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Respiratory Symptoms, Spirometric Respiratory Impairment, and Respiratory Disease in Middle- and Older-Aged Persons

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Abstract

Objectives—To evaluate whether a novel definition of spirometric respiratory impairment (Global Lung Initiative [GLI]) is strongly associated with respiratory symptoms and, in turn, frequently establishes symptomatic respiratory disease.

Design—Cross-sectional.

Setting—Third National Health and Nutrition Examination Survey.

Participants—Community-dwelling, ages 40-80 (N=7,115).

Measurements—GLI-defined spirometric respiratory impairment (airflow-obstruction and restrictive-pattern), dyspnea on exertion (DOE), chronic bronchitis (CB), and wheezing.

Results—Among participants aged 40-80, prevalence rates were 12.7% and 6.2% for airflow-obstruction and restrictive-pattern and 28.6%, 12.6%, and 12.9% for DOE, CB, and wheezing, respectively. Relative to normal spirometry, airflow-obstruction was associated with DOE, CB, and wheezing—adjusted odds ratios (adjORs): 1.69 (1.42, 2.02), 1.92 (1.62, 2.29), and 2.50 (2.08, 3.00), respectively. Similarly, restrictive-pattern was associated with DOE, CB, and wheezing—adjORs: 1.75 (1.36, 2.25), 1.39 (1.08, 1.78) and 1.53 (1.15, 2.04), respectively. Among participants who had airflow-obstruction and restrictive-pattern, however, only a minority had DOE (38.6% and 45.5%), CB (23.3% and 15.9%), and wheezing (24.4% and 19.1%), respectively, yielding a positive predictive value (PPV) of 53% for any respiratory symptom in the setting of any spirometric respiratory impairment. In addition, most participants who had DOE, CB, and wheezing did not have airflow-obstruction or restrictive-pattern (73.0%, 67.8%, and 66.8%, respectively), yielding a PPV of 26% for any spirometric respiratory impairment in the setting of any respiratory symptom. The results differed only modestly when stratified by the age groups of 40-64 and 65-80.

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Conclusion—GLI-defined spirometric respiratory impairment increased the likelihood of respiratory symptoms relative to normal spirometry, but was nonetheless a poor predictor of respiratory symptoms. Similarly, respiratory symptoms were poor predictors of GLI-defined spirometric respiratory impairment. Hence, a comprehensive assessment is needed when evaluating respiratory symptoms, even in the presence of a spirometric respiratory impairment.

Keywords

spirometry; Z-scores; respiratory impairment; respiratory symptoms

Introduction

Respiratory symptoms are prevalent in aging populations and are associated with adverse outcomes. Dyspnea, for example, is reported in a quarter to one-third of adults, occurs most often on exertion (DOE), and is associated with increased disability and risk of death.[1-7] Chronic bronchitis (CB) has a prevalence range of 5%-25% in adults and is associated with reductions in lung function, limitations in physical activity, and exacerbations of chronic obstructive pulmonary disease (COPD).[7-10] Wheezing has a prevalence range of 5%-16% in adults and is associated with limitations in physical activity.[11,12]

The occurrence of respiratory symptoms often prompts an evaluation of respiratory disease.[13-15] Because pathological confirmation is invasive and not routinely available, respiratory disease is frequently established spirometrically as airflow-obstruction or restrictive-pattern, collectively referred to as spirometric respiratory impairment.[13,16] Airflow-obstruction includes diseases such as asthma and COPD, whereas restrictive-pattern includes diseases that involve the chest wall, respiratory muscles, pleura, or lung parenchyma.[13] Importantly, to establish disease in aging populations, the spirometric thresholds that define respiratory impairment must account for reductions in lung function that are due to normal aging, as well as account for age-related increases in the variability of spirometric performance.[17,18]

The diagnostic thresholds that define spirometric respiratory impairment are often based on the Global Initiative for Obstructive Lung Disease (GOLD),[14,19,20] but these do not adequately account for age-related changes.[13,17,18] Because normal aging impairs respiratory mechanics, the GOLD threshold of <0.70 for the spirometric ratio of forced expiratory volume in 1-second (FEV1) to forced vital capacity (FVC) frequently misclassifies normal spirometry as airflow-obstruction in otherwise asymptomatic never-smokers (starting at age 45-50).[13,17,18] Moreover, because normal aging leads to increased variability in spirometric performance (starting at age 40),[17] the GOLD threshold of 80% predicted for FVC, a criterion for establishing restrictive-pattern, incorrectly assumes equivalence to the lower limit of normal across the adult lifespan.[21]

As a result, a novel spirometric method has been proposed, termed Lambda-Mu-Sigma (LMS).[17] The LMS method calculates spirometric Z-scores that incorporate the median (Mu)—representing how spirometric measures change based on predictor variables (age, height, sex, and ethnicity); the coefficient-of-variation (Sigma)—representing the spread of reference values; and skewness (Lambda)—representing departure from normality.[17] A Z-

score of -1.64 defines the lower limit of normal as the 5th percentile of the distribution.[17] Notably, using data from large populations of asymptomatic lifelong never-smokers, the Global Lung Initiative (GLI) has published equations that expand the availability of LMS-calculated Z-scores, across multiple ethnicities and for ages up to 95 years.[18]

With advancing age, as the prevalence of multimorbidity and polypharmacy increases, it is possible that respiratory symptoms may be attributed incorrectly to misidentified respiratory disease.[22-26] Since GLI-defined spirometric respiratory impairment rigorously identifies reduced lung function beyond that which is caused by normal aging,[17,18] we postulated that it would be strongly associated with respiratory symptoms and, in turn, frequently establish symptomatic respiratory disease. In a large national sample of adults aged 40-80,[27] we therefore evaluated GLI-defined airflow-obstruction and restrictive-pattern, including prevalence rates and associations with DOE, CB, and wheezing. For each of these symptoms, we also calculated prevalence rates for GLI-defined airflow-obstruction and restrictive-pattern as a secondary aim.

Methods

Study Population

The Third National Health and Nutrition Examination Survey (NHANES III) is a national probability sample of Americans aged 8-80, assembled in 1988-1994.[27] Our NHANES III analytical sample included participants aged 40-80 who, at baseline, had no self-reported asthma and had completed at least two American Thoracic Society (ATS) acceptable spirometric maneuvers.[16,27-29] We selected age ≥40 as defining of an aging population because age-related changes in lung function and the occurrence of respiratory disease and its associated adverse health outcomes are more prevalent starting at age 40.[9,13-18] We excluded participants who had self-reported asthma to focus on COPD as the cause of airflow-obstruction. Our final analytical sample included 7,115 participants.

The institutional review boards from the Veterans Affairs Connecticut Healthcare System and Yale University approved the study, granting exemption from participant consent because it involved de-identified data that were publicly available.

Clinical Measures

NHANES III recorded respiratory symptoms at the baseline visit, including DOE, CB, and wheezing.[20] DOE was established if the participant responded “yes” to “Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill”. CB was established if the participant responded “yes” to either “Do you usually cough on most days for 3 consecutive months or more during the year?” or “Do you usually bring up phlegm on most days for 3 consecutive months or more during the year?” Wheezing was established if the participant responded “yes” to “Have you had wheezing or whistling in your chest at any time in the past 12 months?”

Other clinical data included age, sex, body mass index (BMI), ethnicity, smoking status, chronic conditions, health status, and assessment of cardiovascular (CV) risk. Ethnicity was based on self-report and included White, African-American, and Mexican-American.

Reduced health status was defined as a self-reported rating of fair-to-poor. Chronic conditions included self-reported, physician-diagnosed hypertension, diabetes, COPD, myocardial infarction, heart failure, and stroke. Smoking history was defined as ≥10 pack-years of cigarette consumption. Participants were classified at high risk for having respiratory symptoms due to CV disease if they had a history of hypertension, diabetes, stroke, myocardial infarction, or heart failure or if they had a BMI ≥30.[30,31] (Because spirometric measures in healthy, obese adults are typically within the normal range,[32] a high BMI is more likely to be a risk factor for CV disease[31] than for reduced spirometric lung function).

Spirometry

At the baseline visit, participants performed the spirometric maneuver using ATS protocols.[16,27-29] The measures of interest included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and FEV1/FVC. The respiratory status of each participant was then categorized as normal spirometry (normal FEV1/FVC and FVC) or respiratory impairment, including airflow-obstruction (reduced FEV1/FVC) or restrictive-pattern (normal FEV1/FVC but reduced FVC), based on spirometric Z-scores.[16]

The spirometric Z-scores were calculated by the LMS method:[17] [(measured ÷ predicted median)^{Lambda} minus 1] ÷ (Lambda × Sigma), with predicted values derived from the GLI equations.[18] A Z-score of -1.64 defined the lower limit of normal as the 5th percentile of distribution (GLI-LLN$_5$).[18] Using GLI-LLN$_5$ as the diagnostic threshold, normal spirometry was defined by FEV1/FVC and FVC both ≥GLI-LLN$_5$, airflow-obstruction by FEV1/FVC<GLI-LLN$_5$, and restrictive-pattern by FEV1/FVC≥GLI-LLN$_5$ but FVC<GLI-LLN$_5$.[30]

Statistical Analysis

The primary analysis focused on participants aged 40-80 for two reasons. First, respiratory aging occurs along a continuum from middle age to old age.[13,17,18] Second, the entire sample was needed to provide adequate power to test our hypotheses. Nonetheless, our analyses were subsequently rerun among participants aged 40-64 and 65-80, respectively.

First, the baseline characteristics of the study sample, including spirometric categories and respiratory symptoms, were summarized as means and standard deviations or as counts and percentages. Next, using logistic regression models that were adjusted for age, height, sex, ethnicity, smoking history, high cardiovascular risk, and fair-to-poor health status, odds ratios with 95% confidence intervals (95%CIs) were calculated as measures of the association of GLI-defined airflow-obstruction and restrictive-pattern with DOE, CB, and wheezing, respectively.

The prevalence rates for GLI-defined spirometric categories were also calculated for each of the respiratory symptoms. The latter included DOE, CB, and wheezing, while the spirometric categories included normal spirometry, airflow-obstruction, and restrictive-pattern.

Lastly, across the age group of 40-80, the positive predictive value (PPV) and negative predictive value (NPV) were calculated for GLI-defined spirometric respiratory impairment

having respiratory symptoms and for respiratory symptoms having GLI-defined spirometric respiratory impairment. In this analysis, composite measures were used for spirometric respiratory impairment, including airflow-obstruction or restrictive-pattern, and for respiratory symptoms, including DOE, CB, or wheezing.

All statistical analyses were performed using SAS v9.3 (SAS Institute; Cary, NC) and included complete case analyses as the amount of missing data in the analytical sample was minimal (<5%).

Results

Table 1 summarizes the baseline characteristics. Among participants aged 40-80, 51.2% were female, 49.3% were white, 26.1% were African-American, and 24.6% were Mexican-American. Their mean BMI was 27.9 kg/m^2 and 37.4% reported a smoking history. Their chronic conditions included hypertension (37.6%), diabetes mellitus (12.1%), COPD (6.7%), myocardial infarction (6.3%), heart failure (4.5%), and stroke (3.6%). A high CV risk was established in 58.2% of participants, while fair-to-poor health status was reported by 28.3%. Their prevalence of GLI-defined airflow-obstruction and restrictive-pattern were 12.7% and 6.2%, whereas their prevalence of DOE, CB, and wheezing were 28.6%, 12.6%, and 12.9%, respectively. As compared with participants aged 40-64, those aged 65-80 had a significantly greater white representation, lower BMI, and higher rates of chronic conditions, CV risk, fair-to-poor health status, airflow-obstruction, DOE, and CB (all $p < .001$)—rates of restrictive-pattern and wheezing were otherwise similar.

Table 2 shows frequency distributions and the adjusted odds ratios (adjORs) for DOE, according to GLI-defined spirometric category. Among all participants, prevalence rates for DOE were 25.8% with normal spirometry, 38.6% with airflow-obstruction, and 45.5% with restrictive-pattern. Relative to normal spirometry, airflow-obstruction and restrictive-pattern were both associated with DOE—adjORs: 1.69 (1.42-2.02) and 1.74 (1.36-2.25), respectively. In stratified analysis, the adjORs for having DOE did not differ significantly by the age group of 40-64 vs. 65-80 (p values for age interaction were .713 for airflow-obstruction and .201 for restrictive-pattern).

Table 3 shows frequency distributions and adjORs for CB, according to GLI-defined spirometric category. Among all participants, the prevalence rates for CB were 10.5% with normal spirometry, 23.3% with airflow-obstruction, and 15.9% with restrictive-pattern. Relative to normal spirometry, airflow-obstruction and restrictive-pattern were both associated with CB—adjORs: 1.92 (1.62, 2.29) and 1.39 (1.08, 1.78), respectively. In stratified analysis, the adjORs for having CB did not differ significantly by the age group of 40-64 vs. 65-80 (p values for age interaction were .208 for airflow-obstruction and .290 for restrictive-pattern).

Table 4 shows frequency distributions and adjORs for wheezing, according to GLI-defined spirometric categories. Among all participants, the prevalence rates for wheezing were 10.7% with normal spirometry, 24.4% with airflow-obstruction, and 19.1% with restrictive-pattern. Relative to normal spirometry, airflow-obstruction and restrictive-pattern were both

associated with wheezing—adjORs: 2.50 (2.08, 3.00) and 1.53 (1.15, 2.04), respectively. In stratified analysis, the adjORs for having wheezing did not differ significantly by the age group of 40-64 vs. 65-80 (p values for age interaction were .822 for airflow-obstruction and .936 for restrictive-pattern).

Table 5 shows frequency distributions of GLI-defined spirometric categories according to respiratory symptoms. Among all participants, the majority of participants who had DOE, CB, and wheezing had normal spirometry — 73.0%, 68.4%, and 66.8%, respectively. The results were comparable when stratified by the age groups of 40-64 and 65-80.

Lastly, using composite measures and across the age group of 40-80, a PPV of 53% (699/1,322) and a NPV of 65% (3,689/5,667) was calculated for having any respiratory symptom in the setting of any spirometric respiratory impairment, whereas a PPV of 26% (699/2,677) and a NPV of 86% (3,689/4,312) was calculated for having any spirometric respiratory impairment in the setting of any respiratory symptom.

Discussion

In a large national sample of adults aged 40-80, we found high rates of GLI-defined spirometric respiratory impairment, including airflow-obstruction (12.7%) and restrictive-pattern (6.2%), as well as high rates of respiratory symptoms, including DOE (28.6%), CB (12.6%), and wheezing (12.9%). In adjusted models, relative to normal spirometry, airflow-obstruction increased significantly the odds of having DOE (69%), CB (92%), and wheezing (150%). Similarly, restrictive-pattern increased significantly the odds of having DOE (75%), CB (39%), and wheezing (53%). Despite these associations, only a minority of participants who had airflow-obstruction and restrictive-pattern had DOE (38.6% and 45.5%), CB (23.3% and 15.9%), and wheezing (24.4% and 19.1%), respectively. In addition, among those who had DOE, CB, and wheezing, most had normal spirometry (73.0%, 68.4%, and 66.8%, respectively).

In stratified analysis, we found that participants aged 65-80 had significantly higher rates of airflow-obstruction, DOE, and CB, but similar rates of restrictive-pattern and wheezing, as compared with those aged 40-64. The associations of airflow-obstruction and restrictive-pattern with each of the three respiratory symptoms were similar in the two age groups (p values for age interaction were not significant). Lastly, as in the entire age group, most middle and older aged participants who had DOE, CB, and wheezing had normal spirometry.

The results of our study suggest that GLI-calculated diagnostic thresholds for airflow-obstruction and restrictive-pattern are clinically meaningful given their significant associations with DOE, CB, or wheezing. Our results also suggest, however, that a large proportion of adults who have GLI-defined airflow-obstruction or restrictive-pattern do not have DOE, CB, or wheezing, yielding a PPV of only 53% for having any respiratory symptom in the setting of any spirometric respiratory impairment. Hence, despite its methodological rigor, GLI-defined spirometric respiratory impairment cannot be presumed to represent symptomatic respiratory disease, and this is especially relevant for older

persons. Given their high rate of multimorbidity, a diagnostic approach that prioritizes symptomatic disease is indicated.[22,23] Conversely, a diagnostic approach that frequently establishes asymptomatic disease may lead to inappropriate and potentially harmful pharmacotherapy, as well as delays in considering other diagnoses.[13,22]

Our results also suggest caution when establishing respiratory disease based on respiratory symptoms. For example, CB is often used in epidemiologic surveys as a surrogate indicator of COPD.[33] In our study, however, two-thirds of participants who had CB had GLI-defined normal spirometry (did not have COPD). Similarly, wheezing is often attributed to airways disease (including COPD), but two-thirds of affected individuals had normal spirometry. Using composite measures, we further confirmed that respiratory symptoms were poor predictors of spirometric respiratory impairment. Specifically, the PPV was only 26% for having any spirometric respiratory impairment in the setting of any respiratory symptom.

Concerns are therefore raised regarding diagnostic algorithms that establish respiratory disease based on spirometric respiratory impairment and respiratory symptoms.[14,16] Additional diagnostic criteria such as disease-specific biomarkers are needed, and are the subject of ongoing research.[34] Although clinical validation is needed, an alternative approach might set the LLN for the FEV1/FVC and FVC at a lower Z-score of -1.96 (2.5 percentile), as this level of impairment is less likely to establish a false-positive diagnosis of respiratory disease.[18] Another option is the use of FEV1, but this has limitations.[16] Although it stratifies severity of disease in established airflow-obstruction, the FEV1 cannot define normal spirometry (airflow-obstruction can occur with a normal FEV1), nor can it identify the type of impairment (obstructive vs. restrictive).[13,16] Importantly, the capacity to establish normal spirometry has strong relevance, since it may prompt the clinician to consider alternative causes for the respiratory symptom(s).[22]

In the interim, until the above issues are resolved, clinicians should prioritize a comprehensive medical evaluation in individuals who have respiratory symptoms, whether or not they have a spirometric respiratory impairment.[22] This diagnostic approach has a strong rationale in both middle and older age groups, given the low rates of spirometric respiratory impairment among those who had respiratory symptoms, and vice-versa. The benefits of a comprehensive evaluation are likely to be most evident in persons aged 65 or older and regarding the outcome of dyspnea.[22,23] Older persons have a high rate of multimorbidity, increasing the likelihood that non-respiratory mechanisms, such as deconditioning, anemia, chronic kidney disease, medication-related adverse events, and psychiatric illness, may contribute to dyspnea.[22,23] In our study, less than one-third of middle and older aged participants who reported DOE had a spirometric respiratory impairment.

Our study design has several strengths, including a diverse study population, an age-appropriate definition of spirometric respiratory impairment, and clinically meaningful respiratory symptoms. We acknowledge, however, several potential limitations. First, because lung function like many clinical phenomena occurs along a continuum,[35] spirometric Z-scores that are just above or below the LLN may misclassify normal spirometry and respiratory impairment, respectively. Second, expiratory flow limitation and

dynamic hyperinflation may develop in response to exercise, and lead to exertional symptoms (dyspnea and wheezing), despite the individual having normal spirometry (measured at rest).[36] This phenomenon, however, is most likely to occur in exercise-induced asthma and in older persons who are highly fit (capable of very high exercise workloads).[13,36] Persons with self-reported asthma were excluded from our sample, and few older participants were likely to be highly fit given the representative nature of the NHANES III cohort.[13,37] Third, the low prevalence of respiratory symptoms among participants who had GLI-defined spirometric respiratory impairment may be due to age-related reductions in symptom awareness. Prior work has shown that, in response to methacholine-induced bronchoconstriction, respiratory symptoms were milder in those aged 60-83 than those aged 20-46, despite the older group having more severe reductions in lung function.[38] Lastly, other symptoms such as self-reported exercise intolerance may have been more strongly associated with spirometric respiratory impairment. To address these limitations, future work should evaluate diagnostic thresholds for spirometric measures that are lower than the recommended Z-score of -1.64, evaluate alternative symptoms related to exercise intolerance, and investigate whether the associations between spirometric respiratory impairment and respiratory symptoms are modified by asthma and level of physical activity.

In conclusion, among adults aged 40-80, GLI-defined spirometric respiratory impairment increased the likelihood of having respiratory symptoms relative to normal spirometry, but was nonetheless a poor predictor of respiratory symptoms. Similarly, respiratory symptoms were poor predictors of GLI-defined spirometric respiratory impairment. Hence, a comprehensive assessment is needed when evaluating respiratory symptoms, even in the presence of a spirometric respiratory impairment.

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References

1. Kroenke K, Arrington ME, Mangelsdorff AD. The prevalence of symptoms in medical outpatients and the adequacy of therapy. Arch Intern Med. 1990; 150:1685–1689. [PubMed: 2383163]
2. 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]
3. Gardener EA, Huppert FA, Guralnik JM, et al. Middle-aged and mobility-limited: prevalence of disability and symptom attributions in a national survey. J Gen Intern Med. 2006; 21(10):1091–1096. [PubMed: 16970558]
4. Eriksson H, Svärdsudd K, Larsson B, et al. Dyspnoea in a cross-sectional and a longitudinal study of middle-aged men: The Study of Men Born in 1913 and 1923. Eur Heart J. 1987; 8(9):1015–1023. [PubMed: 3499319]

5. 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. Fam Pract. 2006; 23:34–39. [PubMed: 16115834]
6. Abidov A, Rozanski A, Hachamovitch R, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. N Engl J Med. 2005; 353:1889–1898. [PubMed: 16267320]
7. 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]
8. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. Chest. 1995; 108:43S–52S. [PubMed: 7634925]
9. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev. 2009; 18:213–221. [PubMed: 20956146]
10. Montes de Oca M, Halbert RJ, Lopez MV, et al. The chronic bronchitis phenotype in subjects with and without COPD: The PLATINO study. Eur Respir J. 2012; 40:28–36. [PubMed: 22282547]
11. Arif AA, Delclos GL, Lee ES, et al. Prevalence and risk factors of asthma and wheezing among US adults: An analysis of the NHANES III data. Eur Respir J. 2003; 21:827–833. [PubMed: 12765429]
12. Bodner C, Ross S, Douglas G, et al. The prevalence of adult onset wheeze: Longitudinal study. BMJ. 1997; 314:792–793. [PubMed: 9080997]
13. 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.
14. GOLD executive summary. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013; 187:347–365. [PubMed: 22878278]
15. Raghu G, Collard HR, Egan JJ, et al. An Official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011; 183:788–824. [PubMed: 21471066]
16. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26:948–968. [PubMed: 16264058]
17. 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]
18. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95 year age range: The global lung function 2012 equations. Eur Respir J. 2012; 40:1324–1343. [PubMed: 22743675]
19. Glady CA, Aaron SD, Lunau M, et al. Spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. Chest. 2003; 123:1939–Y1946. [PubMed: 12796171]
20. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011; 364:897–906. [PubMed: 21388308]
21. Miller MR, Pincock AC. Predicted values: how should we use them? Thorax. 1988; 43:265–267. [PubMed: 3406912]
22. Fried TR, Vaz Fragoso CA, Rabow MW. Caring for the older person with chronic obstructive pulmonary disease. JAMA. 2012; 308:1254–1263. [PubMed: 23011715]
23. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. JAMA. 2005; 294:716–724. [PubMed: 16091574]
24. Vaz Fragoso CA, Gill TM, McAvay G, et al. Respiratory impairment in older persons: When less means more. Am J Med. 2013; 126:49–57. [PubMed: 23177541]
25. 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]
26. Vaz Fragoso CA, Concato J, McAvay G, et al. The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010; 181:446–451. [PubMed: 20019341]
27. U.S. Department of Health and Human Services. National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988-94, NHANES III Laboratory Data File

(CD-ROM), Public Use Data File Documentation Number 76200. Hyattsville, Maryland: Centers for Disease Control and Prevention; 1996.

28. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005; 26:319–338. [PubMed: 16055882]
29. Becklake M, Crapo RO. on behalf of the American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis. 1991; 144:1202–1218. [PubMed: 1952453]
30. Vaz Fragoso CA, McAvay G, Gill TM, et al. Ethnic differences in respiratory impairment. Thorax. 2014; 69:55–62. [PubMed: 23939399]
31. Gonzalez AB, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010; 363:2211–2219. [PubMed: 21121834]
32. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol. 2010; 108:206–211. [PubMed: 19875713]
33. CDC. Chronic Obstructive Pulmonary Disease Among Adults — United States, 2011. Vol. 61. MMWR; 2012. p. 938-943.
34. Faner R, Tal-Singer R, Riley JH, et al. Lessons from ECLIPSE: A review of COPD biomarkers. Thorax. 2014; 69:666–672. [PubMed: 24310110]
35. Feinstein AR. The inadequacy of binary models for the clinical reality of three-zone diagnostic decisions. J Clin Epidemiol. 1990; 43:109–113. [PubMed: 2319275]
36. American Thoracic Society/American College of Chest Physicians (ATS/ACCP). Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med. 2003; 167:211–277. [PubMed: 12524257]
37. Schoenborn CA, Adams PF. Health Behaviors of Adults: United States, 2005–2007. Data from the National Health Interview Survey. DHHS Publication No. (PHS) 2010–1573.
38. Connolly MJ, Crowley JJ, Charan NB, et al. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. Thorax. 1992; 47:410–413. [PubMed: 1496497]

Table 1
Baseline characteristics of NHANES III participants, according to age group

Characteristic	Age 40-80 N=7,115	Age 40-64 N=4,632	Age 65-80 N=2,483	P Value [f]
Age (years), mean (SD)	58.3 (11.9)	51.1 (7.7)	71.7 (4.5)	<.001
Females, No. (%)	3,645 (51.2)	2,391 (51.6)	1,254 (50.5)	.370
Ethnicity, No. (%)				
White	3,506 (49.3)	2,007 (43.3)	1,499 (60.4)	<.001
African-American	1,860 (26.1)	1,343 (29.0)	517 (20.8)	
Mexican-American	1,749 (24.6)	1,282 (27.7)	467 (18.8)	
BMI (kg/m^2), mean (SD)	27.9 (5.6)	28.2 (5.8)	27.3 (5.2)	<.001
Smoking history, No. (%) [a]	2,627 (37.4)	1,677 (36.6)	950 (38.9)	.054
Chronic conditions, No. (%) [b]				
Hypertension	2,668 (37.6)	1,472 (31.9)	1,196 (48.3)	<.001
Diabetes mellitus	857 (12.1)	449 (9.7)	408 (16.4)	<.001
COPD [c]	478 (6.7)	264 (5.7)	214 (8.6)	<.001
Myocardial infarction	440 (6.3)	168 (3.7)	272 (11.1)	<.001
Heart Failure	321 (4.5)	116 (2.5)	205 (8.3)	<.001
Stroke	258 (3.6)	84 (1.8)	174 (7.0)	<.001
High CV risk, No. (%) [d]	4,139 (58.2)	2,470 (53.3)	1,669 (67.2)	<.001
Fair-to-poor health status, No. (%)	2,012 (28.3)	1,186 (25.6)	826 (33.3)	<.001
Spirometry, No. (%) [e]				
Normal	5,764 (81.0)	3,828 (82.6)	1,936 (78.0)	<.001
Airflow-obstruction	905 (12.7)	523 (11.3)	382 (15.4)	
Restrictive-pattern	444 (6.2)	281 (6.1)	163 (6.6)	
Respiratory symptoms, No. (%)				
Dyspnea on exertion (DOE)	2,033 (28.6)	1,187 (25.7)	846 (34.2)	<.001
Chronic bronchitis (CB)	895 (12.6)	520 (11.2)	375 (15.1)	<.001
Wheezing	916 (12.9)	608 (13.1)	308 (12.4)	.390

Abbreviations: ATS, American Thoracic Society; NHANES III, Third National Health and Nutrition Examination Survey; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1-second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; SD, standard deviation.

[a] ≥ 10 pack-years.

[b] Self-reported, physician-diagnosed.

[c] Included chronic bronchitis or emphysema.

[d] Includes the presence of any of the following: BMI ≥ 30, hypertension, diabetes, heart failure, stroke, or myocardial infarction.

[e] Normal pulmonary function was defined by FEV1/FVC and FVC, both ≥GLI-LLN$_5$; airflow-obstruction by FEV1/FVC<GLI-LLN$_5$; and restrictive-pattern by FEV1/FVC≥GLI-LLN$_5$ and FVC<GLI-LLN$_5$.

[f] Comparisons were made between the age groups of 40-64 and 65-80, using chi-square tests for categorical variables and t-tests for continuous variables.

Table 2

Prevalence rates and adjusted odds ratios for having dyspnea on exertion, according to spirometric category and age group

Spiometric Category [a]	N [b]	No. (%) of participants with dyspnea on exertion [c]	Adjusted odds ratio (95% CI) [d]
Age 40-80			
Normal	5,671	1,463 (25.8)	1.00
Airflow-obstruction	892	344 (38.6)	1.69 (1.42, 2.02)
Restrictive-pattern	433	197 (45.5)	1.75 (1.36, 2.25)
Age 40-64			
Normal	3,783	874 (23.1)	1.00
Airflow-obstruction	516	179 (34.7)	1.69 (1.40, 2.03) [e]
Restrictive-pattern	275	115 (41.8)	1.57 (1.11, 2.21) [f]
Age 65-80			
Normal	1,888	589 (31.2)	1.00
Airflow-obstruction	376	165 (43.9)	1.74 (1.32, 2.31) [e]
Restrictive-pattern	158	82 (51.9)	2.09 (1.54, 2.83) [f]

Abbreviations: FEV1, forced expiratory volume in 1-second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GLI-LLN$_5$, lower limit of normal at the 5th percentile distribution, as defined by a GLI-calculated Z-score of -1.64; SD, standard deviation.

[a] Normal spirometry was defined by FEV1/FVC and FVC, both ≥GLI-LLN$_5$; airflow-obstruction by FEV1/FVC<GLI-LLN$_5$; and restrictive-pattern by FEV1/FVC≥GLI-LLN$_5$ and FVC<GLI-LLN$_5$.

[b] Varied from Table 1 because of missing data.

[c] Percentage of the corresponding spirometric category.

[d] Odds ratios were calculated using logistic regression models, adjusted for age, height, sex, ethnicity, BMI, smoking history, high cardiovascular risk, and health status.

[e] Not significantly different in the age group of 40-60 vs. 65-80 (p-value for age interaction was .713).

[f] Not significantly different in the age group of 40-60 vs. 65-80 (p-value for age interaction was .201).

Table 3

Prevalence rates and adjusted odds ratios for having chronic bronchitis, according to spirometric category and age group

Spiometric Category [a]	N [b]	No. (%) of participants with chronic bronchitis [c]	Adjusted odds ratio (95% CI) [d]
Age 40-80			
Normal	5,684	599 (10.5)	1.00
Airflow-obstruction	891	208 (23.3)	1.92 (1.62, 2.29)
Restrictive-pattern	434	69 (15.9)	1.39 (1.08, 1.78)
Age 40-64			
Normal	3,787	356 (9.4)	1.00
Airflow-obstruction	515	118 (22.9)	2.13 (1.70, 2.66) [e]
Restrictive-pattern	276	37 (13.4)	1.35 (0.93, 1.97) [f]
Age 65-80			
Normal	1,897	243 (12.8)	1.00
Airflow-obstruction	376	90 (23.9)	1.83 (1.45, 2.32) [e]
Restrictive-pattern	158	32 (20.3)	1.51 (1.10, 2.06) [f]

Abbreviations: FEV1, forced expiratory volume in 1-second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GLI-LLN$_5$, lower limit of normal at the 5th percentile distribution, as defined by a GLI-calculated Z-score of -1.64; SD, standard deviation.

[a] Normal spirometry was defined by FEV1/FVC and FVC, both ≥GLI-LLN$_5$; airflow-obstruction by FEV1/FVC<GLI-LLN$_5$; and restrictive-pattern by FEV1/FVC≥GLI-LLN$_5$ and FVC<GLI-LLN$_5$.

[b] Varied from Table 1 because of missing data.

[c] Percentage of the corresponding spirometric category.

[d] Odds ratios were calculated using logistic regression models, adjusted for age, height, sex, ethnicity, BMI, smoking history, high cardiovascular risk, and health status.

[e] Not significantly different in the age group of 40-60 vs. 65-80 (p-value for age interaction was .208).

[f] Not significantly different in the age group of 40-60 vs. 65-80 (p-value for age interaction was .290).

Table 4

Prevalence rates and adjusted odds ratios for wheezing, respectively, according to spirometric category and age group

Spiometric Category [a]	N [b]	No. (%) of participants with wheezing [c]	Adjusted odds ratio (95% CI) [d]
Age 40-80			
Normal	5,683	606 (10.7)	1.00
Airflow-obstruction	892	218 (24.4)	2.50 (2.08, 3.00)
Restrictive-pattern	434	83 (19.1)	1.53 (1.15, 2.04)
Age 40-64			
Normal	3,787	414 (10.9)	1.00
Airflow-obstruction	516	131 (25.4)	2.35 (1.83, 3.01) [e]
Restrictive-pattern	276	56 (20.3)	1.57 (1.10, 2.25) [f]
Age 65-80			
Normal	1,896	192 (10.1)	1.00
Airflow-obstruction	376	87 (23.1)	2.85 (1.99, 4.07) [e]
Restrictive-pattern	158	27 (17.1)	1.46 (0.89, 2.41) [f]

Abbreviations: FEV1, forced expiratory volume in 1-second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GLI-LLN$_5$, lower limit of normal at the 5th percentile distribution, as defined by a GLI-calculated Z-score of -1.64; SD, standard deviation.

[a] Normal spirometry was defined by FEV1/FVC and FVC, both ≥GLI-LLN$_5$; airflow-obstruction by FEV1/FVC<GLI-LLN$_5$; and restrictive-pattern by FEV1/FVC≥GLI-LLN$_5$ and FVC<GLI-LLN$_5$.

[b] Varied from Table 1 because of missing data.

[c] Percentage of the corresponding spirometric category.

[d] Odds ratios were calculated using logistic regression models, adjusted for age, height, sex, ethnicity, BMI, smoking history, high cardiovascular risk, and health status.

[e] Not significantly different in the age group of 40-60 vs. 65-80 (p-value for age interaction was .822).

[f] Not significantly different in the age group of 40-60 vs. 65-80 (p-value for age interaction was .936).

Table 5

Prevalence rates of spirometric categories according to respiratory symptoms and age group

Respiratory Symptoms	N	Spiometric Category [a]		
		Normal	Airflow-obstruction	Restrictive-pattern
		No. (%)		
Age 40-80				
Dyspnea on exertion	2,004	1,463 (73.0)	344 (17.2)	197 (9.8)
Chronic bronchitis	876	599 (68.4)	208 (23.7)	69 (7.9)
Wheezing	907	606 (66.8)	218 (24.0)	83 (9.2)
Age 40-64				
Dyspnea on exertion	1,168	874 (74.8)	179 (15.3)	115 (9.9)
Chronic bronchitis	511	356 (69.7)	118 (23.1)	37 (7.2)
Wheezing	601	414 (68.9)	131 (21.8)	56 (9.3)
Age 65-80				
Dyspnea on exertion	836	589 (70.5)	165 (19.7)	82 (9.8)
Chronic bronchitis	365	243 (66.6)	90 (24.7)	32 (8.8)
Wheezing	306	192 (62.8)	87 (28.4)	27 (8.8)

Abbreviations: FEV1, forced expiratory volume in 1-second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GLI-LLN$_5$, lower limit of normal at the 5th percentile distribution, as defined by a GLI-calculated Z-score of -1.64; SD, standard deviation.

[a] Normal spirometry was defined by FEV1/FVC and FVC, both ≥GLI-LLN$_5$; airflow-obstruction by FEV1/FVC<GLI-LLN$_5$; and restrictive-pattern by FEV1/FVC≥GLI-LLN$_5$ and FVC<GLI-LLN$_5$.