, respectively).

Conclusion—Among older persons, the LMS approach (versus the GOLD approach) classifies respiratory impairment less frequently in those who are asymptomatic, and is also more strongly associated with mobility disability.

Keywords

respiratory impairment; respiratory symptoms; gait speed; mobility disability

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].

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Among older person, respiratory symptoms and reduced mobility are highly prevalent and are associated with important adverse outcomes.^{1–12} In this setting, an underlying mechanism is likely to include a respiratory impairment (i.e., a reduction in pulmonary function), given that cumulative exposures to tobacco smoke, respiratory infections, air pollutants, and occupational dusts frequently occur across the lifespan.^{3,4,12} Accordingly, the method by which respiratory impairment is established in older persons is pertinent to providers in primary care, pulmonary medicine, and other specialties. In particular, because non-respiratory factors may also lead to respiratory symptoms and reduced mobility in older persons,^{6,13,14} it is essential that respiratory impairment be identified with a high level of diagnostic relevance.¹⁵

Respiratory impairment is typically established by spirometric measures of pulmonary function, subsequently categorized as airflow limitation (e.g. chronic obstructive pulmonary disease [COPD] or asthma) or restrictive-pattern (e.g. interstitial lung disease or heart failure).¹⁵ The criteria that define airflow limitation and restrictive-pattern are often based on diagnostic thresholds published by the Global Initiative for Obstructive Lung Disease (GOLD)^{16,17} but these have serious limitations, for two major reasons.^{18–25} First, GOLD defines airflow limitation based on a value of <0.70 for the ratio of forced expiratory volume in 1-second to forced vital capacity (FEV1/FVC).¹⁶ Because aging is associated with increased rigidity of the chest wall and decreased elastic recoil of the lung, an FEV1/FVC <0.70 frequently occurs in otherwise healthy never-smokers aged 65.^{18–23} Second, GOLD defines restrictive-pattern based on FVC <80 percent predicted.^{16,17} Because aging is associated with increased variability in spirometric performance, an increased disparity between percent predicted values and the lower limit of normal (LLN) is found with advancing age.^{19, 24,25} Given these age-related limitations, GOLD thresholds may misidentify respiratory impairment in older persons.^{23–30}

An alternative approach for establishing respiratory impairment has been promoted, one that defines the LLN for FEV1/FVC and FVC based on the 5th percentile distribution of Z-scores, as calculated by Lambda-Mu-Sigma (LMS).^{19,20} This method has a strong mathematical rationale because LMS-calculated Z-scores account for age-related changes in pulmonary function, including variability in spirometric performance and skewness of reference data.^{19,20} A strong clinical rationale for the LMS approach also exists, supported by analyses of data from three large cohorts of aging populations. Specifically, prior work has shown that LMS-defined respiratory impairment, including airflow limitation and restrictive-pattern, is associated with respiratory symptoms, slow gait speed, hospitalization, and death.^{12,26–30} As additional evidence supporting the LMS approach in clinical practice, Z-scores are routinely used to diagnose osteoporosis (bone mineral density) and the LMS method is widely applied to construct growth charts.^{19,31}

Whether LMS yields advantages over GOLD within the clinical context of respiratory symptoms and mobility has not been previously evaluated in older persons. Accordingly, and using data from a large cohort of community-living persons aged 65–80,³² we evaluated the association of LMS- and GOLD-defined respiratory impairment with respiratory symptoms, gait speed, and the 5-year cumulative incidence probability of mobility disability.

METHODS

Study Population

We used data from the Cardiovascular Health Study (CHS), after obtaining institutional review board approval. CHS is a population-based, longitudinal study of 5,888 Americans aged 65–100, assembled in 1989–90 as a random sample of Medicare beneficiaries.^{32,33}

For the present study, eligible participants were white, aged 65–80, and completed at least two acceptable spirometric maneuvers at baseline, as defined by the American Thoracic Society (ATS).^{34,35} Our analyses were limited to whites aged 65–80 because reference values derived from the LMS method were not yet available for non-whites and those aged >80.^{19,20} To focus on “irreversible” pathology as the principal group for airflow limitation (i.e., COPD), participants with self-reported asthma were excluded. As per convention, we did not exclude participants based on spirometric reproducibility criteria.³⁴ The final sample included 3,583 participants.

Spirometry

Participants underwent spirometry during the baseline examination, as per ATS protocols.³⁵ 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 meeting ATS-acceptability criteria.^{15,34,35} The respiratory status of each participant was then categorized as normal spirometry (normal FEV1/FVC and normal FVC) or respiratory impairment, including airflow limitation (reduced FEV1/FVC) or restrictive-pattern (normal FEV1/FVC but reduced FVC). The diagnostic thresholds for FEV1/FVC and FVC were based on LMS and GOLD criteria, as described in the Appendix.^{16,17,19,20,36}

Demographic and Clinical Characteristics

These included age, sex, education, body mass index (BMI), smoking status, chronic conditions, health status, dyspnea and other respiratory symptoms, gait speed and mobility disability.^{32,37–40} Dyspnea severity was graded by an ATS-published 5-level scale (ATS-DLD-78-A), with moderate-to-severe dyspnea corresponding to an ATS-grade III—“Yes” response to: “Do you ever have to stop for breath when walking at your own pace on the level?”^{37,38} Respiratory symptoms included:^{32,38} 1) 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?”; 2) dyspnea-on-exertion—“Yes” response to: “Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?”; or 3) wheezing—“Yes” response to: “Does your chest ever sound wheezy or whistling occasionally apart from colds?”. Gait speed was measured at a usual pace during a timed 15-foot walk, with <0.8 m/sec denoting slow gait speed.^{32,39,40} Mobility status was ascertained annually during in-person interviews.³² In the present study, we used the first 5-years of follow-up and a definition for mobility disability based on a “Yes” response to “a lot of difficulty or unable to walk up 10-steps or walk a half-mile”.^{7,41,42}

Statistical Analysis

Baseline characteristics were summarized as mean values accompanied by standard deviations, or counts accompanied by percentages. In a cross-sectional analysis, the frequency distributions of LMS- and GOLD-defined spirometric categories, including normal spirometry and respiratory impairment, were presented in a two-by-two agreement table. Because all participants who had GOLD-defined normal spirometry also had LMS-defined normal spirometry, but not vice-versa, discordant designations occurred exclusively

as respiratory impairment by GOLD but normal by LMS—hereafter termed the “discordant respiratory impairment group.”

The frequency distributions of LMS- and GOLD-defined respiratory impairment were also evaluated within four clinical groups: 1) *asymptomatic*, defined by the absence of respiratory symptoms and chronic conditions; 2) *respiratory symptoms*, defined by the composite of chronic cough or sputum production, dyspnea-on-exertion, or wheezing; 3) *moderate-to-severe dyspnea*, defined by an ATS grade III or higher; and 4) *slow gait speed*, defined by a speed <0.8 m/sec. Each of these clinical groups was further stratified by smoking status, as never- or ever-smokers.

To obtain a longitudinal measure of absolute risk—and because mobility disability may have occurred at a variable point in time during the interval between annual follow-up visits—a complementary log-log model for interval-censored event times was used to estimate the cumulative incidence probabilities of new-onset mobility disability over 5-years, among participants who did not have mobility disability at baseline.⁴³ Three separate models were estimated, including one each for LMS- and GOLD-defined spirometric categories, and a third for discordant respiratory impairment, and these models were adjusted for age and stratified by smoking status.

Among the 3,583 study participants, 149 (4.2%) and 699 (19.5%) had missing baseline and follow-up mobility disability evaluations, respectively. In addition, 142 (4.0%) were deceased prior to the development of mobility disability. Consequently, after investigating the extent and nature of missing data with a random-effects/pattern-mixture model, sequential regression imputation was used to multiply impute binary values for the missing mobility disability values.^{44–46} This process included the imputation of 11 values for each missing value, and the process was performed separately for each of the six waves of data (baseline and five annual follow-up visits). The 11 multiply-imputed data sets for each wave were then merged, and the complementary log-log interval censored model was fit to the longitudinal data sets.⁴⁷ Next, the multiple results were integrated using the Iweware software package, and a single set of parameter estimates was used to calculate the probabilities of mobility disability.⁴⁸ Finally, plots of cumulative incidence probabilities over time, stratified by LMS- and GOLD-defined spirometric categories and discordant respiratory impairment, were created separately for never- and ever-smokers, with a mean age of 71 used to obtain age-adjusted cumulative incidence probabilities.

SAS 9.2 (SAS Institute; Cary, NC) and the Iweware software package were used for all analyses, with $p < 0.05$ (two-sided) denoting statistical significance.^{48,49}

RESULTS

As shown in Table 1, the mean age was 71.5 years and the mean BMI was 26.3 kg/m²; 57.7% (2,066/3,583) were female and 55.9% (2,002/3,583) were ever-smokers. The mean number of chronic conditions was 1.0 and 20.4% (732/3,583) had fair-to-poor health status. Respiratory symptoms were reported by 43.6% (1,561/3,583) and moderate-to-severe dyspnea was reported by 10.2% (365/3,583). A slow gait speed was recorded in 38.5% (1,378/3,583).

Table 2 shows frequency distributions of participants according to baseline spirometric category. GOLD-defined respiratory impairment was present in 49.7% (1,780/3,583), whereas LMS-defined respiratory impairment was present in only 23.2% (831/3,583). The discordant respiratory impairment group (i.e., respiratory impairment by GOLD, but normal by LMS) comprised 26.5% (949/3,583) of all participants.

Table 3 shows frequency distributions of participants within clinical groups, according to baseline respiratory impairment. In all clinical groups, the prevalence of respiratory impairment was greater when determined by GOLD than by LMS. For example, among asymptomatic participants (no respiratory symptoms and no chronic conditions), the prevalence of respiratory impairment using GOLD was 38.1% (326/855), but only 12.3% (105/855) using LMS. Similarly, among participants who had respiratory symptoms, moderate-to-severe dyspnea, or slow gait speed, GOLD identified respiratory impairment in 58.5% (913/1,561), 67.4% (246/365), and 54.9% (757/1,378), whereas LMS identified only 32.2% (502/1,561), 44.7% (163/365), and 29.3% (404/1,378), respectively. The differences in prevalence rates for respiratory impairment were especially prominent in never-smokers. In particular, among asymptomatic never-smokers, GOLD classified 31.6% (134/424) as having respiratory impairment, whereas LMS identified only 8.7% (37/424).

Table 3 also shows frequency distributions of baseline discordant respiratory impairment within clinical groups, indicating that the prevalence of discordant respiratory impairment was similar across all clinical groups (21.3–29.3%). In particular, the prevalence of discordant respiratory impairment was nearly identical in asymptomatic never-smokers (22.9% [97/424]) versus ever-smokers who had moderate-to-severe dyspnea (23.5% [54/230]).

The Figure shows the age-adjusted cumulative incidence of mobility disability over 5-years of annual follow-up, based on spirometric category and smoking status. For both never- and ever-smokers, the 5-year trajectory of incident mobility disability showed a greater slope for LMS- versus GOLD-defined respiratory impairment. In contrast, LMS- and GOLD-defined normal spirometry, as well as discordant respiratory impairment, had lower and nearly identical trajectories of incident mobility disability.

Table 4 shows the age-adjusted cumulative incidence probability of mobility disability at the 5th annual follow-up visit, according to spirometric category and smoking status. Using LMS, the 5-year cumulative incidence probability of incident mobility disability for respiratory impairment in never- and ever-smokers was 0.313 and 0.352, respectively, representing a 62.2% and 60.7% increase relative to normal spirometry, respectively. In contrast, using GOLD, the 5-year cumulative incidence probability of incident mobility disability for respiratory impairment in never- and ever-smokers was lower at 0.249 and 0.289, respectively, representing only a 34.6% and 33.8% increase relative to normal spirometry, respectively. In contrast, the 5-year cumulative incidence probability of incident mobility disability was similar for LMS- and GOLD-defined normal spirometry, and for discordant respiratory impairment.

DISCUSSION

In a representative population of older persons, we found that twice as many participants are given a designation of respiratory impairment using GOLD versus LMS—with almost one-half versus one-quarter of participants, respectively, classified as abnormal. Subsequent analyses revealed that GOLD results in over-diagnosis according to clinically-based assessments. For example, among asymptomatic never-smokers, GOLD was 4-fold more likely than LMS to assign a “diseased” designation. In addition, the 5-year trajectory of incident mobility disability for respiratory impairment showed a greater slope for LMS versus GOLD, such that the percentage increase in the 5-year cumulative incidence probability of mobility disability for respiratory impairment (as compared with normal spirometry) was 2-fold greater for LMS versus GOLD. Importantly, the designation of discordant respiratory impairment (i.e., respiratory impairment by GOLD but normal by LMS) did not differ substantially in prevalence across clinical groups, including

asymptomatic never-smokers versus symptomatic ever-smokers, nor did it differ substantially in the 5-year cumulative incidence probability of mobility disability relative to LMS- and GOLD-defined normal spirometry.

Overall, these results indicate that, among older persons, LMS-defined respiratory impairment is established less frequently in those who are asymptomatic and, in turn, is more strongly associated with mobility disability, compared with GOLD-defined respiratory impairment. These results also suggest that a “GOLD abnormal” but “LMS normal” determination is best characterized as clinically normal.

Strengths of the current study include assessing outcomes that have high clinical relevance. For example, respiratory symptoms are the most distressing feature of respiratory disease and can lead to disability and increased healthcare utilization and mortality.^{1–5} Gait speed, an objective measure of mobility, is strongly associated with disability, hospitalization, and mortality.^{7,11} Mobility disability, as defined in the present study, is associated with higher rates of morbidity, self-care disability, social isolation, healthcare utilization, and mortality.^{6,7,41,42,50}

The present study also provides direct evidence to justify the claim that the excess rate of respiratory impairment identified when using GOLD (i.e., the group designated as having discordant respiratory impairment) is not clinically meaningful, for several reasons. First, prevalence rates for discordant respiratory impairment did not vary substantially when stratified by clinical group and, second, the probability of incident mobility disability for discordant respiratory impairment was comparable to that of LMS-defined normal spirometry. In addition, prior work involving older persons has shown that the prevalence of spirometry-defined COPD is 3-fold greater for GOLD versus LMS, yet the group designated as having discordant COPD (i.e., COPD by GOLD but normal by LMS) had a comparable probability of incident COPD hospitalization as LMS-defined normal spirometry.^{28,30}

As implications of this research, the GOLD approach among older persons may misidentify respiratory impairment and, in turn, may lead to inappropriate use of respiratory therapies with known side effects, as well as potential delays in the consideration of alternative diagnoses.^{51–53} Conversely, because Z-scores rigorously account for age-related changes in pulmonary function, and because corresponding diagnostic thresholds are associated with health outcomes, the LMS method has a high level of mathematical and clinical validity when establishing respiratory impairment. Accordingly, adopting the LMS approach could lead to more targeted delivery of respiratory therapies.^{12,26–30,51}

The finding that the prevalence of respiratory impairment was 4-fold greater for GOLD versus LMS in otherwise very low risk individuals (i.e., never-smokers who had no respiratory symptoms and no chronic conditions), also has important implications for epidemiologic surveys of older populations. In particular, GOLD may incorrectly suggest respiratory impairment as occurring in almost epidemic proportions.^{23,26–30} Moreover, clinical trials of respiratory therapies in older populations can also be affected adversely when using GOLD, because enrollment may include persons at very low risk of having a clinically meaningful respiratory impairment.⁵⁴

As an issue considered to possibly represent a limitation of our study, we did not evaluate relative risks for mobility disability among participants who had LMS- or GOLD-defined respiratory impairment relative to their respective “internal” reference group of normal spirometry. This analytic strategy was intentionally not selected, however, because the reference groups that define normal spirometry for LMS and GOLD differ, and these reference groups would serve as the basis for calculating relative risks. Accordingly, inferences made from a direct comparison of such relative risks would be an “apples-to-

oranges comparison” and would be flawed, particularly given the high likelihood that GOLD misclassifies normal spirometry in older persons.^{19,23,26–30}

Our results were limited to participants who were white, aged 65–80. With new LMS equations having been published recently for other racial and ethnic groups, as well as for age up to 95, future work can extend these results to include non-whites and those older than 80.^{55,56} In addition, the longitudinal analysis which yielded cumulative incidence probabilities for mobility disability was limited because the outcome was recorded within relatively large intervals (yearly), preventing explicit handling of death as a competing risk. Lastly, our longitudinal analysis involved missing data for mobility disability—but this was addressed by using multiple imputation techniques.

In conclusion, among older persons and based on respiratory symptoms and mobility, respiratory impairment is more clinically meaningful when defined by LMS, as compared with GOLD. As two potential “less-is-more” benefits of adopting the LMS approach, both the designation of respiratory impairment in asymptomatic individuals, as well as unnecessary utilization of medications for (“false positive”) respiratory disease, could be reduced.

Acknowledgments

Funding: The study was conducted at the VA Clinical Epidemiology Research Center and the Yale Claude D. Pepper Older Americans Independence Center (P30AG2134). Dr. Vaz Fragoso is 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. Concato is supported by the Department of Veterans Affairs Cooperative Studies Program.

The study was conducted at the Veterans Affairs Clinical Epidemiology Research Center and the Yale Claude D. Pepper Older Americans Independence Center (P30AG2134). Dr. Vaz Fragoso is 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. Concato is supported by the Department of Veterans Affairs Cooperative Studies Program.

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

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.

The Cardiovascular Health Study (CHS) was conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) of the United States of America in collaboration with the CHS Study Investigators. 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.

References

1. Huijnen B, van der Horst F, van Amelsvoort L, et al. Dyspnea in elderly family practice patients. Occurrence, severity, quality of life and mortality over an 8-year period. *Family Practice*. 2006; 23:34–39. [PubMed: 16115834]
2. Tessier JF, Nejjar C, Letteneur L, et al. Dyspnea and 8-year mortality among elderly men and women: the PAQUID cohort study. *Eur J Epidemiol*. 2001; 17:223–229. [PubMed: 11680540]
3. 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]
4. Gross NJ. Chronic obstructive pulmonary disease outcome measurements. *Proc Am Thorac Soc*. 2005; 2:267–271. [PubMed: 16267347]

5. Cherry, DK.; Burt, CW.; Woodwell, DA. Advanced Data from Vital and Health Statistics; no 322. Hyattsville, MD: National Center for Health Statistics; 2001. National ambulatory medical care survey: 1999 summary.
6. Gill TM, Gahbauer EA, Murphy TE, et al. Risk factors and precipitants of long-term disability in community mobility. *Ann Intern Med.* 2012; 156:131–140. [PubMed: 22250144]
7. Guralnik JM, Ferrucci L, Simonsick EM, et al. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med.* 1995; 332:556–561. [PubMed: 7838189]
8. Onder G, Penninx BW, Ferrucci L, et al. Measures of physical performance and risk for progressive and catastrophic disability: results from the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci.* 2005; 60:74–79. [PubMed: 15741286]
9. Montero-Odasso M, Schapira M, Soriano ER, et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. *J Gerontol A Biol Sci Med Sci.* 2005; 60:1304–1309. [PubMed: 16282564]
10. Hardy SE, Perera S, Roumani YF, et al. Improvement in usual gait speed predicts better survival in older adults. *J Am Geriatr Soc.* 2007; 55:1727–1734. [PubMed: 17916121]
11. Rothman MD, Summers LL, Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc.* 2008; 56:2211–2216. [PubMed: 19093920]
12. Vaz Fragoso CA, Enright PL, McAvay G, et al. Frailty and respiratory impairment in older persons. *Am J Med.* 2012; 125:79–86. [PubMed: 22195532]
13. Simonsick EM, Lafferty ME, Phillips CL, et al. Risk due to inactivity in physically capable older adults. *Am J Public Health.* 1993; 83:1443–1450. [PubMed: 8214236]
14. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med.* 2012; 185:435–452. [PubMed: 22336677]
15. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005; 26:948–968. [PubMed: 16264058]
16. 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]
17. 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]
18. Meyer KC. Aging. *Proc Am Thorac Soc.* 2005; 2:433–439. [PubMed: 16322596]
19. 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]
20. [Accessed January 20, 2012.] Spirometry (LMS). At: <http://www.lungfunction.org/growinglungs/software.html>
21. Quanjer PH, Enright PL, Miller MR, et al. The need to change the method for defining mild airway obstruction. *Eur Respir J.* 2011; 37 (3):720–722. [PubMed: 21357929]
22. Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. *Am J Med.* 2005; 118:1364–1372. [PubMed: 16378780]
23. 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.
24. Miller MR, Pinnock AC. Predicted values: how should we use them? *Thorax.* 1988; 43:265–7. [PubMed: 3406912]
25. Official statement of the European Respiratory Society. Lung volumes and forced ventilatory flows. *Eur Respir J.* 1993; 6(S16):5–40. [PubMed: 8381090]
26. 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]

27. Vaz Fragoso CA, Gill TM, McAvay G, et al. Evaluating respiratory impairment in middle-aged persons using lambda-mu-sigma derived Z-scores. *Respir Care*. 2011; 56(11):1771–1777. [PubMed: 21605489]
28. Vaz Fragoso CA, Gill TM, McAvay G, et al. Respiratory impairment and mortality in older persons: a novel spirometric approach. *J Investig Med*. 2011; 59(7):1089–1095.
29. Vaz Fragoso CA, Concato J, McAvay G, et al. Staging the severity of chronic obstructive pulmonary disease in older persons based on spirometric Z-scores. *J Am Geriatr Soc*. 2011; 59:1847–1854. [PubMed: 22091498]
30. Vaz Fragoso CA, Concato J, McAvay G, et al. Respiratory impairment and COPD hospitalization: a competing risk analysis. *Eur Respir J*. 2012; 40:37–44. [PubMed: 22267770]
31. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. *JAMA*. 2002; 288:1889–97. [PubMed: 12377088]
32. Fried LP, Borhani NO, Enright P, et al. The cardiovascular health study: design and rationale. *Annals Epidemiol*. 1991; 1(3):263–276.
33. Tell GS, Fried LP, Hermanson B, et al. Recruitment of adults 65 years and older as participants in the cardiovascular health study. *Ann Epidemiol*. 1993; 3:358–366. [PubMed: 8275211]
34. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26:319–338. [PubMed: 16055882]
35. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991; 144:1202–1218. [PubMed: 1952453]
36. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med*. 1999; 159:179–187. [PubMed: 9872837]
37. [Accessed February 8, 2012.] ATS-DLD-78-A:Adult Dyspnea Questionnaire. At: <http://www.cdc.gov/niosh/respire.html>
38. American Thoracic Society. Recommended respiratory disease questionnaires for use with adults and children in epidemiological research. *Am Rev Respir Dis*. 1978; 6(part 2):7–23.
39. Fried L, Tangen M, Walston J, et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol Med Sci*. 2001; 56A:M146–156.
40. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011; 305(1): 50–58. [PubMed: 21205966]
41. Guralnik JM, Ferrucci L, Balfour JL, et al. Progressive versus catastrophic loss of the ability to walk: implications for the prevention of mobility loss. *J Am Geriatr Soc*. 2001; 49:1463–1470. [PubMed: 11890584]
42. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA*. 2006; 295:2018–2026. [PubMed: 16670410]
43. Collett, D. *Modelling Survival Data in Medical Research*. 2. Chapman & Hall/CRC; Boca Raton, FL: 2003. p. 273–298.
44. Hedeker D, Gibbons RD. Application of random effects pattern mixture models for missing data in longitudinal studies. *Psychological Methods*. 1997; 2:64–78.
45. Arnold AM, Kronmal RA. Multiple imputation of baseline data in the Cardiovascular Health Study. *American Journal of Epidemiology*. 2003; 157:74–84. [PubMed: 12505893]
46. Ning Y, McAvay GJ, Chaudhry SI, et al. Results differ by applying distinctive multiple imputation approaches on the longitudinal Cardiovascular Health Study data. *Exp Aging Res*. 2012 in press.
47. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A Multivariate Technique for Multiply Imputing Missing Values Using a Sequence of Regression Models. *Survey Methodology*. 2001; 27(1):85–95.
48. [Accessed June 4, 2012] IVEWARE software. At <http://www.isr.umich.edu/src/smp/ive/>
49. SAS Institute Inc. *SAS/STAT 9.3 User's Guide*. Cary, NC, USA: 2011.
50. Hardy SE, Kang Y, Studenski SA, Degenholtz HB. Ability to walk 1/4 mile predicts subsequent disability, mortality, and health care costs. *J Gen Intern Med*. 2011; 26:130–5. [PubMed: 20972641]

51. Vaz Fragoso CA, Gill T. Respiratory Impairment and the aging lung: a novel paradigm for assessing pulmonary function. *J Gerontol Med Sci.* 2012; 67:264–275.
52. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA.* 2008; 300:1439–50. [PubMed: 18812535]
53. Drummond MB, Dasenbrook EC, Pitz MW, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA.* 2008; 300:2407–16. [PubMed: 19033591]
54. Brusasco V. Spirometric definition of COPD: exercise in futility or factual debate? *Thorax On-line.* 2012 Mar 30.201210.1136/thoraxjnl-2012-201720
55. Quanjer, PH.; Stanojevic, S.; Stocks, J.; Cole, TJ. [Accessed June 4, 2012] Data conversion software (GLI Equations). At: www.spirxpert.com/download/InstallGLI2012_DataConversion.EXE
56. Quanjer, PH.; Stanojevic, S.; Stocks, J.; Cole, TJ. [Accessed June 4, 2012.] GAMLSS Instructions. At: www.spirxpert.com/download/GAMLSS-in-action.zip

Figure.

Age-adjusted cumulative incidence of mobility disability over five annual follow-up visits,^a among participants who did not have mobility disability at baseline and according to baseline spirometric category and smoking status^b

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; LMS, Lambda-Mu-Sigma.

^a Based on combined results from 11 multiple imputations, with age set at 71 years — see methods.

^b See footnote to Table 2 for definitions of spirometric category.

Table 1

Baseline characteristics of study participants

Characteristic	N = 3,583
Age (years), mean ($\pm$ SD)	71.5 (4.1)
Females, No. (%)	2,066 (57.7)
BMI (kg/m^2), mean ($\pm$ SD)	26.3 (3.9)
<i>Smoking status</i> , No. (%)	
Never	1,580 (44.1)
Ever	2,002 (55.9)
Former	1,576 (44.0)
Current	426 (11.9)
Chronic conditions, mean ($\pm$ SD) ^a	1.0 (0.9)
Fair-to-poor health status, No. (%)	732 (20.4)
Respiratory symptoms, No. (%) ^b	1,561 (43.6)
Moderate-to-severe dyspnea, No. (%) ^c	365 (10.2)
Slow gait speed, No. (%) ^d	1,378 (38.5)

Abbreviations: ATS, American Thoracic Society; BMI, body mass index (kg/m^2); COPD, chronic obstructive pulmonary disease; SD, standard deviation.

^aSelf-reported, physician-diagnosed hypertension, myocardial infarction, heart failure, cancer, stroke, and COPD.

^bChronic cough or sputum production, dyspnea-on-exertion, or wheezing.

^cATS grade III or higher.

^d<0.8 meter/sec.

\$watermark-text

\$watermark-text

\$watermark-text

Table 2
Frequency distributions of study participants, according to baseline spirometric category

GOLD Spirometric Category ^a	LMS Spirometric Category ^b		
	Normal	Respiratory Impairment	Total
Normal	1,803 (50.3)	No. (%) ^c 0	1,803 (50.3)
Respiratory impairment	949 (26.5) ^d	831 (23.2)	1,780 (49.7)
Total	2,752 (76.8)	831 (23.2)	3,583 (100)

Abbreviations: 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; LMS-tile, percentile distribution of LMS derived z-scores.

^a GOLD: normal spirometry was established by FEV1/FVC ≥ 0.70 and FVC ≥ 80% Pred, while respiratory impairment was established by either airflow limitation (FEV1/FVC < 0.70) or restrictive-pattern (FEV1/FVC ≥ 0.70 and FVC < 80% Pred).

^b LMS: normal spirometry was established by FEV1/FVC and FVC, both ≥ 5 LMS-tile, while respiratory impairment was established by either airflow limitation (FEV1/FVC < 5 LMS-tile) or restrictive-pattern (FEV1/FVC ≥ 5 LMS-tile and FVC < 5 LMS-tile).

^c Percent of the study population (N = 3,583).

^d Participants with respiratory impairment by GOLD but normal by LMS represented the discordant respiratory impairment group.

Table 3
Frequency distributions of study participants within clinical groups, according to baseline respiratory impairment

Clinical Group	N	GOLD	Respiratory Impairment ^g	
			LMS No. (%)	Discordant
Symptom-based ^a				
Asymptomatic ^b	855	326 (38.1)	105 (12.3)	221 (25.8)
Never-smokers	424	134 (31.6)	37 (8.7)	97 (22.9)
Ever-smokers	431	192 (44.5)	68 (15.8)	124 (28.8)
Respiratory symptoms ^c	1,561	913 (58.5)	502 (32.2)	411 (26.3)
Never-smokers	602	253 (42.0)	106 (17.6)	147 (24.4)
Ever-smokers	959	660 (68.8)	396 (41.3)	264 (27.5)
Moderate-to-severe dyspnea ^d	365	246 (67.4)	163 (44.7)	83 (22.7)
Never-smokers	135	67 (49.6)	38 (28.2)	29 (21.5)
Ever-smokers	230	179 (77.8)	125 (54.3)	54 (23.5)
Function-based				
Normal gait speed ^e	2,164	1,003 (46.4)	417 (19.3)	586 (27.1)
Never-smokers	927	313 (33.8)	83 (9.0)	230 (24.8)
Ever-smokers	1,237	690 (55.8)	334 (27.0)	356 (28.8)
Slow gait speed ^f	1,378	757 (54.9)	404 (29.3)	353 (25.6)
Never-smokers	635	256 (40.3)	121 (19.1)	135 (21.3)
Ever-smokers	743	501 (67.4)	283 (38.1)	218 (29.3)

Abbreviations: ATS, American Thoracic Society; GOLD, Global Initiative for Obstructive Lung Disease; LMS, Lambda-Mu-Sigma.

^aThe symptom-based groups are not mutually exclusive.

^bNo respiratory symptoms and no chronic conditions.

^cChronic cough or sputum production, dyspnea-on-exertion, or wheezing.

^dATS dyspnea grade III or higher, representing a select subgroup of participants who had respiratory symptoms.

^e0.8 meter/sec.

^f<0.8 meter/sec.

^gSee footnote to Table 2 for definitions of respiratory impairment.

Table 4

Age-adjusted cumulative incidence probability of mobility disability at the 5th annual follow-up visit, among participants who did not have mobility disability at baseline and according to baseline spirometric category and smoking status ^a

Spirometric Category ^b	N	No. (%)	Incident Mobility Disability ^c	
			Age-Adjusted Cumulative Incidence Probability of Mobility Disability Never-Smokers	Ever-Smokers
GOLD				
Normal spirometry	1,699	330 (19.4)	0.185	0.216
Respiratory impairment	1,595	426 (26.7)	0.249	0.289
LMS				
Normal spirometry	2,575	531 (20.6)	0.193	0.219
Respiratory impairment	719	227 (31.6)	0.313	0.352
Discordant respiratory impairment	876	200 (22.8)	0.201	0.237

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; LMS, Lambda-Mu-Sigma.

^aBased on combined results from 11 multiple imputations, with age set at 71 years — see methods.

^bSee footnote to Table 2 for definitions of spirometric category.

^cDefined as “a lot of difficulty or being unable to walk up 10 -steps or walk half a mile”.