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EVALUATING RESPIRATORY IMPAIRMENT IN MIDDLE-AGED PERSONS USING LAMBDA-MU-SIGMA DERIVED Z-SCORES

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Abstract

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, to determine whether the LMS method is clinically valid when evaluating respiratory impairment in aging populations, including those who are middle-aged.

Methods—We used spirometric data on white participants aged 45–64 years from the Third National Health and Nutrition Examination Survey (NHANES III, N=1,569) and the Atherosclerosis Risk in Communities Study (ARIC, N=8,163). Extending prior work, our new objective was to evaluate the association of LMS-defined respiratory impairment (airflow limitation and restrictive-pattern) with mortality and respiratory symptoms.

Results—LMS-defined airflow limitation was significantly associated with mortality — adjusted hazard ratios (95% confidence interval) of 1.90 (1.32–2.72) and 1.28 (1.06–1.57), as well as respiratory symptoms — adjusted odds ratios of 2.48 (1.75–3.51) and 2.27 (1.98–2.62)), in NHANES III and ARIC, respectively. LMS-defined restrictive-pattern was also significantly associated with mortality — adjusted hazard ratios of 1.98 (1.08–3.65) and 1.38 (1.03–1.85), as well as respiratory symptoms — adjusted odds ratios of 2.34 (1.44–3.80) and 1.89 (1.46–2.45), in NHANES III and ARIC, respectively.

Conclusion—In white middle-aged 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.

Keywords

airflow limitation; restrictive-pattern; mortality; respiratory symptoms

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INTRODUCTION

In aging populations, because of widespread and cumulative exposures to tobacco smoke, respiratory infections, occupational dusts, and air pollution, the evaluation of respiratory impairment has clinical and epidemiological implications.[1–4] Most often, the respiratory impairment is established spirometrically as airflow limitation or restrictive-pattern.[5,6] Importantly, to minimize the misidentification of respiratory impairment and to better inform clinical decision making, it is imperative that diagnostic thresholds for spirometric values 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, spirometric measures progressively worsen across the lifespan, principally due to increasing rigidity of the chest wall and decreasing elastic recoil of the lung.[7–10] In addition, between-subject variability 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 diagnostic thresholds for spirometric values.[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 strategies currently used for reporting bone mineral density testing.[8,9,15] Conceptually, LMS-derived Z-scores include: the median (Mu), representing how spirometric variables change based on predictor variables (age and height); 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] By using this approach, the LMS method substantially improves the calculation of spirometric Z-scores, compared to previous calculations based on conventional multiple regression.[11,12] The latter technique has potential limitations, because it uses inadequate methods for modeling the relationships between predictor variables and spirometric measures, including assuming incorrectly that reference values are distributed normally and have constant variability across the lifespan.[8,9]

Beyond a 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, using spirometric data from a large cohort of middle-aged and older-aged persons (40–64 and 65–80 years, respectively), prior work had evaluated different Z-score thresholds for the ratio of forced expiratory volume in 1-second to forced vital capacity (FEV1/FVC) and found that the upper limit that conferred a significantly increased risk occurred at the LMS-LLN$_5$.[13] This prior work 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 FEV1/FVC and FVC (see Methods section).[6] Thus, it remained to be seen whether the LMS method is appropriate when evaluating respiratory impairment in aging populations, including those who are middle-aged.

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

METHODS

Study Population

We used deidentified, publically-available data from the Third National Health and Nutrition Examination Survey (NHANES-III) and Atherosclerosis Risk in Communities Study (ARIC),[16,17] with institutional review board approvals obtained from VA-CT and Yale.

For the present study, eligible participants were white, middle-aged (45–64 years), and had completed at least two ATS-acceptable spirometric maneuvers at the initial baseline examination. Our analyses were limited to whites aged 45–64 years because LMS reference values are currently unavailable for non-whites and because of the age-range in ARIC.[8,9,17] As per current convention, we did not exclude participants based on spirometric reproducibility criteria.[18] Lastly, 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 U.S. 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 within NHANES III included 1,569 participants. ARIC is a population-based, longitudinal study of middle-aged persons, assembled in 1986–1989 as a probability sample from four US communities and followed through 1998, with an age range of 45–64 years (N=15,732).[17] Based on eligibility criteria, our study sample within ARIC included 8,163 participants.

Spirometry

In both study samples, participants underwent spirometry during their baseline examination, according to contemporary ATS protocols.[19] The spirometry was conducted using equipment that met ATS accuracy requirements, including a dry-rolling seal spirometer in NHANES III and a water-sealed spirometer in ARIC.[16,17] 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 for which participant performance met 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 FEV1/FVC and FVC by: [(measured ÷ median predicted)^{Lambda} minus 1] ÷ (Lambda × Sigma), with a Z-score of −1.64 corresponding to the LMS-LLN$_5$.[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 at http://www.ucl.ac.uk/ich/research-ich/paediatric-anaesthesia/growing_lungs/all_age_reference_ranges_for_spirometry. These tables are based on four pooled reference samples, with ages ranging from 4 to 80 years.[8] Using the LMS-LLN$_5$ as a diagnostic threshold, and as per current convention, we then classified participants as having normal pulmonary function if both FEV1/FVC and FVC were ≥LMS-LLN$_5$, airflow limitation if FEV1/FVC<LMS-LLN$_5$, or restrictive-pattern if FEV1/FVC≥LMS-LLN$_5$ and FVC<LMS-LLN$_5$.[5,6,8,11–13]

In our study samples, we also classified the respiratory status of each participant based on current spirometric criteria. Specifically, 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,[5,20] whereas the American Thoracic and European Respiratory Societies (ATS/ERS) recommend a lower limit of normal cut-point for both FEV1/FVC and FVC, calculated as

the 5th percentile of the distribution of reference values (ATS/ERS-LLN_5).[6] Based on these thresholds, GOLD thus defined normal pulmonary function as FEV1/FVC≥0.70 and FVC≥80% predicted, airflow limitation as FEV1/FVC<0.70, and restrictive-pattern as FEV1/FVC≥0.70 and FVC<80% predicted.[5,20] Percent predicted was calculated as ([measured ÷ predicted] × 100), with predicted values derived from published regression equations.[5,21] ATS/ERS, in turn, defined normal pulmonary function as both FEV1/FVC and FVC ≥ATS/ERS-LLN_5, airflow limitation as FEV1/FVC<ATS/ERS-LLN_5, and restrictive-pattern as FEV1/FVC≥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 Measures

Baseline clinical characteristics of each study sample 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.[16,17] Respiratory symptoms were also evaluated, including 1) chronic cough or sputum production, defined by a "yes" response to: "Do you usually cough on most days for 3 consecutive months or more during the year?" or "Do you bring up phlegm on most days for 3 consecutive months or more during the year?" (NHANES III and ARIC), 2) dyspnea-on-exertion, defined by a "yes" response to: "Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?" (NHANES III and ARICS), or 3) wheezing, defined by a "yes" response to: "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 (interquartile range [IQR] 7.5–10.5).[22] ARIC recorded all-cause mortality based on annual phone 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 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, adjusted for baseline clinical characteristics including 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 comprised of participants who had normal pulmonary function. For each Cox regression model, 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 $p<0.20$.[23] 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, in each study sample, the prevalence of respiratory impairment was calculated according to GOLD, ATS/ERS, and LMS criteria. These analyses included determining the frequency of misidentified respiratory impairment (false-positive and false-negative) when using GOLD and ATS/ERS criteria, relative to LMS designations.

SUDAAN version 10 and SAS version 9.2 software were used in the analyses, with a $p<0.05$ (two-sided) denoting statistical significance.[24,25]

RESULTS

Table 1 shows the characteristics of participants in the NHANES III and ARIC study populations. Overall, the two study samples were similar in age, female representation, BMI, smoking status, and frequency of chronic conditions, self-reported COPD, and respiratory symptoms. NHANES III had, however, a greater proportion of self-reported fair-to-poor health status ("reduced health") and a higher mortality rate.

Table 2 shows hazard ratios (HR) for all-cause mortality in each study population, based on LMS-defined respiratory impairment and relative to LMS-defined normal pulmonary function. Airflow limitation had an adjusted HR (95% confidence interval) for mortality of 1.90 (1.32–2.72) and 1.28 (1.06–1.57) in NHANES III and ARIC, respectively. Similarly, a restrictive-pattern had an elevated adjusted HR for mortality of 1.98 (1.08–3.65) and 1.38 (1.03–1.85) in NHANES III and ARIC, respectively.

Table 3 shows odds ratios (OR) for respiratory symptoms in each study population, based on LMS-defined respiratory impairment and relative to LMS-defined normal pulmonary function. Airflow limitation had an adjusted OR for respiratory symptoms of 2.48 (1.75–3.51) and 2.27 (1.98–2.62) in NHANES III and ARIC, respectively. Similarly, a restrictive-pattern had an elevated adjusted OR for respiratory symptoms of 2.34 (1.44–3.80) and 1.89 (1.46–2.45) in NHANES III and ARIC, respectively.

Table 4 compares the prevalence of respiratory impairment in each study sample, based on GOLD, ATS/ERS, and LMS criteria. For airflow limitation, GOLD yielded the highest frequencies at 22.2% and 21.6%, whereas ATS/ERS yielded the second highest frequencies at 17.3% and 15.8%, in NHANES III and ARIC, respectively. In contrast, LMS yielded the lowest frequencies of airflow limitation at 15.7% and 14.3%, in NHANES III and ARIC, respectively. For restrictive-pattern, ATS/ERS yielded the highest frequencies at 10.8% and 5.7%, while GOLD yielded the second highest frequencies at 9.5% and 4.9%, in NHANES III and ARIC, respectively. As in airflow limitation, LMS also yielded the lowest frequencies of restrictive-pattern at 7.2% and 3.9%, in NHANES III and ARIC, respectively.

Table 5 shows the percentages of misidentified respiratory impairment in each study sample when using GOLD and ATS/ERS criteria, relative to LMS designations. As can be seen, GOLD substantially misidentified normal pulmonary function as respiratory impairment (false-positives), with frequencies for airflow limitation of 27.9% and 33.6%, and for restrictive-pattern of 29.2% and 27.6%, in NHANES III and ARIC, respectively. ATS/ERS also misidentified normal pulmonary function as respiratory impairment, but predominantly for restrictive-pattern with false-positive frequencies of 34.7% and 31.4%, and uncommonly for airflow limitation with frequencies of only 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 frequencies for airflow limitation ranging only from 0.8% to 2.6% and for restrictive-pattern ranging from 1.6% to 10.8%.

DISCUSSION

Using spirometric data on white middle-aged participants from NHANES III and ARIC, we found that LMS-defined airflow limitation and restrictive-pattern were associated with a statistically significant increased risk of death and likelihood of having respiratory symptoms. Moreover, relative to LMS, we also found that current spirometric criteria by GOLD and ATS/ERS may potentially misidentify normal pulmonary function as airflow

limitation or restrictive-pattern. These results support the use of LMS-derived Z-scores for spirometric measures as a basis for evaluating respiratory impairment in middle-aged persons.

Evaluating respiratory impairment based on the LMS-method has a strong mathematical and clinical rationale.[8,9,13–15] As discussed previously, LMS-derived Z-scores account for age-related changes in pulmonary function, including variability and skewness in reference data.[8,9] In the current context, LMS-derived Z-score thresholds for spirometric measures were also associated with important health outcomes. All-cause mortality is an objective and definitive outcome that is resistant to miscoding and has been the primary endpoint in landmark studies of oxygen therapy.[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 published by GOLD, ATS/ERS, and the American College of Physicians.[5,28,29]

The results of the present study also quantify how often currently accepted spirometric criteria may potentially misidentify respiratory impairment in middle-aged persons (see Table 5). For example, based on LMS designations, GOLD criteria frequently misidentified normal pulmonary function as airflow limitation or restrictive-pattern. Although yielding designations of airflow limitation that were similar to LMS, 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 FEV1/FVC of 0.70 and for FVC of 80% predicted have methodological weaknesses in adult populations, for at least two reasons. First, because it is associated with increased rigidity of the chest wall and loss of elastic recoil of the lung, normal aging often leads to an FEV1/FVC<0.70 starting at about 40–50 years of age.[6–14] Second, spirometric performance is associated with increased variability starting at about 30 years of age, moving the 80% predicted cut-point for FVC away from the LLN.[6–14] The ATS/ERS-LLN_5 threshold for FEV1/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] Meaning, 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.[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 those 65-years or older.

Whether the potential misidentification of respiratory impairment by GOLD and ATS/ERS, relative to LMS designations, is clinically relevant in middle-age cannot be established by the present study. In particular, airflow limitation has no definitive “standard” against which comparisons can be made and a restrictive-pattern requires confirmation of a reduced total lung capacity (TLC) by body plethysmography or helium dilution.[6,30,31] Consequently, future work should further evaluate the health outcomes of participants who have misidentified respiratory impairment by GOLD and ATS/ERS. This may require an analytical plan that avoids a spirometry-defined reference group for subsequent comparisons, as well as the pooling of several large cohorts to achieve an adequate power for analysis, and a more expanded array of health outcomes that include respiratory-based medication use and hospitalization. In addition, future work should evaluate whether LMS-

defined restrictive-pattern more accurately predicts a reduced TLC, relative to GOLD and ATS/ERS.

We recognize several potential limitations to our study. First, the magnitude of associations between respiratory impairment and mortality were not identical across the study samples, although results were generally consistent and differences could be due to sampling issues (e.g., 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 a bronchodilator. Postbronchodilator values may have had a minimal effect on our results, however, because study participants had high rates of smoking (conferring less reversible airways' pathology) and because those who had self-reported asthma were excluded from the analytical sample. Third, our results were only generated for white middle-aged persons, and prior work has shown that racial and age-group related differences can exist in pulmonary function.[8,9,32] Although not impairing the validity of our study, generalizability is affected. Lastly, our study samples were assembled in the late 1980s and early 1990s and followed through 1988–2000, raising the issue of "timeliness" of data, despite the likelihood of pulmonary physiology remaining stable over time. In view of the above 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, or when using postbronchodilator spirometry.

In conclusion, among white middle-aged 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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Table 1

Baseline clinical characteristics and mortality rates, stratified by study sample

Characteristic	**NHANES III N=1,569**	**ARIC N=8,163**
Age (years), mean (SD)	54.7 (5.8)	54.1 (5.7)
Females, No. (%)	813 (51.8)	4,376 (53.6)
BMI (kg/m^2), mean (SD)	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,[a] mean (SD)	0.6 (0.8)	0.6 (0.7)
Self-reported COPD,[b] No. (%)	131 (8.4)	756 (9.3)
Fair-to-poor health status, No. (%)	254 (16.2)	929 (11.4)
Outcomes		
Respiratory symptoms,[c] No. (%)	627 (40.0)	3,102 (39.6)
Deaths,[d] No. (%)	132 (8.4)	677 (8.3)
Mortality rate (per 1,000 person-years)	9.4	7.8

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Communities Study; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

[a] Number of self-reported, physician-diagnosed.

[b] Based on self-reported, physician-diagnosed chronic bronchitis or emphysema

[c] Included chronic cough or sputum production, dyspnea-on-exertion, or wheezing (see methods). Missing data: NHANES III, n=1 (<1%); ARIC, n=325 (4.0%)

[d] Vital status was available on all participants.

Table 2

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

LMS-defined spirometric category[a]	No. (%) of participants	No. (%) of deaths among participants	Hazard ratio for all-cause mortality (95% CI)[b]	
			Unadjusted	Adjusted
NHANES III (N = 1,548)[c]				
Normal pulmonary function	1,194 (77.1)	75 (6.3)	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)[d]				
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)

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Communities Study; LMS-LLN5, Lambda-Mu-Sigma defined lower limit of normal; FEV1/FVC, forced expiratory volume in 1-second to forced vital capacity.

[a] Normal pulmonary function was defined by FEV1/FVCand FVC, both ≥LMS-LLN5; airflow limitation by FEV1/FVC<LMS-LLN5; and restrictive-pattern by FEV1/FVC≥LMS-LLN5 and FVC<LMS-LLN5.

[b] Values were calculated using Cox regression models, adjusted for multiple potential confounders (see methods).

[c] NHANES III missing data: 21 (1.3%) were excluded because of missing data on covariates.

[d] ARIC missing data: 191 (2.3%) participants were excluded because of missing data on covariates.

Table 3

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

LMS-defined spirometric category[a]	No. (%) of participants	No. (%) of participants with respiratory symptoms	Odds ratio for respiratory symptoms (95% CI)[b]	
			Unadjusted	Adjusted
NHANES III (N = 1,547)[c]				
Normal pulmonary function	1,193 (77.1)	404 (33.9)	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)[d]				
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)

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Communities Study; LMS-LLN5, Lambda-Mu-Sigma defined lower limit of normal; FEV1/FVC, forced expiratory volume in 1-second to forced vital capacity.

[a] Normal pulmonary function was defined by FEV1/FVCand FVC, both ≥LMS-LLN5; airflow limitation by FEV1/FVC<LMS-LLN5; and restrictive-pattern by FEV1/FVC≥LMS-LLN5 and FVC<LMS-LLN5.

[b] Values were calculated using logistic regression models, adjusted for multiple potential confounders (see methods).

[c] NHANES III missing data: 21 (1.3 %) were excluded because of missing data on covariates.

[d] ARIC missing data: 180 (2.2 %) participants were excluded because of missing data on covariates.

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Table 4

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

Spirometric Threshold	Airflow Limitation		Restrictive-pattern	
	No. (%)			
	NHANES III N=1,548	ARIC N=7,972	NHANES III N=1,548	ARIC N=7,972
GOLD[a]	344 (22.2)	1,723 (21.6)	147 (9.5)	387 (4.9)
ATS/ERS[b]	268 (17.3)	1,256 (15.8)	167 (10.8)	452 (5.7)
LMS[c]	243 (15.7)	1,142 (14.3)	111 (7.2)	314 (3.9)

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Communities Study; GOLD, Global Initiative for Obstructive Lung Disease; ATS/ERS, American Thoracic Society/European Respiratory Society; LMS, Lambda-Mu-Sigma method; ATS/ERS-LLN$_5$, ATS/ERS defined lower limit of normal; LMS-LLN$_5$, 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-LLN$_5$, with airflow limitation defined by a FEV1/FVC<ATS/ERS-LLN$_5$, while restrictive-pattern is defined by a FEV1/FVC≥ATS/ERS-LLN$_5$ and FVC<ATS/ERS-LLN$_5$.

[c]Based on a threshold of LMS-LLN$_5$, with airflow limitation defined by a FEV1/FVC<LMS-LLN$_5$, while restrictive-pattern is defined by a FEV1/FVC≥LMS-LLN$_5$ and a FVC<LMS-LLN$_5$.

Table 5

The prevalence of misidentified respiratory impairment by GOLD and ATS/ERS criteria, relative to LMS criteria and stratified by study sample

Spirometric thresholds	No. (%)			
	False-positive airflow limitation[a]		False-positive restrictive-pattern[b]	
	NHANES III	ARIC	NHANES III	ARIC
GOLD	96/344 (27.9)	579/1723 (33.6)	43/147 (29.2)	107/387 (27.6)
ATS/ERS	24/268 (9.0)	119/1256 (9.5)	58/167 (34.7)	142/452 (31.4)
	False-negative airflow limitation[c]		False-negative restrictive-pattern[d]	
	NHANES III	ARIC	NHANES III	ARIC
GOLD	2/243 (0.8)	10/1142 (0.9)	7/111 (6.3)	5/314 (1.6)
ATS/ERS	1/243 (0.4)	30/1142 (2.6)	2/111 (1.8)	34/314 (10.8)

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; ATS/ERS, American Thoracic Society/European Respiratory Society; LMS, Lambda-Mu-Sigma method; NHANES III, Third National Health and Nutrition Examination Survey; ARIC, Atherosclerosis Risk in Communities Study.

[a] Had airflow limitation by GOLD or ATS/ERS (denominator), but not by LMS (numerator).

[b] Had restrictive-pattern by GOLD or ATS/ERS (denominator), but not by LMS (numerator).

[c] Did not have airflow limitation by GOLD or ATS/ERS (numerator), but had airflow limitation by LMS (denominator).

[d] Did not have restrictive-pattern by GOLD or ATS/ERS (numerator), but had restrictive-pattern by LMS (denominator).