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ORIGINAL ARTICLE

Phenotype of Spirometric Impairment in an Aging Population

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Abstract

Rationale: The Global Lung Initiative (GLI) provides age-appropriate criteria for establishing spirometric impairment, including mild, moderate, and severe chronic obstructive pulmonary disease (COPD) and restrictive pattern, but its association with respiratory-related phenotypes has not been evaluated.

Objectives: To evaluate respiratory-related phenotypes in GLI-defined spirometric impairment.

Methods: In COPDGene (N = 10,131 patients; age range, 45–81 yr; average smoking history, 44.3 pack-years), we evaluated spirometry, dyspnea (modified Medical Research Council grade, ⩾2), poor respiratory health-related quality of life (St. George's Respiratory Questionnaire total score, ⩾25), poor exercise performance (6-minute-walk distance, <391 m), bronchodilator reversibility (FEV_1 change, >12% and ⩾200 ml), and computed tomography–diagnosed emphysema and gas trapping (>5% and >15% of lung, respectively).

Measurements and Main Results: GLI established normal spirometry in 5,100 patients (50.3%), mild COPD in 669 (6.6%), moderate COPD in 865 (8.5%), severe COPD in 2,522 (24.9%), and restrictive pattern in 975 (9.6%). Relative to normal spirometry, graded associations with respiratory-related phenotypes were found for mild, moderate, and severe COPD, with respective adjusted odds ratios (95% confidence intervals) as follows: dyspnea—1.31 (1.10–1.56), 2.20 (1.81–2.68), and 10.73 (8.04–14.33); poor respiratory health-related quality of life—1.49 (1.28–1.75), 2.69 (2.08–3.47), and 14.61 (10.09–21.17); poor exercise performance—1.11 (0.94–1.31), 1.58 (1.33–1.88), and 4.58 (3.42–6.12); bronchodilator reversibility—2.76 (2.24–3.40), 5.18 (4.29–6.27), and 6.21 (5.06–7.62); emphysema—4.86 (3.16–7.47), 6.41 (4.09–10.05), and 17.79 (10.79–29.32); and gas trapping—3.92 (3.12–4.93), 5.20 (3.82–7.07), and 16.28 (9.71–27.30). Restrictive pattern was also associated with multiple respiratory-related phenotypes at a level similar to moderate COPD, but it was otherwise not associated with emphysema (0.89 [0.60–1.32]) or gas trapping (1.15 [0.92–1.42]).

Conclusions: GLI-defined spirometric impairment establishes clinically meaningful respiratory disease, as validated by graded associations with respiratory-related phenotypes.

Keywords: chronic obstructive pulmonary disease; emphysema; restriction

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At a Glance Commentary

Scientific Knowledge on the Subject: The Global Lung Initiative (GLI) provides age-appropriate criteria for establishing spirometric impairment, including mild, moderate, and severe chronic obstructive pulmonary disease and restrictive pattern, but its association with respiratory-related phenotypes has not been evaluated. In the absence of pathologic confirmation, the diagnostic accuracy of GLI-defined spirometric impairment in establishing respiratory disease can be based on respiratory-related phenotypes.

What This Study Adds to the Field: Using data from COPDGene, graded associations were found between the type and severity of GLI-defined spirometric impairment and respiratory-related phenotypes, including dyspnea, poor respiratory health-related quality of life, poor exercise performance, bronchodilator reversibility, and computed tomography–diagnosed emphysema and gas trapping. These results suggest that GLI-defined spirometric impairment establishes clinically meaningful respiratory disease.

Diagnostic thresholds that establish spirometric impairment must account for age-related changes in lung function, including progressive airflow limitation and increased variability in spirometric performance (1–5). If these changes are not considered, an age-related change in lung function may be misidentified as spirometric impairment and, in turn, respiratory disease (1–5). The potential misidentification of respiratory disease is a growing clinical and public health concern, given the rapid aging of populations worldwide (6, 7). In particular, advancing age is associated with high symptom burden, multimorbidity, and polypharmacy (8–10), highlighting the importance of diagnostic accuracy when establishing the presence of disease.

A new approach, the LMS (lambda, mu, sigma) method (4), rigorously accounts for age-related changes in lung function by using spirometric *z* scores that incorporate

Table 1. Baseline Characteristics (N = 10,131)

Characteristic	Number of Patients	Mean ± SD or n (%)
Age, yr	10,131	59.6 ± 9.0
Height, m		1.7 ± 0.1
Female sex		4,751 (46.9)
Ethnicity/race (non-Hispanic)		
White	10,131	6,818 (67.3)
African American		3,313 (32.7)
Less than high school education	10,130	1,368 (13.5)
BMI, kg/m^2	10,131	28.8 ± 6.3
Smoking history		
Pack-years	10,023	44.3 ± 24.9
Current smokers	10,131	5,299 (52.3)
Former smokers		4,832 (47.7)
Medical conditions*		
Hypertension	10,130	4,365 (43.1)
Gastroesophageal reflux		2,525 (24.9)
Osteoarthritis		1,923 (19.0)
Diabetes mellitus	10,131	1,316 (13.0)
Osteoporosis	10,130	901 (8.9)
Rheumatoid arthritis		732 (7.2)
Coronary artery disease	10,131	651 (6.4)
Cancer†		497 (4.9)
Compression fractures‡		479 (4.7)
Blood clots (legs or lungs)	10,130	434 (4.3)
Congestive heart failure	10,131	321 (3.2)
Pneumothorax		325 (3.2)
Stroke	10,129	260 (2.6)
Peripheral vascular disease	10,130	230 (2.3)
Phenotypes		
Dyspnea, MMRC grade§	10,117	1.4 ± 1.4
rHRQL, SGRQ total score‖	10,128	27.1 ± 23.0
Exercise performance, 6MWD, m¶	9,992	413 ± 122
Bronchodilator reversibility, FEV_1 % change**	10,131	5.7 ± 10.3
Emphysema, $LAA950_{insp}$ ††	9,459	6.2 ± 9.6
Gas trapping, $LAA856_{exp}$ ‡‡	8,558	21.9 ± 19.9
GLI-defined spirometric categories§§		
Normal	10,131	5,100 (50.3)
COPD		
Mild		669 (6.6)
Moderate		865 (8.5)
Severe		2,522 (24.9)
Restrictive pattern		975 (9.6)

Definition of abbreviations: 6MWD = 6-minute-walk distance; BD = bronchodilator; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; LAA = low attenuation area (measured with computed tomography); $LAA856_{exp}$ = LAA less than −856 Hounsfield units on expiratory scan (evaluates gas trapping); $LAA950_{insp}$ = LAA less than −950 Hounsfield units on inspiratory scan (evaluates emphysema); MMRC = modified Medical Research Council questionnaire; rHRQL = respiratory health-related quality of life; SGRQ = St. George's Respiratory Questionnaire.

*Self-reported, physician-diagnosed.

†Minor skin cancers are not included.

‡Limited to those in the back.

§Grade ranges from 0 to 4. A grade of 2 or higher denotes clinically meaningful dyspnea, indicating that the dyspnea is more severe than a reference group of the same age and is occurring at a low exercise work rate (12–14).

‖Total score ranges from 0 to 100. A score greater than or equal to 25 corresponds to a COPD Assessment Test score greater than or equal to 10 (15).

¶As a basis for comparison, a 6MWD less than 391 meters is defined as poor exercise performance, corresponding to 2 SD below the mean 6MWD of a healthy population ages 40–80 yr (17). In addition, a 6MWD threshold less than 300 meters is associated with mortality in heart failure (18), whereas a 6MWD threshold less than 350 meters is associated with mortality in COPD (19).

**Calculated as [(post-BD − pre-BD)/pre-BD FEV_1] × 100%. Bronchodilator reversibility included a post-BD FEV_1 showing an increase greater than 12% (2).

††More than 5% of lung with emphysema establishes a diagnosis of emphysema (11, 20, 21).

‡‡More than 15% of lung with gas trapping establishes a diagnosis of gas trapping (11, 20, 21).

§§Using GLI equations and pre-BD values (5, 23–27), normal spirometry was defined by FEV_1/FVC ratio and FVC both at or above the lower limit of normal at the fifth percentile of distribution (LLN_5), COPD (airflow obstruction) by FEV_1/FVC ratio lower than LLN_5, and restrictive pattern by FEV_1/FVC ratio at or above LLN_5 and FVC lower than LLN_5 (1, 2, 4, 5). COPD severity is then defined as mild, moderate, or severe based on FEV_1 *z* scores greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, or less than −2.55, respectively (28, 29).

Table 2. Modified Medical Research Council Questionnaire Grade, St. George's Respiratory Questionnaire Score, and 6-Minute-Walk Distance, according to GLI-defined Spirometric Categories

GLI-defined Spirometric Categories*	Number of Patients	MMRC Grade†	SGRQ Score‡	6MWD§ (*m*)
Normal	5,100	0.90 (0.79–1.02)	18.5 (15.9–21.0)	427 (403–450)
COPD				
Mild	669	1.09 (0.95–1.23)	22.0 (19.4–24.6)	424 (399–449)
Moderate	865	1.44 (1.30–1.57)	30.0 (26.6–33.3)	400 (378–422)
Severe	2,522	2.42 (2.30–2.54)	41.8 (39.0–44.7)	336 (316–355)
Restrictive pattern	975	1.40 (1.27–1.53)	28.4 (25.7–31.0)	390 (368–411)

Definition of abbreviations: 6MWD = 6-minute-walk distance; BD = bronchodilator; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; MMRC = modified Medical Research Council questionnaire; SGRQ = St. George's Respiratory Questionnaire.
Data are presented as adjusted mean (95% confidence interval) values [adjusted for age, height, sex, body mass index, ethnicity, education (less than high school), current smoking, and type of medical condition]. Missing values are provided by multiple imputation.
*Using GLI equations and pre-BD values (5, 23–28), normal spirometry was defined by FEV_1/FVC ratio and FVC both being greater than or equal to the lower limit of normal at the fifth percentile of distribution (LLN_5), COPD (airflow obstruction) by FEV_1/FVC ratio less than LLN_5, and restrictive pattern by FEV_1/FVC ratio greater than or equal to LLN_5 and FVC less than LLN_5. COPD severity is then defined as mild, moderate, or severe based on FEV_1 *z* scores greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, or less than −2.55, respectively (1, 2, 4, 29, 30).
†Grade ranges from 0 to 4. A grade of 2 or higher denotes clinically meaningful dyspnea, indicating that the dyspnea is more severe than a reference group of the same age and is occurring at a low exercise work rate (12–14).
‡Total score ranges from 0 to 100. A score of 25 or higher corresponds to a COPD Assessment Test score of 10 or higher (15).
§As a basis for comparison, a 6MWD less than 391 meters is defined as poor exercise performance, corresponding to 2 SD below the mean 6MWD of a healthy population ages 40–80 years (17). In addition, a 6MWD threshold less than 300 meters is associated with mortality in heart failure (18), whereas a 6MWD threshold less than 350 meters is associated with mortality in COPD (19).

the median (mu), representing how spirometric measures change based on predictor variables (age and height); the coefficient of variation (sigma), representing the spread of reference values; and skewness (lambda), representing departure from normality. A *z* score of −1.64 defines the lower limit of normal as the fifth percentile of distribution (LLN_5) (4). Of note, using data from large reference populations of asymptomatic lifelong nonsmokers, the Global Lung Initiative (GLI) has published equations that expand the availability of LMS-calculated spirometric *z* scores to persons up to 95 years of age and for specific ethnic groups (5).

In the absence of pathologic confirmation, the diagnostic accuracy of spirometric impairment in establishing clinically meaningful respiratory disease can be based on respiratory-related phenotypes. Whether GLI-defined spirometric impairment is associated with respiratory-related phenotypes has not yet been evaluated. In the present study, we used high-quality data derived from the Genetic Epidemiology of COPD study (COPDGene) (11) to evaluate the association of GLI-defined spirometric impairment, including mild, moderate, and severe chronic obstructive pulmonary disease (COPD) and restrictive pattern, with several respiratory-related phenotypes. The latter were defined by dyspnea, respiratory health-related quality of life (rHRQL), exercise performance, bronchodilator (BD) reversibility, and percentage of lung with emphysema and gas trapping, as measured by volumetric chest computed tomography (CT).

Methods

Study Population

COPDGene is a multicenter study designed to identify genetic factors in COPD and related phenotypes (11). Twenty-one clinical study centers throughout the United States enrolled participants between 2007 and 2011, including non-Hispanic white and African American adults who were between 45 and 81 years of age and had a smoking history of at least 10 pack-years (11). Participants were excluded if they had lung diseases other than COPD or asthma (n = 63, including 30 with bronchiectasis and 33 with interstitial lung disease). In the present study, participants were excluded if they did not complete spirometry (n = 170). Hence, the final analytical sample included 10,131 participants, of whom 6,818 were non-Hispanic white and 3,313 were African American. The COPDGene study protocol was approved by the institutional review boards of the 21 participating centers, and informed consent was obtained from all participants (11).

Baseline Characteristics and Respiratory-related Phenotypes

Baseline characteristics included age, height, sex, ethnicity/race, education, body mass index (BMI), smoking history, and self-reported medical conditions (11). Respiratory-related phenotypes included dyspnea severity, rHRQL, exercise performance, BD reversibility, and CT-measured emphysema and gas trapping (11). Our use of the term "phenotype" in this context refers to clinical, physiological, and radiological features that are often included in the evaluation and management of respiratory disease.

Dyspnea was graded on a scale of 0–4 using the modified Medical Research Council (MMRC) questionnaire (higher grades denoted greater severity) (12). Clinically meaningful dyspnea was defined by a grade of 2 or higher, given that this threshold is based on a comparison with a peer group of the same age, occurs at a low exercise work rate ("walking at my own pace on the level"), and is associated with adverse health outcomes (12–14). The rHRQL was evaluated using the St. George's Respiratory Questionnaire (SGRQ), with a total score ranging from 0 to 100 (higher scores denoted worse rHRQL) (15). A SGRQ total score of 25 or higher is indicative of a COPD Assessment Test score of 10 or higher (15).

Exercise performance was evaluated using the 6-minute-walk test (16), with participants instructed to achieve maximal 6-minute-walk distance (6MWD). A poor exercise performance was defined by a 6MWD less than 391 meters, representing 2 SD below the mean 6MWD of a healthy population ages 40–80 years (mean ± SD,

Table 3. Dyspnea, Poor Respiratory Health-related Quality of Life, and Poor Exercise Performance, according to GLI-defined Spirometric Categories

GLI-defined Spirometric Categories*	Number of Patients	Dyspnea†	Poor rHRQL‡	Poor Exercise Performance§
Normal	5,100		1.00	
COPD				
Mild	669	1.31 (1.10–1.56)	1.49 (1.28–1.75)	1.11 (0.94–1.31)
Moderate	865	2.20 (1.81–2.68)	2.69 (2.08–3.47)	1.58 (1.33–1.88)
Severe	2,522	10.73 (8.04–14.33)	14.61 (10.09–21.17)	4.58 (3.42–6.12)
Restrictive pattern	975	1.87 (1.52–2.30)	2.06 (1.81–2.34)	1.99 (1.73–2.28)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative; rHRQL = respiratory health-related quality of life.
Data are presented as adjusted odds ratios (95% confidence intervals) [adjusted for age, height, sex, body mass index, ethnicity, education (less than high school), current smoking, and type of medical condition]. Missing values are provided by multiple imputation.
*Using GLI equations and prebronchodilator (5, 23–27), normal spirometry was defined by FEV_1/FVC ratio and FVC both greater than or equal to the lower limit of normal at the fifth percentile of distribution (LLN_5), COPD (airflow obstruction) by FEV_1/FVC ratio less than LLN_5, and restrictive pattern by FEV_1/FVC ratio greater than or equal to LLN_5 and FVC less than LLN_5. COPD severity is then defined as mild, moderate, or severe based on FEV_1 *z* scores greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, or less than −2.55, respectively (1, 2, 4, 29, 30).
†Established by modified Medical Research Council questionnaire grade 2 or higher, denoting clinically meaningful dyspnea (i.e., the dyspnea is more severe than a reference group of the same age and is occurring at a low exercise work rate) (12–14).
‡Established by St. George's Respiratory Questionnaire score of 25 or higher, correlating with a COPD Assessment Test score of 10 or higher (15).
§Established by 6-minute-walk distance (6MWD) less than 391 meters, representing 2 SD below the mean 6MWD of a healthy population ages 40–80 years (17).

571 ± 90 m) (17). A 6MWD threshold less than 391 meters is greater than the value of less than 300 meters that is associated with mortality in heart failure (18) and also greater than the value of less than 350 meters that is associated with mortality in COPD (19).

BD reversibility was evaluated during spirometric testing (described below), calculated as change in FEV_1 (post-BD vs. pre-BD) (2). BD reversibility was considered present if the post-BD FEV_1 showed an increase greater than 12% and greater than or equal to 200 ml.

Volumetric chest CT was performed to evaluate the percentage of lung with emphysema and the percentage of lung with gas trapping (11, 20, 21). The percentage of the lung with emphysema was calculated as the percentage with a low attenuation area less than −950 Hounsfield units (HU) on an inspiratory scan; values greater than 5% established a diagnosis of emphysema (11, 20, 21). The percentage of the lung with gas trapping was calculated as the percentage with a low attenuation area less than −856 HU on an expiratory scan; values greater than 15% established a diagnosis of gas trapping (11, 20, 21).

Spirometry

Spirometric data were collected by certified staff using an EasyOne spirometer (ndd Medical Technologies, Zurich, Switzerland), as per protocols issued by the American Thoracic Society and the European Respiratory Society (2, 22). Spirometric performance was evaluated by an independent overreader who evaluated each set of spirometry tracings. Grades were assigned to each FEV_1 and FVC, where "C" or better ratings were used in the analysis. Further oversight was provided by a COPDGene quality control committee to adjudicate borderline quality.

The spirometric measures used included pre-BD values for FEV_1 and FVC, with the FEV_1/FVC ratio calculated from the largest FEV_1 and FVC values that were recorded in any of the accepted spirometric maneuvers (2, 22). The use of pre-BD values offers at least three advantages over the current standard of using post-BD values. First, older persons have limited capacity to perform multiple FVC maneuvers (pre- and post-BD) and may have an adverse response to BDs (23, 24). Second, post-BD values have limited clinical relevance in distinguishing COPD from asthma, as well as low reproducibility over time (25–27). Third, diagnostic thresholds for spirometric interpretation are based on reference populations in which only the equivalents of pre-BD values were recorded (4, 5).

Based on GLI spirometric reference equations, including variables for age, height, sex, and ethnicity (5), *z* scores were calculated for FEV_1, FVC, and FEV_1/FVC ratio. The diagnostic algorithm was first based on a single *z* score threshold of −1.64, establishing the LLN_5, and used as follows: normal spirometry was defined by FEV_1/FVC ratio greater than or equal to LLN_5 and FVC greater than or equal to LLN_5, COPD (airflow obstruction) by FEV_1/FVC ratio less than LLN_5, and restrictive pattern by FEV_1/FVC ratio greater than or equal to LLN_5 and FVC less than LLN_5 (1, 2, 4, 5). COPD severity was next evaluated using two diagnostic thresholds for FEV_1, as follows: FEV_1 *z* scores greater than or equal to −1.64 (mild), less than −1.64 but greater than or equal to −2.55 (moderate), and less than −2.55 (severe), respectively, with a *z* score of −2.55 corresponding to the 0.5 percentile distribution and −1.64 corresponding to the LLN_5 (28, 29). These *z* score cut points have been validated previously on the basis of associations with health outcomes (28, 29). Methodology regarding the GLI calculation of spirometric *z* scores and the spirometers that include GLI software can be found online (http://www.lungfunction.org/ and www.ers-education.org/lungfunction).

In a supplemental analysis, because *z* scores are not commonly used in clinical practice, percent predicted values [(measured/predicted) × 100%] were also calculated for the *z* scores of FEV_1 and FVC that established GLI-defined COPD and restrictive pattern, respectively.

Statistical Analysis

Baseline characteristics, respiratory-related phenotypes, and GLI-defined spirometric categories were first summarized as means and standard deviations or as counts and percentages. Although these descriptive data were published previously (30), the results were included in the present study as a convenient basis for describing the COPDGene cohort.

Adjusted mean values with 95% confidence intervals (95% CIs) for phenotypic features were calculated across

GLI-defined spirometric categories. Several covariates, including age, height, sex, BMI, ethnicity/race, less than a high school education, and current smoking, were identified *a priori* as clinically plausible confounders and were entered into adjusted models. In addition, backward elimination was used to retain medical conditions using a $P \leq 0.05$ significance level. Higher-order terms were tested for age, height, and BMI, and they were included in the model if significant at the $P \leq 0.01$ level. Generalized estimating equations were used to obtain robust variance estimates to account for the clustering of individuals within different centers. For each model, adjusted least squares means and 95% CIs were estimated by spirometric group.

The statistical models used to calculate adjusted means were selected on the basis of distribution of the phenotypic measure and examination of model residuals: negative binomial model for the MMRC grade, γ-distribution for SGRQ and percentage of lung with gas trapping, normal distribution for 6MWD and BD reversibility, and log-normal distribution for percentage of lung with emphysema. Model goodness of fit was assessed by analysis of residuals, and influence diagnostics were calculated.

Next, the associations between GLI-defined spirometric impairment and dichotomous measures of the phenotypic features were evaluated by using logistic regression models adjusted for the previously described covariates. In these analyses, the reference group included participants who had normal spirometry.

Baseline clinical data in COPDGene were nearly complete, with less than 2% missing for most factors, although a percentage of lung with a low attenuation area less than −950 HU on an inspiratory scan was reported in 93.4% of participants (9,459 of 10,131) and a percentage of lung with a low attenuation area less than −856 HU on an expiratory scan in 84.5% of participants (8,558 of 10,131). The pattern, nature, and mechanism of missing data were assessed. For instance, indicator variables for missing values for each phenotypic feature were created, and explanatory variables were regressed on the binary outcomes. Variables associated with these missingness indicators were then used in a multiple imputation analysis (31). Ten datasets were imputed with use of fully conditional specification methods (31). Multiple imputation was performed using the PROC MI procedure in SAS version 9.4 software (SAS Institute, Cary, NC), and the PROC MIANALYZE procedure (SAS 9.4) was used to combine the imputations to obtain the relevant adjusted mean values and standard errors.

SAS version 9.4 software was used in the analyses.

Results

Table 1 summarizes baseline characteristics of the COPDGene cohort: mean age was 59.6 years, 46.9% were female, 32.7% were African American, 13.5% had less than a high school education, mean BMI was 28.8 kg/m^2, and smoking history averaged 44.3 pack-years. The five most prevalent medical conditions were hypertension (43.1%), gastroesophageal reflux (24.9%), osteoarthritis (19.0%), diabetes mellitus (13.0%), and osteoporosis (8.9%). Respiratory-related phenotypes, as unadjusted mean values, included MMRC grade of 1.4, SGRQ score of 27.1, 6MWD of 413 meters, FEV_1 percentage change of 5.7% (post-BD), percentage of lung with emphysema of 6.2%, and percentage of lung with gas trapping of 21.9%. GLI-calculated *z* scores established normal spirometry in 5,100 patients (50.3%), mild COPD in 669 (6.6%), moderate COPD in 865 (8.5%), severe COPD in 2,522 (24.9%), and restrictive pattern in 975 (9.6%). As a basis for comparison, *see* the appendix in the online supplement for additional information on percent predicted values for *z* scores of FEV_1 and FVC that established GLI-defined COPD and restrictive pattern, respectively.

Table 2 reports adjusted mean values with 95% CIs for MMRC grade, SGRQ score, and 6MWD across GLI-defined spirometric categories. Severe COPD had adjusted mean values that were the highest for MMRC grade and SGRQ score and the lowest for 6MWD: 2.42 (95% CI, 2.30–2.54), 41.8 (95% CI, 39.0–44.7), and 335 (95% CI, 316–355), respectively. Moderate COPD and restrictive pattern had intermediate adjusted mean values for MMRC grade and SGRQ score, but the values for 6MWD in these categories were similar to normal spirometry. Mild COPD had adjusted mean values for MMRC grade, SGRQ score, and 6MWD statistically similar to normal spirometry.

Table 4. FEV_1 Percentage Change (Post-BD) and Percentage of Lung with Emphysema and Gas Trapping, according to GLI-defined Spirometric Categories

GLI-defined Spirometric Categories*	Number of Patients	FEV_1 Change Post- BD (%)†	Emphysema (*% of Lung*)‡	Gas Trapping (*% of Lung*)§
Normal	5,100	2.7 (2.4–3.1)	1.8 (1.2–2.3)	12.0 (10.5–13.6)
COPD				
Mild	669	4.4 (3.8–5.0)	4.4 (3.5–5.2)	19.1 (17.0–21.3)
Moderate	865	6.5 (5.7–7.3)	5.3 (4.2–6.4)	22.0 (19.3–24.6)
Severe	2,522	11.7 (10.7–12.6)	11.0 (9.5–12.5)	29.4 (26.0–32.8)
Restrictive pattern	975	5.7 (4.9–6.5)	1.9 (1.4–2.5)	12.2 (10.7–13.7)

Definition of abbreviations: BD = bronchodilator; COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative.

Data are presented as adjusted mean (95% confidence interval) values [adjusted for age, height, sex, body mass index, ethnicity, education (less than high school), current smoking, and type of medical condition]. Missing values are provided by multiple imputation.

*Using GLI equations and pre-BD values (5, 23–27), normal spirometry was defined by FEV_1/FVC ratio and FVC both greater than or equal to the lower limit of normal at the fifth percentile of distribution (LLN_5), COPD (airflow obstruction) by FEV_1/FVC ratio less than LLN_5, and restrictive pattern by FEV_1/FVC ratio greater than or equal to LLN_5 and FVC less than LLN_5 (1, 2, 4, 5). COPD severity is then defined as mild, moderate, or severe based on FEV_1 *z* scores greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, or less than −2.55, respectively (28, 29).

†Calculated as ([post-BD − pre-BD]/pre-BD FEV_1) × 100%. Bronchodilator reversibility included a post-BD FEV_1 showing an increase greater than 12% (2).

‡More than 5% of lung with emphysema (low attenuation area measured with computed tomography less than −950 Hounsfield units on inspiratory scan) establishes a diagnosis of emphysema (11, 20, 21).

§More than 15% of lung with gas trapping (low attenuation area measured with computed tomography less than −856 Hounsfield units on expiratory scan) establishes a diagnosis of gas trapping (11, 20, 21).

Table 3 reports adjusted odds ratios (ORs) with 95% CIs for cross-sectional associations of GLI-defined spirometric impairment with dyspnea (MMRC grade ⩾2), poor rHRQL (SGRQ score ⩾25), and poor exercise performance (6MWD <391 m). Relative to normal spirometry, severe COPD had the strongest associations with dyspnea, poor rHRQL, and poor exercise performance, with adjusted ORs of 10.73 (95% CI, 8.04–14.33), 14.61 (95% CI, 10.09–21.17), and 4.58 (95% CI, 3.42–6.12), respectively. Moderate COPD and restrictive pattern had lower adjusted ORs across these phenotypes but still remained significantly higher than normal spirometry. Mild COPD also had substantially lower adjusted ORs than severe COPD; the values remained significantly higher than normal spirometry only for dyspnea and poor rHRQL.

Table 4 reports adjusted mean values with 95% CIs for FEV_1 percentage change (post-BD), percentage of lung with emphysema, and percentage of lung with gas trapping across GLI-defined spirometric categories. Severe COPD had the highest adjusted mean values for FEV_1 percentage change, percentage of lung with emphysema, and percentage of lung with gas trapping: 11.7 (95% CI, 10.7–12.6), 11.0 (95% CI, 9.5–12.5), and 29.4 (95% CI, 26.0–32.8), respectively. Mild and moderate COPD had intermediate adjusted mean values across these phenotypes, whereas restrictive pattern had an intermediate value for FEV_1 percentage change but otherwise had values for percentage of lung with emphysema and percentage of gas trapping similar to normal spirometry.

Table 5 reports adjusted ORs with 95% CIs for cross-sectional associations of GLI-defined spirometric impairment with BD reversibility (FEV_1 change, >12% and ⩾200 ml), emphysema (>5% emphysema), and gas trapping (>15% gas trapping). Relative to normal spirometry, severe COPD had the strongest associations with BD reversibility, emphysema, and gas trapping, with adjusted ORs of 6.21 (95% CI, 5.06–7.62), 17.79 (95% CI, 10.79–29.32), and 16.28 (95% CI, 9.71–27.30), respectively. Mild and moderate COPD had weaker but still highly significant associations with these phenotypes, whereas restrictive pattern was associated only with BD reversibility.

Table 5. Bronchodilator Reversibility, Emphysema, and Gas Trapping, according to GLI-defined Spirometric Categories

GLI-defined Spirometric Categories*	Number of Patients	Bronchodilator Reversibility†	Emphysema‡	Gas Trapping§
Normal	5,100		1.00	
COPD				
Mild	669	2.76 (2.24–3.40)	4.86 (3.16–7.47)	3.92 (3.12–4.93)
Moderate	865	5.18 (4.29–6.27)	6.41 (4.09–10.05)	5.20 (3.82–7.07)
Severe	2,522	6.21 (5.06–7.62)	17.79 (10.79–29.32)	16.28 (9.71–27.30)
Restrictive pattern	975	4.01 (3.13–5.14)	0.89 (0.60–1.32)	1.15 (0.92–1.42)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GLI = Global Lung Initiative.

Data are presented as adjusted odds ratios (95% confidence intervals) [adjusted for age, height, sex, body mass index, ethnicity, education (less than high school), current smoking, and type of medical condition]. Missing values are provided by multiple imputation.

*Using GLI equations and prebronchodilator (pre-BD) values (5, 23–27), normal spirometry was defined by FEV_1/FVC ratio and FVC both greater than or equal to the lower limit of normal at the fifth percentile of distribution (LLN_5), COPD (airflow obstruction) by FEV_1/FVC ratio less than LLN_5, and restrictive pattern by FEV_1/FVC ratio greater than or equal to LLN_5 and FVC less than LLN_5 (1, 2, 4, 5). COPD severity is then defined as mild, moderate, or severe based on FEV_1 *z* scores greater than or equal to −1.64, less than −1.64 but greater than or equal to −2.55, or less than −2.55, respectively (28, 29).

†Established by FEV_1 change greater than 12% and greater than or equal to 200 ml (post-BD vs. pre-BD FEV_1) (2).

‡More than 5% of lung with emphysema (low attenuation area measured with computed tomography less than −950 Hounsfield units on inspiratory scan) establishes a diagnosis of emphysema (11, 20, 21).

§More than 15% of lung with gas trapping (low attenuation area measured with computed tomography less than −856 Hounsfield units on expiratory scan) establishes a diagnosis of gas trapping (11, 20, 21).

Discussion

Among 10,131 participants ages 45–81 years and with a smoking history averaging 44.3 pack-years (COPDGene), the GLI approach identified spirometric impairment in 5,031 patients (49.7%), including mild COPD in 669 (6.6%), moderate COPD in 865 (8.5%), severe COPD in 2,522 (24.9%), and restrictive pattern in 975 (9.6%). In addition, the type and severity of GLI-defined spirometric impairment yielded graded associations with respiratory-related phenotypes, expressed as either continuous or categorical variables. For example, as shown in Tables 3 and 5, severe COPD had the strongest associations with dyspnea, poor rHRQL, poor exercise performance, BD reversibility, emphysema, and gas trapping. In contrast, mild COPD had weaker associations, with moderate COPD being intermediate between mild and severe COPD. Restrictive pattern was also associated with multiple respiratory-related phenotypes at a level similar to moderate COPD, but it was otherwise not associated with emphysema or gas trapping.

Our results suggest that the GLI approach calculates spirometric *z* scores across a range of COPD severity that is associated with progressive impairments in respiratory-related phenotypes. This finding has clinical implications regarding prioritization of diagnostic and therapeutic strategies. To illustrate, GLI-defined severe COPD should arguably receive high clinical priority, given its strong associations with dyspnea, poor rHRQL, and poor exercise performance (Table 3). Moreover, GLI-defined severe COPD was strongly associated with emphysema (adjusted OR, 17.79; 95% CI, 10.79–29.32) (Table 5), including the highest adjusted mean value for percentage of lung with emphysema of 11.0 (95% CI, 9.5–12.5) (Table 4). Prior work has shown that the emphysema phenotype is characterized by highly impaired respiratory mechanics and poor exercise performance (32). Conversely, GLI-defined mild COPD may represent early disease. Although associated with multiple categorical phenotypes (Tables 3 and 5), GLI-defined mild COPD had only a borderline adjusted mean value for

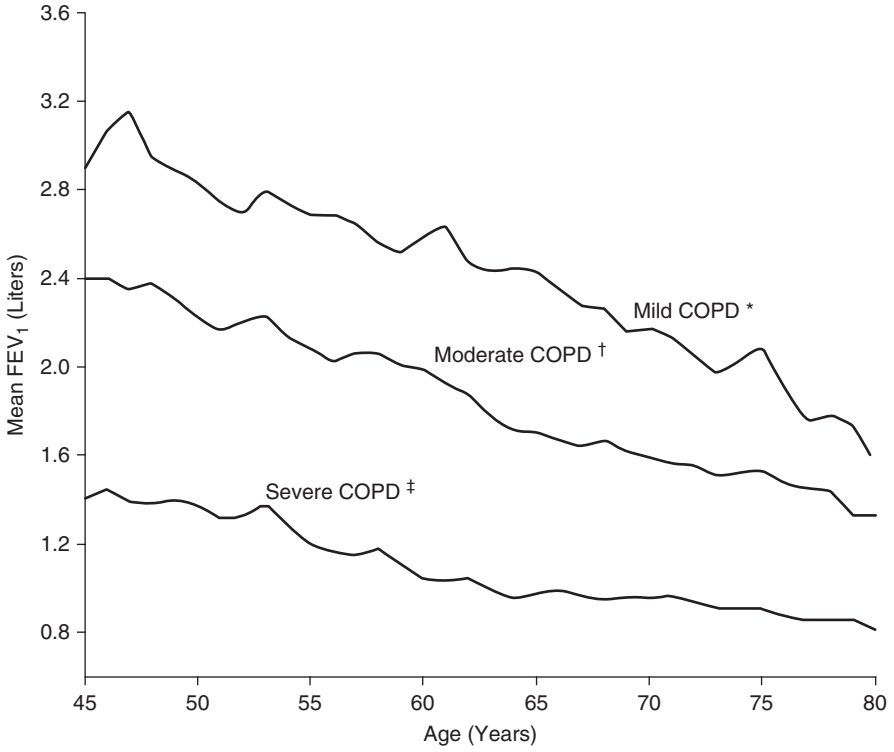

Figure 1. Mean FEV_1 in liters by age and according to chronic obstructive disease (COPD) severity, as defined by Global Lung Initiative–calculated *z* scores and corresponding percentile groups. *FEV_1 *z* score greater than or equal to −1.64, corresponding to the 5th percentile or higher (n = 669). †FEV_1 *z* score less than −1.64 but greater than or equal to −2.55, corresponding to below the 5th percentile but at or above the 0.5th percentile (n = 865). ‡FEV_1 *z* score less than −2.55, corresponding to below the 0.5th percentile (n = 2,522).

percentage of lung with emphysema of 4.4 (95% CI, 3.5–5.2) and had normal adjusted mean values (and 95% CIs) for MMRC grade, SGRQ, and 6MWD (Tables 2 and 4). Our results are consistent with prior work showing that the same *z* score stratification of COPD severity had graded associations with respiratory symptoms, COPD hospitalization, and mortality (28, 29). To further summarize the stratification of COPD severity in the COPDGene cohort, Figure 1 plots the FEV_1 in liters by age and according to categories defined by GLI-calculated *z* scores and corresponding percentile groups (*see* METHODS for diagnostic algorithm).

The present study also highlights the clinical importance of GLI-defined spirometric restrictive pattern. In adjusted analyses and relative to normal spirometry, restrictive pattern was associated with 87% greater odds of having dyspnea, 106% greater odds of having poor rHRQL, and 99% greater odds of having poor exercise performance (Table 3). The present study was not designed to assess the mechanisms underlying restrictive pattern, but participants with CT-confirmed interstitial lung disease were excluded from the analytical sample (*see* METHODS) and restrictive pattern was not associated with CT-measured emphysema or gas trapping (Table 5). In this context, we hypothesize that cardiovascular mechanisms may have contributed to the restrictive pattern, with respiratory muscle weakness as a possible mediator, for three reasons (33–36). First, a reduced FVC has been shown to be associated with the metabolic syndrome, coronary heart disease, and sudden cardiac death (33–35). Second, a reduced FVC is a criterion for restrictive pattern and can result from respiratory muscle weakness (1, 2, 36). Third, smoking is a major cardiovascular risk factor, and the COPDGene participants' smoking history averaged 44.3 pack-years. Future work should be done to evaluate the mechanisms underlying restrictive pattern in persons with a smoking history but an otherwise normal chest CT. Beyond cardiovascular mechanisms and respiratory muscle weakness, other considerations include obesity, osteoporotic kyphosis, and pulmonary hypertension (33–39).

An additional mechanism may underlie the spirometric restrictive pattern of COPDGene participants. Specifically, our results showed that GLI-defined spirometric restrictive pattern was associated with 301% greater odds of having BD reversibility, implying coexisting airflow obstruction. This finding is consistent with prior work suggesting a high prevalence of airways disease in spirometric restrictive pattern (40). Nonetheless, a cardiovascular mechanism remains possible because chronic heart failure is also associated with increased airway resistance that is reversible in response to a BD (41). To address the mechanism of BD reversibility in GLI-defined spirometric restrictive pattern, future work should be done to evaluate whether measures of airway resistance and static lung volumes (e.g., total lung capacity) suggest coexisting airflow obstruction and lung restriction, including their association with heart failure. In particular, as per published guidelines, establishing lung restriction would require confirmation of a reduced total lung capacity (2).

As discussed earlier, the GLI approach rigorously accounts for age-related changes in lung function, thus increasing diagnostic accuracy when establishing a spirometric impairment and, in turn, respiratory disease (1, 4, 5). This strategy has strong clinical and public health implications, given the rapid aging of populations worldwide. By 2050, 400 million people worldwide will be 80 years of age and older (6). The aging shift includes developing countries, where the population 65 years of age and older will double over the next 20 years (6). Developed countries also have rapidly aging populations. For example, the percentage of Americans 65 years of age and older will have increased from 12.9% in 2009 to 20% in 2030 (7).

The current standard of practice (and alternative approach) for establishing spirometric impairment is based on criteria put forth by the Global Initiative for Obstructive Lung Disease (GOLD) (42), but these criteria have limitations regarding age-related changes in lung function. Specifically, GOLD applies a fixed ratio of 0.70 for FEV_1/FVC ratio across all ages,

obscuring the distinction between age-related airflow limitation and COPD-related airflow obstruction. GOLD additionally expresses FEV_1 and FVC as percentage of predicted values, assuming incorrectly that variability in spirometric performance is constant across all ages (1–5). To illustrate the effect of aging on spirometric function, an FEV_1/FVC ratio less than 0.70 is frequently seen in otherwise healthy, asymptomatic never-smokers starting at age 45–50 years and older (1–5, 43), and the FEV_1 in a white male of average height at the fifth percentile of distribution (calculated in a reference population of healthy never-smokers) is equal to 74% of the predicted value at age 30 years but equal to only 63% of the predicted value at age 70 years (44).

The age-related limitations of GOLD criteria may misidentify respiratory disease. Using data derived from COPDGene, prior work has shown that GLI-defined normal spirometry, even when identified as spirometric impairment by GOLD, yielded adjusted mean values and 95% CIs in the normal range for respiratory-related phenotypes, including CT-measured emphysema and gas trapping (30). Other work has additionally shown that the GOLD misidentification of normal spirometry as spirometric impairment was not associated longitudinally with impaired mobility, COPD hospitalization, or mortality (29, 43, 45, 46). Consequently, the practice of validating GOLD spirometric criteria on the basis of associations with respiratory-related phenotypes has serious limitations. In particular, a requisite step for the accurate calculation of risk (e.g., ORs for categories of spirometric impairment) is the appropriate identification of a normal-for-age spirometric group.

Accordingly, in an era of rapidly aging populations worldwide, the use of spirometric criteria that do not rigorously consider age-related changes in lung function may misidentify respiratory disease and, in turn, misdirect patient care and public health policy. We posit that the GLI approach addresses these concerns by providing a more age-appropriate spirometric definition of respiratory disease. As discussed earlier, advancing age is associated with high symptom burden, multimorbidity, and polypharmacy (8–10), highlighting the importance of greater diagnostic accuracy. There is additionally a strong clinical precedent for z scores, as evidenced by their use in bone mineral density testing to diagnose osteopenia and osteoporosis as well as their wide application in constructing percentile growth curves in children (1, 4).

With regard to the limitations of diagnostic criteria for establishing disease, it is important to note that clinical decisions often require a three-zone interpretation of present, absent, or uncertain, rather than yes versus no (47). Although the results of the present study suggest that GLI-defined spirometric impairment establishes clinically meaningful respiratory disease, clinical judgment is required in patients who have spirometric results just above or below diagnostic thresholds (e.g., normal spirometry vs. mild COPD). An additional diagnostic limitation is that current threshold values for CT-based diagnoses of emphysema and gas trapping require further validation, as they have not been specifically established in healthy reference populations of asymptomatic lifelong never-smokers (48, 49). Specifically, normal aging can lead to structural changes of the lung parenchyma and airways, yielding senile emphysema and increased gas trapping, respectively (1, 50).

In conclusion, using data from COPDGene, we found graded associations between the type and severity of GLI-defined spirometric impairment and respiratory-related phenotypes. On the basis of these results, we posit that GLI-defined spirometric impairment establishes clinically meaningful respiratory disease. ■

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