Use of Lambda-Mu-Sigma-Derived Z Score for Evaluating Respiratory Impairment in Middle-Aged Persons

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BACKGROUND: The lambda-mu-sigma (LMS) method calculates the lower limit of normal for spirometric values as the 5th percentile of the distribution of Z scores. Conceptually, LMS-derived Z scores account for normal age-related changes in pulmonary function, including variability and skewness in reference data. Evidence is limited, however, on whether the LMS method is valid for evaluating respiratory impairment in middle-aged persons. OBJECTIVE: To evaluate the association of LMS-defined respiratory impairment (airflow limitation and restrictive pattern) with mortality and respiratory symptoms. METHODS: We analyzed spirometric data from white participants ages 45–64 years in the Third National Health and Nutrition Examination Survey (NHANES III, $n = 1,569$) and the Atherosclerosis Risk in Communities study (ARIC, $n = 8,163$). RESULTS: LMS-defined airflow limitation was significantly associated with mortality (adjusted hazard ratios: NHANES III 1.90, 95% CI 1.32–2.72, ARIC 1.28, 95% CI 1.06–1.57), and respiratory symptoms (adjusted odds ratios: NHANES III 2.48, 95% CI 1.75–3.51, ARIC 2.27, 95% CI 1.98–2.62). LMS-defined restrictive-pattern was also significantly associated with mortality (adjusted hazard ratios: NHANES III 1.98, 95% CI 1.08–3.65, ARIC 1.38, 95% CI 1.03–1.85), and respiratory symptoms (adjusted odds ratios: NHANES III 2.34, 95% CI 1.44–3.80, ARIC 1.89, 95% CI 1.46–2.45). CONCLUSIONS: In white middle-age persons, LMS-defined airflow limitation and restrictive-pattern were significantly associated with mortality and respiratory symptoms. Consequently, an approach that reports spirometric values based on LMS-derived Z scores might provide an age-appropriate and clinically valid strategy for evaluating respiratory impairment. *Key words: spirometry; airflow limitation; restrictive-pattern; mortality; respiratory symptoms.* [Respir Care 2011;56(11):1771–1777. © 2011 Daedalus Enterprises]

Introduction

In aging populations, because of widespread and cumulative exposure to tobacco smoke, respiratory infections, occupational dust, and air pollution, the evaluation of respiratory impairment has clinical and epidemiological implications.[1-4] Most often, respiratory impairment is established spirometrically, as airflow limitation (eg, COPD or asthma) and restrictive-pattern (eg, thoracic kyphosis, heart failure, or interstitial lung disease).[5,6] Importantly, to minimize misidentification of respiratory impairment and to better inform clinical decision making, it is imperative that

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spirometric diagnostic thresholds consider normal age-related changes in pulmonary function and health outcomes.[6-14]

Developmentally, after achieving peak pulmonary function at about 20 years of age, spirometry values progressively decrease with age, principally due to increasing rigidity of the chest wall and decreasing elastic recoil of the lung.[7-10] In addition, between-subject differences in spirometric performance also increases progressively in adults, starting at about age 30 years.[8,9] Accordingly, to account for normal age-related changes in pulmonary function, the lambda-mu-sigma (LMS) method has been proposed as a basis for establishing spirometric diagnostic thresholds.[8,9] Specifically, the LMS method calculates the lower limit of normal as the 5th percentile of the distribution of Z scores (LMS LLN_5), analogous to current strategies for reporting bone mineral density testing.[8,9,15] Conceptually, LMS-derived Z scores include: the median (mu), which represents how spirometry variables change based on predictor variables (age and height); the coefficient of variation (sigma), which models the spread of reference values and adjusts for non-uniform dispersion; and skewness (lambda), which models departure from normality.[8,9] The LMS method substantially improves the calculation of spirometric Z scores, compared to previous calculations based on conventional multiple regression.[11,12] Multiple regression has potential limitations, because it uses inadequate methods for modeling the relationships between predictor variables and spirometric variables, including incorrectly assuming that reference values are distributed normally and have constant variability across an individual's lifespan.[8,9]

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Beyond the strong mathematical rationale, the LMS LLN_5 threshold may also have "clinical validity," namely a documented association with health outcomes, as a basis for establishing respiratory impairment.[13,14] Specifically, with spirometric data from a large cohort of middle-age (40–64 years) and older-age (65–80 years) persons, prior work evaluated different Z score thresholds for the ratio of FEV_1 to FVC and found that the upper limit that was associated with significantly higher risk was the LMS LLN_5.[13] That study was based on a single cohort, however, and did not specifically evaluate the clinical validity of LMS-defined airflow limitation and restrictive-pattern, relative to normal pulmonary function—a diagnostic process that requires consideration of both FVC and FEV_1/FVC (see Methods section).[6] Thus, it remained to be seen whether the LMS method is appropriate for evaluating respiratory impairment in middle-age and older persons.

In the present study we analyzed LMS-derived Z scores for spirometry data from 2 large cohorts of community-living middle-aged persons, to evaluate the association of respiratory impairment with mortality and respiratory symptoms. We also calculated the frequency of misidentification of respiratory impairment with the current spirometric criteria, relative to LMS-based assessment of respiratory impairment.

Methods

This study was approved by the institutional review boards of Veterans Affairs Connecticut Healthcare System and Yale University School of Medicine. The study was conducted at the Yale Claude D Pepper Older Americans Independence Center and the Clinical Epidemiology Research Center, Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut.

Study Population

We used de-identified, publically available data from the Third National Health and Nutrition Examination Survey (NHANES III) and Atherosclerosis Risk in Communities study (ARIC).[16,17] We included only white, middle-age (45–64 years) participants, because LMS reference values are currently unavailable for non-whites and because of the age range of ARIC participants.[8,9,17] We analyzed only data from participants who had completed at least 2 spirometry maneuvers acceptable by the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria, at initial baseline examination. Per current convention, we did not exclude participants based on spirometric reproducibility criteria.[18] To focus on "irreversible" pathology, participants with self-reported asthma were excluded.

NHANES III was designed to provide national estimates of the health and nutritional status of the United States non-institutionalized population.[16] The NHANES III sample, assembled in 1988–1994 and followed through 2000, used a complex design to generate a nationally representative sample, with an age range of 8–80 years (n = 33,994).[16] Based on eligibility criteria, our study sample from NHANES III included 1,569 participants. ARIC was a population-based, longitudinal study of middle-age persons, assembled in 1986–1989 as a probability sample from 4 United States communities and followed through 1998, with an age range of 45–64 years (n = 15,732).[17] Based on eligibility criteria, our study sample from ARIC included 8,163 participants.

Spirometry

In both study samples, participants underwent spirometry during their baseline examination, according to the contemporary ATS protocol,[19] with equipment that met

ATS accuracy requirements (a dry rolling-seal spirometer in NHANES III, and a water-seal spirometer in ARIC).[16,17] With each subject, FEV_1/FVC was calculated from the largest set of FEV_1 and FVC values from maneuvers that met the ATS acceptability criteria.[18,19]

In both study samples, based on measured values for each participant and as recommended, we calculated LMS-derived Z scores for FEV_1/FVC and FVC as:

$$[(\text{measured/median predicted})^{\text{lambda}} - 1]/(\text{lambda} \times \text{sigma})$$

A Z score of −1.64 corresponded to the LMS LLN_5.[8,9] We used the LMS prediction equations to calculate values for the median, lambda, and skewness. We obtained cubic splines for age from tables at http://www.lungfunction-.org/growinglungs/software.html. Those tables are based on 4 pooled reference samples with age range 4–80 years.[8] Using the LMS LLN_5 as a diagnostic threshold, and per current convention, we classified participants as having normal pulmonary function if both FEV_1/FVC and FVC were $\geq$ LMS LLN_5, airflow limitation if FEV_1/FVC was $<$ LMS LLN_5, or restrictive-pattern if FEV_1/FVC was $\geq$ LMS LLN_5 and FVC was $<$ LMS LLN_5.[5,6,8,11-13]

We also classified each subject's respiratory status based on current Global Initiative for Obstructive Lung Disease (GOLD) and ATS/ERS spirometric criteria. GOLD advocates a fixed FEV_1/FVC of 0.70 and an FVC of 80% of predicted.[5,20] The ATS/ERS recommend the 5th percentile of the distribution of reference values as the LLN cut-point for both FEV_1/FVC and FVC (ATS/ERS LLN_5).[6] Based on those thresholds, GOLD defines normal pulmonary function as an FEV_1/FVC $\geq$ 0.70 and an FVC $\geq$ 80% of predicted, airflow limitation as an FEV_1/FVC $<$ 0.70, and restrictive-pattern as an FEV_1/FVC $\geq$ 0.70 and FVC $<$ 80% of predicted.[5,20] We calculated percent of predicted as: [measured/predicted] × 100 with predicted values derived from published regression equations.[5,21]

ATS/ERS defines normal pulmonary function as both FEV_1/FVC and FVC $\geq$ ATS/ERS LLN_5, airflow limitation as FEV_1/FVC $<$ ATS/ERS LLN_5, and restrictive-pattern as FEV_1/FVC $\geq$ ATS/ERS LLN_5 and FVC $<$ ATS/ERS LLN_5.[6] The ATS/ERS LLN_5 threshold was derived from published regression equations.[21]

Clinical Variables

We recorded baseline clinical characteristics, including age, sex, height, body mass index, self-reported chronic conditions, health status, and smoking history.[16,17] Respiratory symptoms were also evaluated, including:

- Chronic cough or sputum production, defined by a yes response to either of the questions, "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?" (NHANES III and ARIC)
- Dyspnea on exertion, defined by a yes response to the question, "Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?" (NHANES III and ARICS)
- Wheezing, defined by a yes response to the question, "Have you had wheezing or whistling in your chest at any time in the past 12 months?" (NHANES III) or "Does your chest ever sound wheezy or whistling, apart from colds?" (ARIC).[16,17]

All-cause mortality was recorded in NHANES III, based on the National Death Index, with a median follow-up of 9.2 years (IQR 7.5–10.5 y).[22] ARIC recorded all-cause mortality based on annual telephone calls, hospital surveillance, vital statistics databases, and the National Death Index, with median follow-up of 11.0 years (IQR 10.9–11.1).[17]

Statistical Analysis

Baseline characteristics of each study sample were first summarized as mean ± SD or as counts and percentages. We analyzed the association between LMS-defined respiratory impairment and death with Cox regression models, adjusted for baseline clinical characteristics, including age, height, sex, ethnicity, smoking history, body mass index, number of chronic conditions, and health status. LMS-defined airflow limitation and restrictive-pattern were treated as nominal categories, and the reference group was participants with normal pulmonary function. With each Cox regression model, goodness-of-fit was assessed with model-fitting procedures and analysis of residuals. We tested the proportional hazards assumption with interaction terms for the time-to-event outcome and each variable in the multivariable model; the terms were retained if $P < .05$ after adjusting for the multiplicity of comparisons. We tested higher-order effects for the continuous covariates and included them in the final model if they met the forward selection criterion of $P < .20$.[23] Similarly, we evaluated the association between LMS-defined respiratory impairment and the presence of respiratory symptoms by calculating odds ratios with logistic regression models.

We also calculated the prevalence of respiratory impairment according to the GOLD, ATS/ERS, and LMS criteria, as well as determined the frequency of misidentified respiratory impairment (false positive and false negative) with the GOLD and ATS/ERS criteria, relative to the LMS-based assessment.

We used statistics software (SUDAAN 10, RTI International, Research Triangle Park, North Carolina, and SAS 9.2, SAS Institute, Cary, North Carolina) for all the analyses. A 2-sided $P < .05$ was considered statistically significant.[24,25]

Table 1. Baseline Characteristics and Mortality

	NHANES III (n = 1,569)	ARIC (n = 8,163)
Age (mean ± SD y)	54.7 ± 5.8	54.1 ± 5.7
Female, no. (%)	813 (51.8)	4,376 (53.6)
Body mass index (mean ± SD kg/m^2)	27.7 ± 5.4	27.0 ± 4.8
Smoking status, no. (%)		
Never	603 (38.4)	3,077 (37.7)
Former	552 (35.2)	2,934 (36.0)
Current	414 (26.4)	2,143 (26.3)
Chronic conditions (mean ± SD)*	0.6 ± 0.8	0.6 ± 0.7
Self-reported COPD, no. (%)†	131 (8.4)	756 (9.3)
Fair-to-poor health status, no. (%)	254 (16.2)	929 (11.4)
Outcomes		
Respiratory symptoms, no. (%)‡	627 (40.0)	3,102 (39.6)
Deaths, no. (%)§	132 (8.4)	677 (8.3)
Mortality rate (per 1,000 person-years)	9.4	7.8

* Self-reported, physician-diagnosed.
† Based on self-reported, physician-diagnosed chronic bronchitis or emphysema.
‡ Included chronic cough or sputum production, dyspnea on exertion, or wheezing (see methods section). Missing data: NHANES III 1 patient (< 1%), ARIC 325 patients (4.0%).
§ Vital status data were available from all participants.
NHANES III = Third National Health and Nutrition Examination Survey
ARIC = Atherosclerosis Risk in Communities study

Results

Table 1 describes the participants. Overall, the NHANES II and ARIC samples were similar in age, female representation, body mass index, smoking status, frequency of chronic conditions, self-reported COPD, and respiratory symptoms. However, the NHANES III participants had a greater proportion of self-reported fair-to-poor health status ("reduced health") and a higher mortality rate.

Table 2 shows the hazard ratios for all-cause mortality. Airflow limitation had an adjusted hazard ratio for mortality of 1.90 (95% CI 1.32–2.72) and 1.28 (95% CI 1.06–1.57) in the NHANES III and ARIC groups, respectively. Restrictive-pattern had an adjusted hazard ratio for mortality of 1.98 (95% CI 1.08–3.65) and 1.38 (95% CI 1.03–1.85) in the NHANES III and ARIC groups, respectively.

Table 3 shows the odds ratios for respiratory symptoms. Airflow limitation had an adjusted odds ratio for respiratory symptoms of 2.48 (95% CI 1.75–3.51) and 2.27 (95% CI 1.98–2.62) in the NHANES III and ARIC groups, respectively. Restrictive-pattern had an adjusted odds ratio for respiratory symptoms of 2.34 (95% CI 1.44–3.80) and 1.89 (95% CI 1.46–2.45) in the NHANES III and ARIC groups, respectively.

Table 4 shows the prevalence of respiratory impairment. For airflow limitation, GOLD yielded the highest frequencies (NHANES III 22.2%, ARIC 21.6%), ATS/ERS yielded the second highest frequencies (NHANES III 17.3%, ARIC 15.8%), and LMS yielded the lowest frequencies (NHANES III 15.7%, ARIC 14.3%). For restrictive-pattern, ATS/ERS yielded the highest frequencies (NHANES III 10.8%, ARIC 5.7%), GOLD yielded the second highest frequencies (NHANES III 9.5%, ARIC 4.9%), and LMS yielded the lowest frequencies (NHANES III 7.2%, ARIC 3.9%).

Table 5 shows the percentages of misidentified respiratory impairment. GOLD substantially misidentified normal pulmonary function as respiratory impairment (false positives), with frequencies of 27.9% and 33.6% for airflow limitation, and frequencies of 29.2% and 27.6% for restrictive-pattern, in the NHANES III and ARIC groups, respectively. ATS/ERS also misidentified normal pulmonary function as respiratory impairment, but predominantly for restrictive-pattern, with frequencies of 34.7% and 31.4%, and uncommonly for airflow limitation, with frequencies of 9.0% and 9.5%, in NHANES III and ARIC, respectively. Otherwise, GOLD and ATS/ERS infrequently misidentified respiratory impairment as normal (false negatives), with a frequency range of 0.4–2.6% for airflow limitation and a frequency range of 1.6–10.8% for restrictive-pattern.

Discussion

LMS-defined airflow limitation and restrictive-pattern were associated with a significantly higher risk of death and likelihood of having respiratory symptoms. Moreover, relative to LMS, we also found that the current GOLD and ATS/ERS spirometric criteria may misidentify normal pulmonary function as airflow limitation or restrictive-pattern. These results support the use of LMS-derived Z scores for evaluating spirometry data in middle-aged persons.

Evaluating respiratory impairment based on the LMS method has a strong mathematical and clinical rationale.[8,9,13-15] LMS-derived Z scores account for age-related changes in pulmonary function, including variability and skewness in reference data.[8,9] We found that LMS-derived Z score thresholds for spirometric variables were also associated with important health outcomes. All-cause mortality is an objective and definitive outcome that is resistant to miscoding and was the primary end point in landmark studies of oxygen therapy.[26] In addition, respiratory symptoms are the most distressing feature of respiratory disease and can lead to disability and increased healthcare utilization.[26,27] Although lacking specificity, the use of respiratory symptoms as a basis for establishing validation recognizes their importance in clinical decisions, as evident in practice guidelines from GOLD, ATS/ERS, and the American College of Physicians.[5,28,29]

Our results also quantify how often the currently accepted spirometric criteria may misidentify respiratory impairment in middle-aged persons (see Table 5). For exam-

Table 2. Hazard Ratios for All-Cause Mortality

Lambda-Mu-Sigma-Defined Spirometry Category*	Participants no. (%)	Deaths Among Participants no. (%)	Hazard Ratio for All-Cause Mortality (95% CI)†	
			Unadjusted	Adjusted
NHANES III (n = 1,548)‡				
Normal pulmonary function	1,194 (77.1)	75 (6.3)	1.00	1.00
Airflow limitation	243 (15.7)	38 (15.6)	2.63 (1.90–3.63)	1.90 (1.32–2.72)
Restrictive-pattern	111 (7.2)	16 (14.4)	2.61 (1.51–4.50)	1.98 (1.08–3.65)
ARIC (n = 7,972)§				
Normal pulmonary function	6,516 (81.7)	465 (7.1)	1.00	
Airflow limitation	1,142 (14.3)	138 (12.1)	1.63 (1.35–1.97)	1.28 (1.06–1.57)
Restrictive-pattern	314 (3.9)	54 (17.2)	2.32 (1.75–3.08)	1.38 (1.03–1.85)

* Normal pulmonary function was defined with FVC and FEV_1/FVC, both $\geq$ the lambda-mu-sigma-defined lower limit of normal of the 5th percentile of the distribution of Z scores ($LMS\text{-}LLN_5$). Airflow limitation was defined as $FEV_1/FVC < LMS\text{-}LLN_5$. Restrictive-pattern was defined as $FEV_1/FVC \geq LMS\text{-}LLN_5$ and $FVC < LMS\text{-}LLN_5$.
† Hazard ratio values were calculated with Cox regression models, adjusted for multiple potential confounders (see methods section).
‡ The Third National Health and Nutrition Examination Survey (NHANES III) had data missing on 21 patients (1.3%), excluded because of missing data on covariates.
§ The Atherosclerosis Risk in Communities study had data missing on 191 patients (2.3%), excluded because of missing data on covariates.

Table 3. Odds Ratios for Respiratory Symptoms

Lambda-Mu-Sigma-Defined Spirometry Category*	Participants no. (%)	Participants With Respiratory Symptoms no. (%)	Odds Ratio for Respiratory Symptoms (95% CI)†	
			Unadjusted	Adjusted
NHANES III (n = 1,547)‡				
Normal pulmonary function	1,193 (77.1)	404 (33.9)	1.00	1.00
Airflow limitation	243 (15.7)	147 (60.5)	2.99 (2.16–4.13)	2.48 (1.75–3.51)
Restrictive-pattern	141 (9.6)	84 (59.6)	3.33 (2.10–5.30)	2.34 (1.44–3.80)
ARIC (n = 7,658)§				
Normal pulmonary function	6,253 (81.6)	2,213 (35.4)	1.00	
Airflow limitation	1,113 (14.5)	622 (55.9)	2.31 (2.03–2.63)	2.27 (1.98–2.62)
Restrictive-pattern	292 (3.8)	175 (59.9)	2.73 (2.15–3.47)	1.89 (1.46–2.45)

* Normal pulmonary function was defined with FVC and FEV_1/FVC, both $\geq$ the lambda-mu-sigma-defined lower limit of normal of the 5th percentile of the distribution of Z scores ($LMS\text{-}LLN_5$). Airflow limitation was defined as $FEV_1/FVC < LMS\text{-}LLN_5$. Restrictive-pattern was defined as $FEV_1/FVC \geq LMS\text{-}LLN_5$ and $FVC < LMS\text{-}LLN_5$.
† Odds ratio values were calculated using logistic regression models, adjusted for multiple potential confounders (see methods section).
‡ The Third National Health and Nutrition Examination Survey (NHANES III) had data missing on 21 patients (1.3%), excluded because of missing data on covariates.
§ The Atherosclerosis Risk in Communities Study had data missing on 180 patients (2.2%), excluded because of missing data on covariates.

ple, based on LMS-based assessment, the GOLD criteria frequently misidentified normal pulmonary function as airflow limitation or restrictive-pattern. Although they yielded assessments of airflow limitation that were similar to LMS, the ATS/ERS criteria nonetheless frequently misidentified normal pulmonary function as restrictive-pattern.

The misidentification of respiratory impairment by current spirometric criteria may reflect age-related methodological limitations.[6-14] Specifically, the GOLD thresholds for FEV_1/FVC (0.70) and FVC (80% of predicted) have methodological weaknesses in adults, for at least 2 reasons. First, because normal aging is associated with increased chest-wall rigidity and loss of elastic recoil of the lung, normal aging often leads to an $FEV_1/FVC < 0.70$, starting at about 40–50 years of age.[6-14] Second, spirometric performance shows increasing variability starting at about 30 years of age, which moves the 80%-of-predicted cut-point for FVC away from the LLN.[6-14] The ATS/ERS LLN_5 threshold for FEV_1/FVC and FVC is also potentially flawed, principally because it does not adequately account for the age-related increased variability and skewness in spirometric reference data.[8,9,13] This means that the ATS/ERS LLN is based only on the distribution of reference values, whereas the LMS LLN is based on a Z score that additionally accounts for variability in spirometric performance and skewness of reference data.[8,9] Importantly, as shown in prior work,[8,9,13] these age-related methodological limitations become progressively worse with advancing age and, hence, should be the focus of future work on the spirometric definition of respiratory impairment in people $\geq$ 65 years old.

Whether the potential misidentification of respiratory impairment with the GOLD and ATS/ERS criteria, relative

Table 4. Prevalence of Respiratory Impairment

	Airflow Limitation, no. (%)		Restrictive-Pattern, no. (%)	
	NHANES III (n = 1,548	ARIC (n = 7,972	NHANES III (n = 1,548	ARIC (n = 7,972
GOLD*	344 (22.2)	1,723 (21.6)	147 (9.5)	387 (4.9)
ATS/ERS†	268 (17.3)	1,256 (15.8)	167 (10.8)	452 (5.7)
Lambda-mu-sigma‡	243 (15.7)	1,142 (14.3)	111 (7.2)	314 (3.9)

* Based on a fixed ratio threshold, the Global Initiative for Obstructive Lung Disease (GOLD) defines airflow limitation as $FEV_1/FVC < 0.70$, and restrictive-pattern as $FEV_1/FVC \geq 0.70$ and $FVC < 80\%$ of predicted.
† The American Thoracic Society/European Respiratory Society defines airflow limitation as FEV_1/FVC less than the 5th percentile of the distribution of reference values (ATS/ERS LLN_5), and restrictive-pattern as $FEV_1/FVC \geq$ ATS/ERS LLN_5 and $FVC <$ ATS/ERS LLN_5.
‡ The lambda-mu-sigma system defines airflow limitation as FEV_1/FVC less than the 5th percentile of the distribution of Z scores (LMS-LLN_5), and restrictive-pattern as $FEV_1/FVC \geq$ LMS-LLN_5 and $FVC <$ LMS-LLN_5.

Table 5. Misidentified Respiratory Impairment by GOLD and ATS/ERS Criteria, Relative to Lambda-Mu-Sigma Criteria

	False Positive Airflow Limitation, no. (%)*		False Positive Restrictive-Pattern, no. (%)†	
	NHANES III	ARIC	NHANES III	ARIC
GOLD	96/344 (27.9)	579/1,723 (33.6)	43/147 (29.2)	107/387 (27.6)
ATS/ERS	24/268 (9.0)	119/1,256 (9.5)	58/167 (34.7)	142/452 (31.4)
	False Negative Airflow Limitation, no. (%)‡		False Negative Restrictive-Pattern, no. (%)§	
	NHANES III	ARIC	NHANES III	ARIC
GOLD	2/243 (0.8)	10/1,142 (0.9)	7/111 (6.3)	5/314 (1.6)
ATS/ERS	1/243 (0.4)	30/1,142 (2.6)	2/111 (1.8)	34/314 (10.8)

* Had airflow limitation by Global Initiative for Obstructive Lung Disease (GOLD) or American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (denominator), but not by lambda-mu-sigma (numerator) criteria.
† Had restrictive-pattern by GOLD or ATS/ERS (denominator) criteria, but not by lambda-mu-sigma (numerator) criteria.
‡ Did not have airflow limitation by GOLD or ATS/ERS (numerator) criteria, but had airflow limitation by lambda-mu-sigma (denominator) criteria.
§ Did not have restrictive-pattern by GOLD or ATS/ERS (numerator) criteria, but had restrictive-pattern by lambda-mu-sigma (denominator) criteria.

to LMS-based assessment, is clinically relevant in middle-aged persons cannot be established by the present study. In particular, airflow limitation has no definitive "standard" against which comparisons can be made, and restrictive-pattern requires confirmation of reduced total lung capacity via body plethysmography or helium dilution.[6,30,31] Consequently, future work should further evaluate the health outcomes of participants who had misidentified respiratory impairment with the GOLD and ATS/ERS criteria. This may require an analytical plan that avoids a spirometry-defined reference group for subsequent comparisons, pooling of several large cohorts to achieve an adequate power for analysis, and a larger array of health outcomes, including respiratory medication use and hospitalization. In addition, future work should evaluate whether LMS-defined restrictive-pattern more accurately predicts a reduced total lung capacity, relative to GOLD and ATS/ERS.

Limitations

First, the magnitude of the associations between respiratory impairment and mortality were not identical across the study samples, although the results were generally consistent and the differences could be due to sampling issues (eg, ARIC had a lower frequency of fair-to-poor health status and a lower mortality rate). Of note, greater consistency was found in the magnitude of associations between respiratory impairment and respiratory symptoms across the study samples.

Second, spirometry in NHANES III and ARIC was not specifically obtained after bronchodilator. Post-bronchodilator values may have had a minimal effect on our results, however, because study participants had high rates of smoking (conferring less reversible airway pathology) and because those who had self-reported asthma were excluded from the analytical sample.

Third, we studied only white middle-aged persons, and racial and age-group related differences can exist in pulmonary function.[8,9,32] Although this does not impair the validity of our study, it does affect the generalizability.

Fourth, our study samples were assembled in the late 1980s and early 1990s and followed through 1988–2000, which raises the issue of the "timeliness" of the data, despite the likelihood of pulmonary physiology remaining stable over time. In view of these limitations, future work

should evaluate the clinical validity of LMS-defined respiratory impairment in more contemporary study populations,[33] including other racial, ethnic, and (older) age groups, and with post-bronchodilator spirometry data.

Conclusions

Among white middle-age persons, LMS-defined airflow limitation and restrictive-pattern were significantly associated with mortality and respiratory symptoms. Consequently, an approach that reports spirometric values based on LMS-derived Z scores potentially provides an age-appropriate and clinically valid strategy for evaluating respiratory impairment.

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