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A Novel Spirometric Measure Identifies Mild COPD Unidentified by Standard Criteria

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BACKGROUND: In chronic obstructive pulmonary disease, both smaller and larger airways are affected. FEV_1 mainly reflects large airways obstruction, while the later fraction of forced exhalation reflects reduction in terminal expiratory flow. In this study, the objective was to evaluate the relationship between spirometric ratios, including the ratio of forced expiratory volume in 3 and 6 seconds (FEV_3/FEV_6), and small airways measures and gas trapping at quantitative chest CT scanning, and clinical outcomes in the Genetic Epidemiology of COPD (COPDGene) cohort.

METHODS: Seven thousand eight hundred fifty-three current and ex-smokers were evaluated for airflow obstruction by using recently defined linear iteratively derived equations of Hansen et al to determine lower limit of normal (LLN) equations for prebronchodilator FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6, and FEV_3/FVC. General linear and ordinal regression models were applied to the relationship between prebronchodilator spirometric and radiologic and clinical data.

RESULTS: Of the 10,311 participants included in the COPDGene phase I study, participants with incomplete quantitative CT scanning or relevant spirometric data were excluded, resulting in 7,853 participants in the present study. Of 4,386 participants with FEV_1/FVC greater than or equal to the LLN, 15.4% had abnormal FEV_3/FEV_6. Compared with normal FEV_3/FEV_6 and FEV_1/FVC, abnormal FEV_3/FEV_6 was associated with significantly greater gas trapping; St. George's Respiratory Questionnaire score; modified Medical Research Council dyspnea score; and BMI, airflow obstruction, dyspnea, and exercise index and with shorter 6-min walking distance (all $P < .0001$) but not with CT scanning evidence of emphysema.

CONCLUSIONS: Current and ex-smokers with prebronchodilator FEV_3/FEV_6 less than the LLN as the sole abnormality identifies a distinct population with evidence of small airways disease in quantitative CT scanning, impaired indexes of physical function and quality of life otherwise deemed normal by using the current spirometric definition.

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KEY WORDS: airway obstruction; COPD; spirometry; thoracic radiology

ABBREVIATIONS: 6MWD = 6-min walking distance; BODE = BMI, airflow obstruction, dyspnea, and exercise; COPDGene = Genetic Epidemiology of COPD; E/I MLA = expiratory to inspiratory ratio of mean lung attenuation; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal; mMRC = modified Medical Research Council; NHANES III = third National Health and Nutrition Examination Survey; SGRQ = St. George's Respiratory Questionnaire; WA = wall area

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Expiratory airflow obstruction is the key finding supporting COPD diagnosis. Airflow obstruction prevalence varies widely by definition used.[1-5] Recently, Hansen et al[1] defined equations characterizing prebronchodilator normal values for several spirometric variables by using the third National Health and Nutrition Examination Survey (NHANES III) database. For this analysis, the lower limit of normal (LLN) resides at the 5th percentile of each decade of age and results in a more balanced estimation of LLN than have previous approaches.[6,7] These new reference ranges were further evaluated here.[1]

Small airways are frequently involved early in the course of COPD, with significant pathologic changes before symptom onset and spirometric changes.[8-10] FEV_1 mainly reflects large airway obstruction. Because the later fraction of forced exhalation (eg, forced expiratory volume in 3 s [FEV_3]) better reflects smaller airway contributions, it may be a more sensitive measure to diagnose early airway obstruction in COPD.[11,12] Spirometric ratios have less variability than do timed forced expirations.[12,13] Accumulating evidence suggests many current or former smokers have clinical, radiologic, and physiologic abnormalities not identified by means of currently used spirometric measures.[9,14-16] The FEV_1 FVC ratio may remain within the normal range even after considerable airway damage has occurred. FEV_3/forced expiratory volume in 6 s (FEV_6) and FEV_3/FVC have been proposed as measures capable of detecting small airway disease and, hence, mild COPD manifestations.[11,17] In support of this concept, a greater number of smokers were below the LLN for FEV_3/FEV_6 than for FEV_1/FEV_6[1] and below the LLN for FEV_3/FVC than for FEV_1/FVC.[1,18] However, the clinical importance of an isolated low prebronchodilator FEV_3/FEV_6 or FEV_3/FVC in smokers remains unknown.

We aimed to determine whether FEV_3/FEV_6 less than the LLN and FEV_3/FVC less than the LLN were associated with quantitative CT scanning and other COPD-related clinical outcomes in subjects with normal prebronchodilator spirometric findings according to standard criteria (eg, FEV_1/FVC greater than the LLN) in the Genetic Epidemiology of COPD (COPDGene) cohort.[19] Quantitative CT scanning is useful for in vivo assessment of lung morphologic changes and provides visual and quantitative assessment of COPD.[20,21] In particular, quantitative CT scanning is useful to quantify emphysema percentage and distribution, airway dimension changes, and gas trapping severity in COPD.[22-24] We hypothesized that abnormal FEV_3/FEV_6 and FEV_3/FVC would be associated with quantitative CT scanning abnormalities and adverse clinical manifestations.

Materials and Methods

Study Population and Data Collection

We used data from COPDGene for participants enrolled between 2007 and 2011.[19] The cohort includes 10,311 non-Hispanic white and black men and women, 45 to 80 years old, with a smoking history $\geq$ 10 pack-years. The COPDGene study excluded those who were pregnant and those with previous lung resection surgery, active cancer treatment, or history of lung disease other than asthma and COPD.[19] For the present study, excluding those with incomplete CT scanning and spirometric data yielded 7,853 participants (e-Appendix 1). As clinical and functional correlates, we used St. George's Respiratory Questionnaire (SGRQ)[25] (permission was obtained for use of this instrument); modified Medical Research Council (mMRC) dyspnea scale[26]; BMI, airflow obstruction, dyspnea, and exercise (BODE) scores[27]; and 6-min walking distance (6MWD).[28] Institutional review boards approved the study at 21 participating centers (e-Appendix 1). Participants provided written informed consent.

Spirometry and Quality Control

Spirometry was performed using an ultrasound-based spirometer (EasyOne Model 2001, ndd Medizintechnik AG) before and after albuterol administration according to European Respiratory Society/American Thoracic Society recommendations.[29] Positive bronchodilator response was defined as an increase in FEV_1 and/or FVC $\geq$ 12% of baseline and 200 mL.[29] e-Appendix 1 presents quality control assurance details.

In our analysis, we defined LLN criteria abnormality originating from spirometric data as in the NHANES III, in which only prebronchodilator responses were collected.[1] For our analysis, values of the prebronchodilator FEV_1, FVC, FEV_3, and FEV_6 from the best test were chosen; the best test was defined as the maneuver with the largest FVC and FEV_1 sum, and % predicted values were calculated from NHANES III equations.[6,30]

Quantitative CT Scanning Analysis

CT scans were acquired at full inspiration and after tidal expiration (e-Appendix 1). Emphysema is defined as morphologic loss of alveolar tissue.[31] Percentage of low attenuation areas below −950 Hounsfield units on end-inspiratory CT scans is thought to represent

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emphysema percentage.[22] Airway disease was assessed by using the segmental airway wall area (WA) percentage.[32] Two additional measurements assessed small airway disease by means of expiratory scans. Gas trapping percentage was defined as the percentage of lung voxels below −856 Hounsfield units on expiratory scans.[33] Expiratory to inspiratory ratio of mean lung attenuation (E/I MLA) was defined as the ratio of mean lung attenuation from density histograms on inspiratory and expiratory scans.[34]

Statistical Analyses

SPSS 22.0 procedures were used (IBM Corp.) (e-Appendix 1). Relationships between spirometry (independent variable) and CT scanning, clinical, and functional correlates (dependent variables) were assessed by means of multiple linear regression models by using age, sex, race, smoking pack-years, BMI, and CT scanner type (only for CT scanning measures) as covariates. Covariates were retained if $P < .10$. Quantitative CT scanning, SGRQ, and 6MWD data were log transformed; regression coefficients (βs) were then back transformed to aid interpretation. Compared with a reference category, relative differences for outcome variables were determined by using the formula $(e^{\beta} - 1) \times 100\%$, while holding other predictors constant (e-Appendix 1). A proportional odds model was used for ordinal outcomes (BODE and mMRC scores). Analyses were performed separately for the whole study population and the FEV_1/FVC greater than or equal to the LLN subgroup. $P < .05$ was considered statistically significant.

To define impairments in the FEV_1/FVC greater than or equal to the LLN subgroup, we selected explanatory variables predicting important outcomes and reasonable thresholds in COPD: FEV_1 % predicted < 65%, mMRC dyspnea score ≥ 2, 6MWD < 350 meters, SGRQ score > 25, and BODE score > 2.[27,35] To define clinically meaningful radiologic abnormality, we used newly described cutoffs: 3.5 for emphysema percentage and 21 for gas trapping percentage.[36]

Results

Spirometric Characterization

Subject characteristics for the 7,853 participants are presented in Table 1. Prebronchodilator FEV_1/FVC was less than the LLN in 3,467 participants (44.1%), thus defining, by standard criteria, those having airflow obstruction; the remaining 4,386 participants (55.9%) had no recognizable airflow obstruction.

Abnormality of FEV_1/FVC and FEV_3/FEV_6 in the Overall Group

In the overall group, participants with either FEV_1/FVC (3,467; 44.1%) or FEV_3/FEV_6 (3,965; 50.5%) criteria less than the LLN were older, had lower BMI, had a longer smoking history, and were more likely white. These individuals also had lower spirometric measurements; higher pulmonary structural impairments, dyspnea scores, and SGRQ and BODE scores; and shorter 6MWD (Table 1). Correlates of FEV_1/FVC and FEV_3/FEV_6 abnormality in the overall subject group are presented in e-Table 1.

Correlates of FEV_3/FEV_6 Abnormality in Participants With FEV_1/FVC Greater Than or Equal to the LLN

Of subjects with normal FEV_1/FVC, more (677; 15.4%) had FEV_3/FEV_6 less than the LLN than had FEV_3/FVC less than the LLN (312; 7.1%). Those with FEV_3/FEV_6 less than the LLN had significantly worse spirometric and clinical outcomes and CT scanning indexes (with the exception of emphysema percentage) than did those with FEV_3/FEV_6 greater than or equal to the LLN (Fig 1, Table 2). Although individuals with FEV_3/FVC less than the LLN had significantly worse spirometric and SGRQ results, their quantitative CT scanning results (except E/I MLA) were not significantly different from those with FEV_3/FVC greater than or equal to the LLN (Table 2).

Importantly, association of FEV_3/FEV_6 abnormality with structural and clinical outcomes was significant—though somewhat weaker than in the overall group (e-Table 1)—in participants without obstruction (FEV_1/FVC greater than or equal to the LLN) (Table 3): gas trapping percentage was 27.5% greater, WA percentage was 1.8% greater, and E/I MLA was 2.0% greater than in those with FEV_3/FEV_6 greater than or equal to the LLN. We also observed 40.8% greater SGRQ score and 7.2% shorter 6MWD in those with abnormal FEV_3/FEV_6. They were also more likely to be in the higher mMRC category (adjusted OR, 1.6; 95% CI, 1.4-1.9; $P < .0001$) and BODE index (adjusted OR, 2.8; 95% CI, 2.1-3.7; $P < .0001$) than were subjects with FEV_3/ FEV_6 greater than or equal to the LLN (Table 3).

Finally, to understand better whether reversible smooth muscle contraction was a significant determinant of these findings, we excluded 1,708 (21.7%) participants with a positive bronchodilator response. Results in those 3,868 with a negative bronchodilator response and with FEV_1/FVC greater than or equal to the LLN showed essentially the same associations of FEV_3/FEV_6 abnormality as in the wider group (e-Table 2).

Multivariable analyses in the subgroup without airflow obstruction but with FEV_3/FVC less than the LLN (Table 4) showed significant associations with CT scanning parameters reflecting small airway disease (gas trapping percentage and E/I MLA), SGRQ score, mMRC score, and BODE score. Notably, however, the strength of these associations was lower than for FEV_3/FEV_6 (Tables 3, 4).

TABLE 1] Characteristics of the Study Population Regarding FEV_1/FVC and FEV_3/FEV_6 LLN

Characteristic	FEV_1/FVC		FEV_3/FEV_6	
	≥ LLN (n = 4,386)	< LLN (n = 3,467)	≥ LLN (n = 3,888)	< LLN (n = 3,965)
Age, y	56.9 (51-64)	62.7 (55-69)[a]	57.1 (51-64)	61.9 (54-69)[b]
Male sex, %	51.7	55.8[a]	53.8	53.3
Race, %				
White	64	79	66	76
Black	36	21[a]	34	24[b]
BMI, kg/m^2	29.4 ± 6.0	27.8 ± 6.1[a]	29.6 ± 5.9	27.8 ± 6.1[b]
Smoking history,[c] pack-y	36 (24-48)	45 (34-65)[a]	35 (23-48)	45 (33-65)[b]
Spirometric results				
Post-BD $FEV_1/FVC \geq 70$, %	86.8	8.6[a]	87.8	17.5[b]
Pre-BD FEV_1, % predicted	88.7 ± 15.7	52.7 ± 22.2[a]	89.9 ± 15.3	56.0 ± 23.2[b]
Pre-BD FEV_3, % predicted	95.2 ± 17.6	67.3 ± 23.4[a]	91.8 ± 15.1	78.7 ± 20.4[b]
Pre-BD FEV_6, % predicted	91.0 ± 15.1	70.1 ± 20.5[a]	91.6 ± 14.7	72.1 ± 20.8[b]
Pre-BD FVC, % predicted	91.1 ± 15.4	77.7 ± 20.7[a]	91.8 ± 15.1	78.7 ± 20.4[b]
Post-BD FEV_1, % predicted	91.3 ± 15.8	56.9 ± 23.2[a]	92.4 ± 15.4	60.2 ± 24.0[b]
Pre-BD FEV_1/FVC, %	75.3 (71.4-79.1)	52.8 (39.6-62.2)[a]	76.1 (72.1-79.6)	56.2 (41.8-65.0)[b]
Post-BD FEV_1/FVC, %	77.0 (72.8-81.3)	53.9 (40.6-63.9)[a]	77.7 (73.3-81.7)	57.4 (42.5-67.2)[b]
Pre-BD FEV_1/FEV_6, %	78.4 (75.3-81.5)	59.8 (48.3-67.9)[a]	79.0 (76.1-81.9)	62.7 (50.0-70.1)[b]
Pre-BD FEV_3/FVC, %	89.9 (87.4-92.3)	75.0 (64.9-81.6)[a]	90.4 (87.8-92.6)	77.3 (66.6-83.9)[b]
Pre-BD FEV_3/FEV_6, %	93.3 (92.0-94.5)	85.3 (78.5-89.1)[a]	93.6 (92.5-94.6)	86.7 (79.6-89.8)[b]
Quantitative CT scanning indexes				
Emphysema,[d] %	1.0 (0.4-2.5)	7.2 (2.2-18.7)[a]	1.1 (0.4-2.6)	5.3 (1.5-16.8)[b]
Gas trapping,[e] %	9.0 (4.2-15.6)	34.0 (18.0-53.6)[a]	8.9 (4.2-15.4)	30.0 (14.4-50.8)[b]
E/I MLA	0.83 (0.80-0.87)	0.91 (0.87-0.95)[a]	0.83 (0.79-0.87)	0.91 (0.86-0.94)[b]
Segmental airway WA, %	60.4 ± 3.0	62.5 ± 3.1[a]	60.3 ± 3.0	62.4 ± 3.2[b]
HRQL and functional measures				
mMRC dyspnea score[f]	0.9 ± 1.2	1.9 ± 1.5[a]	0.8 ± 1.2	1.8 ± 1.5[b]
SGRQ, total score	11.3 (3.5-29.5)	36.5 (18.2-54.5)[a]	10.5 (3.2-27.2)	34.8 (16.2-53.1)[b]
6MWD,[g] m	440 ± 109	376 ± 122[a]	445 ± 108	379 ± 122[b]
BODE score[g,h]	0.9 ± 1.2	1.9 ± 1.5[a]	0.8 ± 1.2	1.8 ± 1.5[b]

Data are mean ± SD or median (interquartile range 25-75), as appropriate. Statistical significance was determined by means of the two-sample *t*-test for normally distributed continuous variables and the Mann-Whitney *U* test for comparison of continuous nonnormal data between the FEV_3/FEV_6 greater than or equal to the LLN and less than the LLN groups. 6MWD = 6-min walking distance; BD = bronchodilator; BODE = BMI, airflow obstruction, dyspnea, and exercise; E/I MLA = expiratory to inspiratory ratio of mean lung attenuation; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; HRQL = health-related quality of life; LLN = lower limit of normal; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire; WA = wall area.

[a]Denotes $P < .0001$ compared with participants with FEV_1/FVC greater than or equal to the LLN.

[b]Denotes $P < .0001$ compared with participants with FEV_3/FEV_6 greater than or equal to the LLN.

[c]Data available for 7,755 participants.

[d]Lung attenuation area percentage < −950 Hounsfield units on inspiration.

[e]Lung attenuation area percentage < −856 Hounsfield units on expiration.

[f]Data available for 7,849 participants.

[g]Data available for 7,756 participants.

[h]BMI, postbronchodilator FEV_1 % predicted, mMRC score, and 6MWD were integrated to calculate the 10-point BODE index.[27]

Impairments in Subjects With FEV_3/FEV_6 Abnormality and FEV_1/FVC Greater Than or Equal to the LLN

Among those with normal spirometric results according to FEV_1/FVC criteria, impairments in radiologic and clinical outcomes were significantly more common among those with FEV_3/FEV_6 less than the LLN than among participants with FEV_3/FEV_6 greater than or equal to the LLN, except CT scanning evidence of emphysema (Fig 2, e-Table 3). This finding further

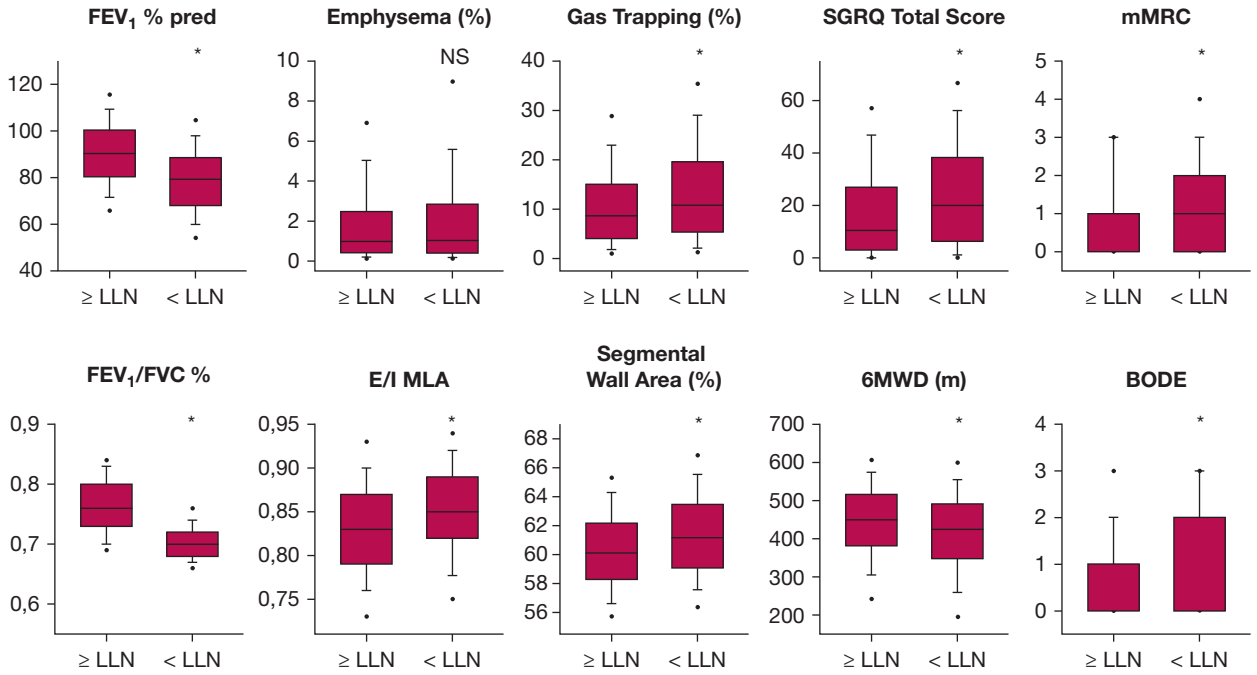

Figure 1 – *Comparison of functional, structural, and COPD-related clinical indexes of participants with forced expiratory volume in 3 s/forced expiratory volume in 6 s (FEV_3/FEV_6) greater than or equal to the LLN (n = 3,709) vs those with FEV_3/FEV_6 less than the LLN (n = 677) among those without clinically defined airflow obstruction according to prebronchodilator FEV_1/FVC greater than or equal to the LLN (n = 4,386). Participants with FEV_3/FEV_6 less than the LLN had significantly more impairment on quantitative CT scans (gas trapping percentage, E/I MLA, segmental wall area), worse FEV_1 % predicted and FEV_1/FVC, greater dyspnea perception and SGRQ score, and lower 6MWD. The central horizontal line on each box represents the median, the ends of the boxes are 25th and 75th percentiles, and the error bars are the 10th and 90th percentiles. The lower and upper solid circles (•) represent minimum and maximum values in each group, respectively. P values were derived from the two-sample t-test for normally distributed continuous variables and from the Mann-Whitney U test for continuous nonnormal data. *P < .0001; not significant (NS) = P > .05. The BODE index includes BMI, postbronchodilator FEV_1 % predicted, mMRC score, and 6MWD. 6MWD = 6-min walking distance; BODE = BMI, airflow obstruction, dyspnea, and exercise; E/I MLA = expiratory to inspiratory ratio of mean lung attenuation; LLN = lower limit of normal; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.*

supports that abnormal FEV_3/FEV_6 in patients with otherwise normal spirometric results have worse clinical symptoms, less functional capacity, and worse gas trapping but not significantly greater emphysema percentage.

Discussion

We identified 677 current and former smokers (15.4%) classified as nonobstructed by using standard prebronchodilator spirometric criteria (FEV_1/FVC greater than or equal to the LLN) in the COPDGene population in whom FEV_3/FEV_6 was abnormal. This group with FEV_3/FEV_6 as the sole abnormality showed impairments in quantitative CT scanning indexes (gas trapping percentage, E/I MLA, and segmental airway WA but not emphysema percentage), as well as shorter 6MWD and increased mMRC, SGRQ, and BODE scores. We believe that this analysis establishes a criterion that detects mild structural, functional, and clinical abnormalities in subjects otherwise deemed healthy according to standard spirometric definitions.

Increasing evidence suggests that a large fraction of current or former smokers have clinical, radiologic, and physiologic disease not consistently identified by means of spirometry.[9,14-16] FEV_3/FEV_6 and FEV_3/FVC identified significantly more subjects below the LLN than did FEV_1/FVC and FEV_1/FEV_6 in the never-smoker NHANES III population, but the clinical importance of these abnormalities is unknown.[1]

Our study, to our knowledge, is the first to characterize extensively smokers with FEV_3/FVC or FEV_3/FEV_6 as the sole abnormality with respect to pulmonary structural impairment and functional and patient-reported outcomes. We found abnormality in small airway measures (gas trapping percentage and E/I MLA), segmental airway WA, FEV_1 % predicted, FEV_1/FVC % predicted, SGRQ score, mMRC score, BODE score, and 6MWD, each associated with abnormal FEV_3/FEV_6 (Tables 1-3, e-Tables 4, 5).

Compared with FEV_1/FVC, FEV_3/FVC more sensitively identified reductions in terminal expiratory flow and, accordingly, was able to be used to diagnose mild airflow

TABLE 2] Functional, Structural, and Clinical Characteristics of Participants With Prebronchodilator FEV_1/FVC Greater Than or Equal to the LLN Divided Into Subgroups of Normal and Abnormal FEV_3/FEV_6 and FEV_3/FVC

Characteristic	$FEV^1/FVC \geq LLN$						
	Total	$FEV_3/FEV_6 \geq LLN$	$FEV_3/FEV_6 < LLN$	*P* value[a]	$FEV_3/FVC \geq LLN$	$FEV_3/FVC < LLN$	*P* value[b]
No. (%)	4,386 (100)	3,709 (84.6)	677 (15.4)	…	4,074 (92.9)	312 (7.1)	…
Age, y	58.0 ± 8.7	58.0 ± 8.7	57.9 ± 8.6	.78	58.2 ± 8.7	56.2 ± 7.6	< .0001
Male sex, %	51.7	53.0	44.9	< .0001	51.2	58.0	.02
Smoking history, pack-y	35.7 (23.7-48.3)	35.1 (23.0-48.0)	38.0 (27.7-52.8)	< .0001	35.5 (23.3-48.1)	36.7 (25.9-48.8)	.15
FEV_1, % predicted	88.7 ± 15.7	90.4 ± 15.1	79.1 ± 15.6	< .0001	89.0 ± 15.7	85.0 ± 14.7	< .0001
FEV_3, % predicted	95.2 ± 17.6	96.5 ± 17.2	88.3 ± 18.0	< .0001	95.6 ± 17.6	90.7 ± 16.1	< .0001
FEV_6, % predicted	91.0 ± 15.1	91.8 ± 14.6	86.7 ± 16.8	< .0001	91.1 ± 15.1	89.8 ± 14.9	< .0001
FVC, % predicted	91.1 ± 15.4	91.8 ± 14.9	87.4 ± 17.1	< .0001	90.8 ± 15.3	94.8 ± 16.1	< .0001
FEV_1/FVC, %	75.3 (71.4-79.1)	76.4 (72.7-79.8)	70.2 (68.2-72.1)	< .0001	75.8 (72.0-79.4)	69.5 (67.8-71.4)	< .0001
FEV_3/FEV_6, %	93.3 (92.0-94.5)	93.6 (92.6-94.7)	90.6 (89.8-91.4)	< .0001	93.4 (92.1-94.6)	91.7 (90.6-92.7)	< .0001
FEV_3/FVC, %	89.9 (87.5-92.3)	90.6 (88.2-92.6)	86.9 (84.9-88.4)	< .0001	90.2 (88.0-92.5)	83.8 (82.3-85.4)	< .0001
Emphysema,[c] %	0.98 (0.39-2.53)	0.97 (0.40-2.47)	1.03 (0.38-2.85)	.18	0.98 (0.39-2.48)	1.08 (0.41-3.09)	.12
Gas trapping,[d] %	9.0 (4.2-15.6)	8.6 (4.0-15.1)	10.8 (5.3-19.6)	< .0001	9.0 (4.1-15.6)	10.0 (5.2-15.4)	.09
E/I MLA	0.83 (0.80-0.87)	0.83 (0.79-0.87)	0.85 (0.81-0.89)	< .0001	0.83 (0.79-0.87)	0.84 (0.80-0.87)	.04
Segmental airway WA, %	60.4 ± 3.0	60.3 ± 3.0	61.4 ± 3.2	< .0001	60.4 ± 3.1	60.4 ± 3.0	.87
SGRQ, total score	11.3 (3.5-29.5)	10.4 (3.0-27.0)	19.9 (6.2-38.3)	< .0001	11.1 (3.5-29.1)	15.0 (3.8-34.7)	.01
mMRC dyspnea score[e]	0.88 ± 1.25	0.8 ± 1.2	1.2 ± 1.4	< .0001	0.9 ± 1.2	1.0 ± 1.3	.05
6MWD,[f] m	440 ± 109	444 ± 108	415 ± 116	< .0001	439 ± 109	447 ± 118	.22
BODE score[f,g]	0.6 ± 1.0	0.5 ± 0.9	0.9 ± 1.3	< .0001	0.6 ± 1.0	0.7 ± 1.1	.09

Data are expressed as mean ± SD or median (interquartile range 25-75) as appropriate. Statistical significance was determined by means of the two-sample *t*-test for normally distributed continuous variables and the Mann-Whitney *U* test for comparison of continuous nonnormal data between the FEV_3/FEV_6 greater than or equal to the LLN vs less than the LLN groups and the FEV_3/FVC greater than or equal to the LLN vs less than the LLN groups. See Table 1 legend for expansion of abbreviations.

[a]Univariate comparison between FEV_3/FEV_6 greater than or equal to the LLN and FEV_3/FEV_6 less than the LLN.

[b]Univariate comparison between FEV_3/FVC greater than or equal to the LLN and FEV_3/FVC less than the LLN.

[c]Lung attenuation area percentage < −950 Hounsfield units on inspiration.

[d]Lung attenuation area percentage < −856 Hounsfield units on expiration.

[e]Data available for 4,385 participants.

[f]Data available for 4,364 participants.

[g]The BODE index includes BMI, postbronchodilator FEV_1 % predicted, mMRC score, and 6MWD.[27]

TABLE 3] General Linear Regression Models of Difference in Quantitative CT Scanning Indexes, Quality of Life, and 6MWD in Participants With FEV_3/FEV_6 Less Than the LLN Among Those With FEV_1/FVC Greater Than or Equal to the LLN (n = 4,386)

	% Difference					OR	
Parameter	Gas Trapping,[a,b] %	Wall Area,[a,b] %	E/I MLA,[a,b] %	SGRQ Score[a,c]	6MWD[a,c]	mMRC Score[c,d]	BODE Score[c,d]
FEV_3/FEV_6 < LLN vs FEV_3/FEV_6 ≥ LLN[e]	27.5	1.8	2.0	40.8	−7.2	1.6	2.8
95% CI[f]	18.1-37.8	1.4-2.2	1.6-2.4	28.0-5.0	−9.4 to −5.0	1.4-1.9	2.1-3.7
e^{β}	1.275	1.018	1.020	1.408	0.928	…	…
P value	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001

e^{β} = exponential (back-transformed) regression coefficient. See Table 1 legend for expansion of other abbreviations.
[a]Gas trapping percentage, wall area percentage, E/I MLA, SGRQ score, and 6MWD were natural log transformed. The displayed coefficients (percentage difference and 95% CI) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. For example, for gas trapping percentage, the expected mean gas trapping percentage of the FEV_3/FEV_6 less than the LLN group is higher than that of the FEV_3/FEV_6 greater than or equal to the LLN group by 27.5%.
[b]Models controlled for sex, age, race, BMI, smoking history (pack-years of smoking), and CT scanner type.
[c]Models controlled for sex, age, race, BMI, and smoking history (pack-years of smoking).
[d]Data are ORs indicating the relative odds increase for a higher mMRC or BODE score between the two groups. For example, the estimated odds of having a 1-unit higher mMRC dyspnea score (worsening from 0 to 4) for FEV_3/FEV_6 less than the LLN is 1.6 of the odds compared with that for FEV_3/FEV_6 greater than or equal to the LLN. BODE index scores were categorized into 4 severity stages, with scores of 0-2, 3-4, 5-6, and 7-10.
[e]FEV_3/FEV_6 greater than or equal to the LLN data were used as the reference category.
[f]Exponential (back-transformed) 95% CIs.

obstruction.[37] Morris et al[37] suggested that isolated reduction in FEV_3/FVC (without other spirometric abnormality) may indicate early injury accompanied by hyperinflation and gas trapping.[38] We found that an isolated FEV_3/FVC abnormality was not diagnostic of either CT scanning abnormalities or of COPD-related patient-reported or functional outcomes (Tables 2, 4).

Structural features in quantitative CT scanning were correlated with FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6, and FEV_3/FVC (e-Table 6). The CT scanning features that had the strongest correlation with spirometric ratios were small airway measures. These findings are similar to previous results showing that airflow obstruction correlates with emphysema percentage, gas trapping

TABLE 4] General Linear Regression Models of Difference in Quantitative CT Scanning Indexes and Quality of Life in Participants With FEV_3/FVC Less Than the LLN Among Those With FEV_1/FVC Greater Than or Equal to the LLN (n = 4,386)

	% Difference			OR	
Parameter	Gas Trapping,[a,b] %	E/I MLA,[a,b] %	SGRQ Score[a,c]	mMRC Score[c,d]	BODE Score[c,d]
FEV_3/FVC < LLN vs FEV_3/FVC ≥ LLN[e]	18.8	1.2	15.4	1.3	1.8
95% CI[f]	6.6-32.3	0.4-2.0	0.9-32.1	1.03-1.61	1.2-2.6
e^{β}	1.188	1.012	1.154	…	…
P value	.002	< .0001	.037	.029	.004

See Table 1 and 3 legends for expansion of abbreviations.
[a]Gas trapping percentage, E/I MLA, and SGRQ score were natural log transformed. The displayed coefficients (percentage difference and 95% CI) are back-transformed regression coefficients that correspond to the relative differences between the two groups in percent in ratios. For example, for gas trapping percentage, the expected mean gas trapping percentage of the FEV_3/FEV_6 less than the LLN group is higher than that of the FEV_3/FEV_6 greater than or equal to the LLN group by 18.8%.
[b]Models controlled for sex, age, race, BMI, smoking history (pack-years of smoking), and CT scanner type.
[c]Models controlled for sex, age, race, BMI, and smoking history (pack-years of smoking).
[d]Data are ORs indicating the relative odds increase for a higher mMRC or BODE score between the two groups. For example, the estimated odds of having a 1-unit higher mMRC dyspnea score (worsening from 0 to 4) for FEV_3/FEV_6 less than the LLN is 1.3 of the odds compared with that for FEV_3/FEV_6 greater than or equal to the LLN. BODE index scores were categorized into 4 severity stages, with scores of 0-2, 3-4, 5-6, and 7-10.
[e]FEV_3/FVC greater than or equal to the LLN data were used as the reference category.
[f]Exponential (back-transformed) 95% CIs.

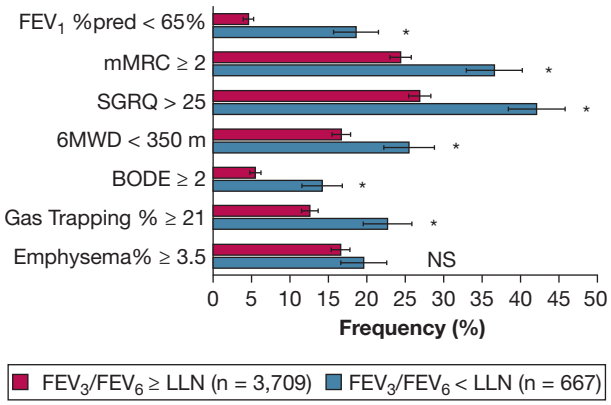

Figure 2 – *Comparison of participants with prebronchodilator FEV_1/FVC greater than or equal to the LLN (n = 4,386) divided into subgroups of normal (red bars, n = 3,709) and abnormal (blue bars, n = 677) FEV_3/FEV_6 deemed to be abnormal by means of functional, structural, and clinical outcomes. The bars represent the proportion of the population, and the error bars represent the lower and upper bounds of the 95% CIs. Statistical significance was determined by using the Pearson χ^2 statistic. * = P < .0001; NS = P > .05. The BODE index includes BMI, postbronchodilator FEV_1 % predicted, mMRC score, and 6MWD. See Figure 1 legend for expansion of abbreviations.*

percentage, and airway dimensions.[22,23,39] Hersh et al[34] found that gas trapping percentage, a prominent indirect sign of small airway disease, had a strong correlation with emphysema percentage and may fail to distinguish between gas trapping caused by emphysema and by small airway disease.[24,40] These authors described an index, the E/I MLA, using paired inspiratory and expiratory images, as a more reliable small airway disease measure in smokers.[34,41] We found a strong correlation between E/I MLA and all spirometric airflow obstruction indexes, including FEV_3/FEV_6 ($r = -0.65$) and FEV_3 % predicted ($r = -0.51$). It is reasonable to infer that significant correlations of gas trapping and E/I MLA with spirometric measurements are a consequence of hyperinflation due to small airway injury.

Lung elastic recoil loss causing expiratory airflow limitation results from emphysematous lung destruction. However, the presence of emphysema does not consistently elicit spirometric airway obstruction. Mohamed Hoesein et al[42] presented a longitudinal analysis showing that patients initially exhibiting emphysema on CT scans but without airflow abnormality (defined as $FEV_1/FVC < 70\%$) were prone to develop FEV_1 and FEV_1/FVC decline in follow-up studies. Their results suggested that FEV_1/FVC is not sensitive enough for diagnosing mild structural changes until emphysema severity exceeds a certain threshold. Our results indicate indirect CT scanning measures of small airway disease in a subset of subjects with otherwise normal spirometric results (Table 2). We observed significantly lower FEV_1 % predicted and FEV_1/FVC in participants with FEV_3/FEV_6 less than the LLN compared with those with FEV_3/FEV_6 greater than or equal to the LLN; however these values do not reach diagnostic criteria for abnormality in the FEV_1/FVC LLN (Table 2). This finding supports that there is lung structure and function loss in the subgroup not yet recognized as abnormal according to an FEV_1/FVC less than the LLN.[17] Targeting this population with undiagnosed disease is of great importance because functional small airway dysfunction is associated with FEV_1 decline in smokers whose airways are not obstructed, and small airway function improves starting from the first week of smoking cessation in smokers who do not have airflow obstruction.[43,44]

Small airways have been regarded as the lung's quiet zone because obstruction within them causes little spirometric abnormality until obstruction is far advanced.[45] Microstructural studies in COPD showed that morphologic small airway changes begin before emphysematous destruction starts.[46,47] In our study, subjects in whom FEV_3/FEV_6 was the sole abnormality had significantly greater gas trapping percentage, E/I MLA, and segmental airway WA percentage without significantly greater emphysema percentage (Fig 1, Table 2). The reason for lack of association between emphysema and an FEV_3/FEV_6 abnormality may be that isolated FEV_3/FEV_6 abnormality can be used to diagnose COPD in the early stages before emphysematous destruction is detectable. However, to confirm this suggestion, further longitudinal analysis is required.

A vigorous physical effort and expiration time as long as 20 s are needed to measure FVC accurately, which is hard to achieve in elderly patients and those with severe obstruction. A shorter expiratory time causes FVC underestimation and FEV_1/FVC overestimation that may lead to false-negative interpretation in patients with mild airway obstruction.[12,48,49] FEV_6 has the advantage over FVC of being independent of forced expiration duration; previous studies have shown that FEV_1/FEV_6 is a valid alternative to FEV_1/FVC to diagnose airflow obstruction.[48-54] The present study supports previous observations showing that an FEV_1/FEV_6 abnormality had significantly stronger association with structural impairment (emphysema percentage, gas trapping percentage, E/I MLA, and increased WA percentage) and with COPD-related outcomes and 6MWD, compared with using an FEV_1/FVC abnormality (e-Tables 7, 8).

Our results should be considered in light of their limitations and strengths. Distal airway walls are composed predominantly of smooth muscle.[55] Distal airway smooth muscle hypertrophy contributes to bronchodilator reversibility in COPD.[56] Varying degrees of smooth muscle contraction may cause variation in airflow limitation. Smooth muscle contraction can be partially reversed by inhaled bronchodilator administration. For this reason, using prebronchodilator spirometry for detection of airflow obstruction may lead to overestimation of airflow obstruction. This is the main reason for using postbronchodilator spirometry in the current COPD definition.[57] In our analysis, we defined abnormality regarding prebronchodilator LLN criteria. From this perspective, unreversed smooth muscle contraction may be one reason why we detected increased gas trapping and E/I MLA and impaired airway dimensions in individuals with FEV_3/FEV_6 less than or equal to the LLN. However, these structural differences remained significant after excluding bronchodilator-responsive smokers from our analysis. Whether impairments defined in this study precede full-blown COPD warrants further longitudinal analysis of this cohort.

Absence of an LLN criterion for postbronchodilator FEV_3/FEV_6 prevents us from comparing the diagnostic capabilities of FEV_3/FEV_6 between pre- and postbronchodilator measurements. Studies that have evaluated diagnostic performance of different spirometric criteria have usually made comparisons by accepting FEV_1/FVC (less than the LLN or < 0.70) as the criterion standard in diagnosing airflow obstruction.[3,58,59] Our data demonstrate that this approach may be suboptimal for diagnosing airflow obstruction, especially mild, early, or small airway disease. We acknowledge, though, that we have not demonstrated that a finding of isolated abnormality in FEV_3/FEV_6 has prognostic or therapeutic implications. Furthermore, like all spirometric measures, day-to-day variability in lung function and measurement error can contribute to the variability of classification of patients with results on the border between normal and mild abnormality.

Another point deserving consideration is the COPDGene inclusion strategy, which did not exclude smokers with self-reported asthma history. This inclusion strategy may cause overdiagnosis or misdiagnosis in patients who actually have asthma as having COPD or include those with both asthma and COPD. Such patients who smoke and have asthma may demonstrate all of the impairments in functional, structural, and quality-of-life indexes observed in our study. We believe spirometric monitoring during CT scanning might improve standardization and decrease variability in the quantitative CT scanning measures. However, to our knowledge, this is not routinely done in quantitative CT imaging and was not done in the studies of the COPDGene cohort. CT scans were, however, performed by experienced staff, who coached participants to perform a maximal inspiratory maneuver and a relaxed end-expiratory maneuver. Finally, testing new LLN equations in never-smoker adults with available quantitative CT scanning data would be advantageous to discriminate the effects of aging and smoking on structural and functional alterations. Nevertheless, we believe our findings discriminate a subgroup with impairment in physiologic, functional, structural, and quality-of-life dimensions resembling COPD not identified by using FEV_1/FVC greater than the LLN regardless of whether these smokers are considered to have asthma-COPD overlap syndrome, smoking asthma, or COPD.

Conclusions

In conclusion, increasing evidence supports the presence of structural lung changes before airflow obstruction becomes evident according to routine spirometric criteria.[9,14-16] Our findings, based on the examination of the largest smoker population with available quantitative CT scanning data, demonstrate the presence of structural lung changes before airflow obstruction becomes evident according to the FEV_1/FVC ratio. We report, to our knowledge, for the first time that, in those with normal FEV_1/FVC, low FEV_3/FEV_6 is associated significantly with impaired CT scanning measures, shorter 6MWD, increased dyspnea perception, and lower respiratory quality of life. It seems capable of diagnosing spirometric abnormality at an early stage before marked emphysematous changes start. Whether the population with normal FEV_1/FVC but abnormal FEV_3/FEV_6 defined in this study will show more rapid COPD progression is unknown. Longitudinal analysis of COPDGene and other cohorts may provide the answer to this question.

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