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Significance of FEV_3/FEV_6 in Recognition of Early Airway Disease in Smokers at Risk of Development of COPD

Analysis of the SPIROMICS Cohort

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BACKGROUND: Small airways are known to be affected early in the course of COPD; however, traditional spirometric indices may not accurately identify small airways disease.

RESEARCH QUESTION: Can forced expiratory volume in 3 s/forced expiratory volume in 6 s (FEV_3/FEV_6) identify early airflow abnormalities and predict future clinically important respiratory-related outcomes, including development of COPD?

STUDY DESIGN AND METHODS: The study included 832 current and former smokers with post-bronchodilator $FEV_1/FVC \geq 0.7$ from the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) cohort. Participants were classified as having a reduced pre-bronchodilator FEV_3/FEV_6 based on lower limit of normal (LLN) values. Repeatability analysis was performed for FEV_3 and FEV_6. Regression modeling was used to evaluate the relationship between baseline FEV_3/FEV_6 and outcome measures, including functional small airways disease, on thoracic imaging and respiratory exacerbations. Interval-censored analysis was used to assess progression to COPD.

RESULTS: FEV_3/FEV_6 less than the LLN at baseline, defined as reduced compared with FEV_3/FEV_6 at or above the LLN, was associated with lower FEV_1, poorer health status (St. George's Respiratory Questionnaire score), more emphysema, and more functional small airways disease on quantitative imaging. FEV_3 and FEV_6 showed excellent agreement between repeat measurements. A reduced FEV_3/FEV_6 was associated with increased odds of a severe respiratory exacerbation within the first year of follow-up and decreased time to first exacerbation. A low FEV_3/FEV_6 was also associated with development of COPD according to spirometry results (post-bronchodilator $FEV_1/FVC < 0.7$) during study follow-up.

INTERPRETATION: FEV_3/FEV_6 is a routinely available and repeatable spirometric index that can be useful in the evaluation of early airflow obstruction in current and former smokers without COPD. A reduced FEV_3/FEV_6 can identify those at risk for future development of COPD and respiratory exacerbations.

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KEY WORDS: COPD; early airflow obstruction; FEV_3; FEV_6; FEV_3/FEV_6; small airways disease; spirometry

ABBREVIATIONS: 6MWD = 6-min walk distance; CAT = COPD Assessment Test; D_{LCO} = diffusing capacity of the lung for carbon monoxide; $FEF_{25\%-75\%}$ = forced expiratory flow at 25% to 75% of FVC; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; fSAD = functional small airways disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal; PRM = parametric response mapping; QoL = quality of life; SAD = small airways disease; SGRQ = St. George's Respiratory Questionnaire

Early in the course of COPD, pathophysiological changes are known to occur in small airways prior to meeting accepted spirometric criteria for COPD based on an FEV_1 to FVC ratio < 0.7.[1,2] Although spirometry is routinely used to diagnose obstructive lung disease and monitor progression, commonly used measures including FEV_1 may not fully reflect the small airways disease (SAD) seen early in the course of COPD.[1,3-6] This is problematic because current and former smokers with preserved pulmonary function according to conventional spirometric measures can have evidence of low diffusing capacity, radiographic abnormalities (including emphysema and airway wall thickening), and/or may experience respiratory symptoms and respiratory exacerbations.[7-11]

Measurement of the forced expiratory volume in 3 s (FEV_3) includes a greater fraction of forced exhalation and may better reflect small airway obstruction compared with FEV_1, which may not fully capture distal airway pathology.[12-16] There have been limited studies evaluating the utility of FEV_3 in identifying airway disease. Reductions in FEV_3/FVC have been associated with early air trapping, hyperinflation, and reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) and thus have been proposed as an indicator of mild airway pathology.[14] FEV_3/forced expiratory volume in 6 s (FEV_6) has also been evaluated in current and former smokers. FEV_3/FEV_6 less than the lower limit of normal (LLN) in individuals with normal FEV_1/FVC has been associated with gas trapping on quantitative imaging and worsened clinical and quality of life (QoL) metrics, including St. George's Respiratory Questionnaire (SGRQ) and modified Medical Research Council dyspnea scores, suggesting that FEV_3/FEV_6 may be a spirometric index that reflects SAD.[13,17] Given that FEV_6 has been shown to be an acceptable surrogate for FVC and is more easily repeatable, FEV_3/FEV_6 is a promising measure of SAD that occurs early in the disease course, prior to diagnosis of COPD according to

Take-home Points

Study Question: Can FEV_3/FEV_6 identify early airflow abnormalities and predict future clinically important respiratory-related outcomes, including development of COPD?

Results: A reduced FEV_3/FEV_6 was associated with more SAD on quantitative imaging, decreased time to first respiratory exacerbation and increased odds of a severe respiratory exacerbation, and future development of COPD.

Interpretation: FEV_3/FEV_6 is a routinely available and repeatable spirometric index that, in current and former smokers without COPD, can be useful in identifying those at risk for future development of COPD and respiratory exacerbations.

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spirometry results.[13,18,19] These findings have yet to be confirmed, however. In addition, the relationship between reduced FEV_3/FEV_6 and the future progression to overt airflow obstruction and a diagnosis of COPD has not yet been established. We hypothesized that FEV_3/FEV_6 less than the LLN in ever-smokers with normal FEV_1/FVC would be associated with increased measures of disease severity and increased likelihood of future COPD development and respiratory exacerbations.

Analyzing the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) cohort, we aimed to investigate whether a reduced FEV_3/FEV_6 in current or former smokers with a normal FEV_1/FVC is associated with longitudinal clinical outcomes, including acute respiratory exacerbations and progression to COPD.[20] We also aimed to further investigate the association between reduced FEV_3/FEV_6 and radiographic, functional, and clinical markers of airway disease.

Study Design and Methods

Study Design and Participants

SPIROMICS is a multicenter observational study that enrolled current and former smokers (≥ 20 pack-years) aged 40 to 80 years with and without COPD defined according to post-bronchodilator spirometry results who were followed up longitudinally from 2010 to 2015.[20] This study focused on participants who were current or former smokers (≥ 20 pack-years) without a diagnosis of COPD at baseline (post-bronchodilator $FEV_1/FVC \geq 0.7$) with available FEV_3 and FEV_6 measurements (N = 832). In this study, pre-bronchodilator FEV_3/FEV_6 less than the LLN was defined as reduced. The LLN for FEV_3/FEV_6 was defined based on pre-bronchodilator spirometric data from the National Health and Nutrition Examination Survey III, using age, sex, and ethnicity to determine LLN values as previously described by Hansen et al.[17] LLN values for FEV_3/FEV_6 range from approximately 0.93 at age 40 years to approximately 0.89 at age 80 years. SPIROMICS was approved by the institutional review board at each center, and all participants provided written informed consent (e-Table 1).

Data Collection

Participants reported demographic data, medical history, and smoking history at enrollment. There were up to three subsequent annual in-person follow-up visits with additional quarterly surveys. Respiratory symptoms and health status according to the modified Medical Research Council dyspnea score, COPD Assessment Test (CAT), and SGRQ were obtained by self-report at enrollment and annual visits. Pre- and post-bronchodilator spirometry (performed based on 2005 American Thoracic Society/European Respiratory Society guidelines) and 6-min walk distance (6MWD) data were obtained at enrollment and annual follow-up visits.[21] Assessment of repeatability of FEV_3 and FEV_6 was performed in participants with complete FEV_3 and FEV_6 values from the SPIROMICS Repeatability Sub-study, which assessed repeatability of spirometric indices in 98 participants who repeated spirometry 6 weeks from the baseline visit.[22] High-resolution chest CT scans were acquired at enrollment and 1-year follow-up. Total lung capacity and residual volume were measured based on CT imaging parameters obtained at full inspiration (total lung capacity) and full expiration (residual volume).[20] Parametric response mapping (PRM), a CT-based biomarker that links expiratory- and inspiratory-based CT metrics, was used to quantitatively assess functional SAD (PRM^{fSAD}) and emphysema (PRM^{Emph}).[23,24] Acute respiratory exacerbation data were elicited through quarterly telephone calls and yearly follow-up visits. Acute respiratory exacerbations were defined according to symptom worsening requiring treatment with antibiotics and/or systemic corticosteroids or treatment in a clinic, ED, or hospital setting. Severe exacerbations were defined as events requiring an ED visit or hospital admission.

Statistical Analyses

Demographic, comorbid, and baseline clinical characteristics of participants were evaluated by using χ^2 or Kruskal-Wallis tests for categorical or continuous variables, respectively, and stratified according to FEV_3/FEV_6 less than the LLN vs FEV_3/FEV_6 at or above the LLN. Linear regression modeling was used for cross-sectional analyses of PRM^{fSAD} and PRM^{Emph} and was adjusted for age, sex, race, BMI, smoking status, and asthma. Due to the skewed distribution of SGRQ, PRM^{fSAD}, and PRM^{Emph} data, values were log transformed and summarized as geometric means to aid interpretation. Mixed model comparisons of mean rates of change per year were used to evaluate the relationship between baseline FEV_3/FEV_6 status and changes in clinical measures (FEV_1, CAT, 6MWD, and SGRQ) over time. Logistic regression modeling was used to evaluate acute respiratory exacerbation outcomes within the first 365 days based on FEV_3/FEV_6 status. Exacerbations were modeled as a binary outcome (0 vs ≥ 1 episode) in the aforementioned logistic models. For exacerbation analysis through the third annual follow-up visit, rates of exacerbations were compared by FEV_3/FEV_6 using the Poisson regression model with adjustment of the SEs to account for overdispersion. Time to first exacerbation and associated hazard ratios were calculated by using Fine-Gray competing risk regression models with death as a competing risk. Covariates included in regression analyses were age, sex, race, BMI, smoking status (current or former smoking and life-time history in pack-years), and history of asthma or chronic bronchitis. Interval-censored analysis was used to assess the association between reduced FEV_3/FEV_6 and progression to COPD (defined by using Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria, $FEV_1/FVC < 0.7$) based on spirometry performed at annual visits. P values <.05 were considered statistically significant. All analyses were conducted by using SAS 9.4 (SAS Institute, Inc.).

Results

In the cohort of current or former smokers without COPD (≥ 20 pack-years with post-bronchodilator $FEV_1/FVC \geq 0.7$), pre-bronchodilator FEV_3/FEV_6 was abnormal in 17.2% (n = 143) of participants at baseline. The corresponding proportions for the overall SPIROMICS cohort with available FEV_3/FEV_6 data are included in e-Table 2. Median follow-up time was

TABLE 1] Baseline Characteristics in Ever-Smokers With Post-Bronchodilator $FEV_1/FVC \geq 0.7$ Stratified According to Pre-Bronchodilator FEV_3/FEV_6

Baseline Variable	FEV_3/FEV_6 Less Than the LLN (n = 143)	FEV_3/FEV_6 at or Above the LLN (n = 689)	*P* Value
Age, y	57.1 ± 10.3	60.5 ± 9.4	< .001
Female sex	81 (56.6)	347 (50.4)	.17
Race:			
White	87 (60.8)	473 (68.7)	.34
African American	46 (32.2)	175 (25.4)	
Other	9 (6.3)	36 (5.2)	
BMI, kg/m^2	27.7 ± 5.3	29.5 ± 4.9	< .001
BODE index	0.6 ± 1.0	0.4 ± 0.7	.02
Smoking status			
Currently smoking	88 (61.5)	338 (49.1)	.025
Pack-years	46.8 (30.3)	41.6 (22.9)	.11
History of asthma	32 (22.4)	90 (13.8)	.049
Chronic bronchitis	29 (20.3)	79 (11.5)	.012
On ICS	26 (18.3)	73 (10.7)	.011
On bronchodilator	53 (37.3)	134 (19.6)	< .001
FEV_3/FEV_6	0.90 ± 0.02	0.93 ± 0.01	
FEV_1			
Liters	2.6 ± 0.7	2.9 ± 0.7	.001
Percent predicted	90.3 (11.3)	98.6 (13.2)	< .001
FVC			
Liters	3.6 ± 1.0	3.7 ± 0.9	.18
Percent (%) predicted	90.3 ± 11.3	98.6 ± 13.2	< .001
FEV_1/FVC	0.74 ± 0.03	0.78 ± 0.05	< .001
TLC_{CT}, L	5.5 ± 1.4	5.4 ± 1.3	.68
RV_{CT}, L	2.9 ± 0.7	2.8 ± 0.7	.16
mMRC dyspnea score ≥ 2	23 (16.1)	78 (11.3)	.26
CAT score ≥ 10	75 (52.5)	318 (46.2)	.37
SGRQ	29.1 ± 21.1	23.2 ± 18.3	.003
6MWD, m	428.3 ± 99.5	439.0 ± 95.8	.27
PRM^{Emph}, %	0.7 ± 1.2	0.4 ± 0.8	.001
PRM^{fSAD}, %	9.3 ± 9.5	7.8 ± 9.1	.017

Data are expressed as mean ± SD or No. (%). 6MWD = 6-min walk test distance; BODE = BMI, airway obstruction, dyspnea, and exercise tolerance; CAT = COPD Assessment Test; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; ICS = inhaled corticosteroids; LLN = lower limit of normal; mMRC = modified Medical Research Council; PRM^{Emph} = parametric response mapping emphysema; PRM^{fSAD} = parametric response mapping functional small airways disease; RV_{CT} = residual volume by CT imaging; SGRQ = St. George's Respiratory Questionnaire score; TLC_{CT} = total lung capacity by CT imaging.

48.0 months for participants with normal FEV_3/FEV_6 and 50.4 months for participants with reduced FEV_3/FEV_6. Baseline characteristics of this cohort are presented in Table 1.

Ever-smokers with a reduced FEV_3/FEV_6, compared with those with a preserved FEV_3/FEV_6 were younger and had, on average, lower BMI and higher BODE (BMI, airway obstruction, dyspnea, exercise tolerance) index scores. The low FEV_3/FEV_6 group had a higher prevalence of a reported diagnosis of chronic bronchitis, a larger proportion of current smokers compared with those with normal FEV_3/FEV_6, and a higher proportion with reported inhaled corticosteroid or bronchodilator use at baseline. Participants with FEV_3/FEV_6 less than the LLN were more likely to report inhaled steroid or bronchodilator use at baseline and had lower percent predicted FEV_1 and FVC values and higher SGRQ scores compared with participants with a normal FEV_3/FEV_6.

Variability of FEV_3/FEV_6 Measurement

Repeatability of pre-bronchodilator FEV_3 and FEV_6 was analyzed by using the SPIROMICS Repeatability Sub-study data. Repeatability of post-bronchodilator FEV_1 was also assessed for comparison. Based on spirometric testing repeated 6 weeks following the baseline evaluation, intraclass correlation was 0.97 for FEV_1, 0.98 for FEV_3, and 0.98 for FEV_6, indicating excellent agreement between repeat measurements (e-Table 3).

Quantitative CT Imaging

Complete PRM and spirometry data were available for 740 participants who were ever-smokers with FEV_1/FVC $\geq$ 0.7 (612 participants with a normal FEV_3/FEV_6 and 128 with a reduced FEV_3/FEV_6). In adjusted linear regression analysis of baseline PRM data, individuals with an abnormal FEV_3/FEV_6 compared with those with a preserved FEV_3/FEV_6 had a significantly higher percentage of PRM^{Emph} (geometric mean 0.47% vs 0.27%, respectively; adjusted $P = .004$) and PRM^{fSAD} (geometric mean, 5.1% vs 3.7%; adjusted $P = .004$).

Respiratory Exacerbations

In this cohort of current and former smokers without COPD according to GOLD criteria, participants with reduced FEV_3/FEV_6 at baseline were significantly more likely to have a severe acute respiratory exacerbation in the first 365 days following enrollment (adjusted OR, 4.28; 95% CI, 1.17-15.66; $P = .028$) compared with participants with normal FEV_3/FEV_6 (Table 2). Reduced FEV_3/FEV_6 was associated with shorter time to first respiratory exacerbation in participants without COPD in both unadjusted (hazard ratio, 1.68; 95% CI, 1.15-2.44; $P = .006$) and adjusted (hazard ratio, 1.52; 95% CI, 1.02-2.25; $P = .039$) analyses.

Longitudinal Change in Lung Function, Functional Capacity, and Health Status

At baseline, compared with those with a normal FEV_3/FEV_6, participants with FEV_3/FEV_6 less than the LLN had significantly lower FEV_1 values and higher SGRQ scores (Table 1). However, over the course of study follow-up, participants with reduced FEV_3/FEV_6 had no significant differences in annual mean rate of change for FEV_1, CAT score, SGRQ score, or 6MWD values based on mixed model comparisons (Fig 1).

Progression to COPD and Risk of COPD Development

Based on interval-censored analysis, reduced FEV_3/FEV_6 was significantly associated with increased probability of COPD development during study follow-up ($P < .001$) in the cohort of current or former smokers with preserved FEV_1/FVC ratio at baseline (Fig 2). Regression analysis of interval-censored data showed that a reduced FEV_3/FEV_6 was significantly associated with development of COPD in both unadjusted (hazard ratio, 2.75; 95% CI, 2.75-3.78; $P < .001$) and adjusted (hazard ratio, 2.11; 95% CI, 1.48-3.03; $P < .001$) models compared with participants with FEV_3/FEV_6 at or above the LLN (Table 2).

Discussion

The current study evaluated FEV_3/FEV_6 as a metric of early airflow obstruction and explored the role and significance of this spirometric measure in predicting outcomes in the SPIROMICS cohort. Among current and former smokers without COPD (baseline post-bronchodilator FEV_1/FVC $\geq$ 0.7), we found that participants with a reduced pre-bronchodilator FEV_3/FEV_6 had a greater burden of respiratory disease, more emphysema, and functional SAD by quantitative imaging, and higher rates of respiratory exacerbations, compared with participants with normal FEV_3/FEV_6. A reduced FEV_3/FEV_6 in ever-smokers without COPD at baseline was also associated with decreased time to first exacerbation and increased risk of progression to COPD during follow-up compared with participants with a preserved FEV_3/FEV_6.

Pathologic changes in small airways have been known to occur early in COPD with airway inflammation, plugging, and thickening.[1,2,25] In addition, changes in small airways have been noted in smokers without COPD both on CT imaging and on histology.[7,26-28] Although prior studies have described activity limitation, clinically significant symptoms, and respiratory exacerbations in current or former smokers without COPD, traditional spirometric measures commonly fail to detect early airway changes that may contribute to development of these clinical features.[9,13,29-31] Based on physiological studies in both animal and normal human lungs, it is estimated that peripheral airways account for a small percentage of total airway resistance, which may explain why detection of small airway pathology may be difficult using common spirometry measures.[32-35]

Although a reduced FEV_1 mainly reflects larger airways obstruction, except in far-advanced COPD, abnormalities in other spirometric measures such as forced expiratory flow at 25% to 75% of FVC ($FEF_{25\%-75\%}$) and FEV_3 can be

TABLE 2] Exacerbation and COPD Progression Outcomes in Ever-Smokers With Post-Bronchodilator $FEV_1/FVC \geq 0.7$ Stratified According to Pre-Bronchodilator FEV_3/FEV_6

COPD Outcome Measure (FEV_3/FEV_6 Less than the LLN vs FEV_3/FEV_6 at or Above the LLN)	OR[a]	
	Unadjusted	Adjusted[b]
Any respiratory exacerbation (first 365 d following enrollment)	1.97 (1.13-3.44; $P = .016$)	1.75 (0.94-3.28; $P = .078$)
Severe respiratory exacerbation (first 365 d following enrollment)[c]	4.14 (1.37-12.52; $P = .012$)	4.28 (1.17-15.66; $P = .028$)
	Rate Ratio[d]	
	Unadjusted	Adjusted[b]
Any type of respiratory exacerbation (through the third annual follow-up visit)[e]	1.32 (1.01-1.71; $P = .04$)	1.00 (0.72-1.34; $P = .99$)
Severe respiratory exacerbation (through the third annual follow-up visit)[c,e]	1.73 (1.14-2.62; $P = .01$)	1.02 (0.68-1.53; $P = .93$)
	Hazard Ratio	
	Unadjusted	Adjusted[b]
Time to first exacerbation[f]	1.68 (1.15-2.44; $P = .006$)	1.52 (1.02-2.25; $P = .039$)
Risk of progression to COPD by GOLD criteria[g]	2.75 (2.00-3.78; $P < .001$)	2.11 (1.48-3.03; $P < .001$)

FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal.
[a]Logistic regression modeling; exacerbations as binary variable 0 vs ≥ 1.
[b]Adjusted for age, sex, race, BMI, smoking status (current smoking and cumulative pack-years), and reported diagnosis of chronic bronchitis or asthma.
[c]ED visit or hospitalization.
[d]Poisson regression modeling.
[e]Per person-time of follow-up through the third annual visit.
[f]Competing risks regression model.
[g]Interval-censored analysis.

suggestive of SAD.[1,3] $FEF_{25\%-75\%}$ has been regarded as a sensitive measure of distal airway obstruction, but clinical utility has been limited due to concerns regarding high variability, reliance on patient effort, and the wide range of normal values.[1,3,36,37] There are also concerns regarding the ability of $FEF_{25\%-75\%}$ to detect obstruction in older patients, particularly starting at age 60 years, as reported in the National Health and Nutrition Examination Survey III cohort.[12] FEV_3/FVC has been proposed as a routinely available and reproducible measure of small airways obstruction, although a large study from COPDGene found stronger associations between reduced FEV_3/FEV_6 and CT imaging abnormalities or COPD-related outcomes than with reduced FEV_3/FVC.[13] FEV_3/FEV_6 has also been evaluated because FEV_6 has been shown to be an acceptable surrogate for FVC with less variability and higher reproducibility.[13,18,19]

In a prior cross-sectional analysis of the COPDGene cohort, Dilektasli et al[13] found that in participants with a normal FEV_1/FVC, reduced FEV_3/FEV_6 was associated with a significantly poorer QoL, increased respiratory symptoms, air trapping, shorter 6MWD, and abnormal quantitative CT imaging, including gas trapping, compared with those with a normal FEV_3/FEV_6. Consistent with the latter findings, the SPIROMICS cohort of ever-smokers with normal FEV_1/FVC and low FEV_3/FEV_6 at baseline had, on average, significantly worse spirometric volumes (FEV_1 and FVC), worse QoL (SGRQ score), and increased functional SAD and emphysema on quantitative CT imaging. There was no difference between groups in baseline dyspnea, air trapping, or 6MWD. Of note at baseline, a significantly higher proportion of participants in the current study with a reduced FEV_3/FEV_6 reported use of inhaled corticosteroids and bronchodilators compared with those with normal FEV_3/FEV_6, which may have affected baseline dyspnea symptoms.

In addition to observing cross-sectional findings similar to Dilektasli et al,[13] we further evaluated the role of FEV_3/FEV_6 in longitudinal outcomes. In the SPIROMICS cohort, mean rate of change in spirometric indexes, QoL, CAT score, SGRQ score, and 6MWD did not significantly differ for participants with a reduced

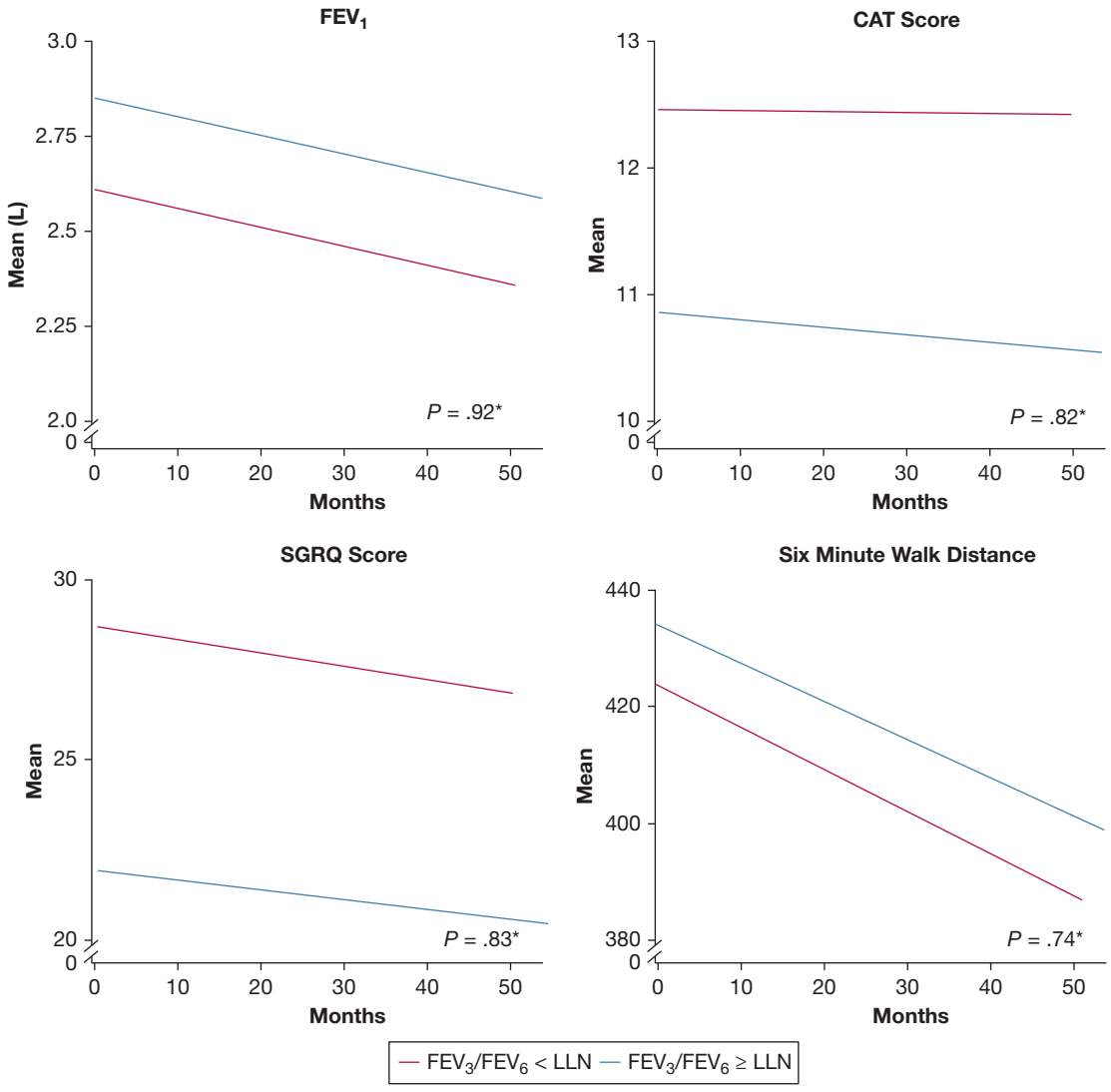

Figure 1 – *Longitudinal clinical outcomes in ever-smokers with post-bronchodilator $FEV_1/FVC \geq 0.7$ stratified according to pre-bronchodilator FEV_3/FEV_6. CAT = COPD Assessment Test; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal; SGRQ = St. George's Respiratory Questionnaire.* [a]P *value for slope difference.*

FEV_3/FEV_6 compared with those with a preserved FEV_3/FEV_6 (Fig 1). This outcome may be due to the relatively preserved lung function and limited follow-up time of this cohort and is consistent with prior studies showing only small changes in reported health-related QoL over time in people with COPD but only mild airflow obstruction.[38]

Our findings support FEV_3/FEV_6 as a useful clinical metric obtained on routine spirometry that can be predictive of disease progression in smokers at risk of COPD. Among current or former smokers without COPD according to the GOLD criteria, subjects with reduced FEV_3/FEV_6 at baseline were more likely to experience a severe respiratory exacerbation requiring an ED visit or hospitalization in the first year following enrollment compared with those with normal FEV_3/FEV_6. In addition, subjects with reduced FEV_3/FEV_6 had a shorter time to first respiratory exacerbation. Although there were significant differences in exacerbation outcomes between groups within the first year, this was not observed by the end of study follow-up. Of note, 14.2% of participants with normal FEV_3/FEV_6 at baseline progressed to a reduced FEV_3/FEV_6 during study follow up (e-Table 4). These participants tended to be more likely to report a respiratory exacerbation during later follow-up years (e-Table 5), which may explain the diminished difference in exacerbations between groups with normal compared with reduced baseline FEV_3/FEV_6 by the end of study follow-up.

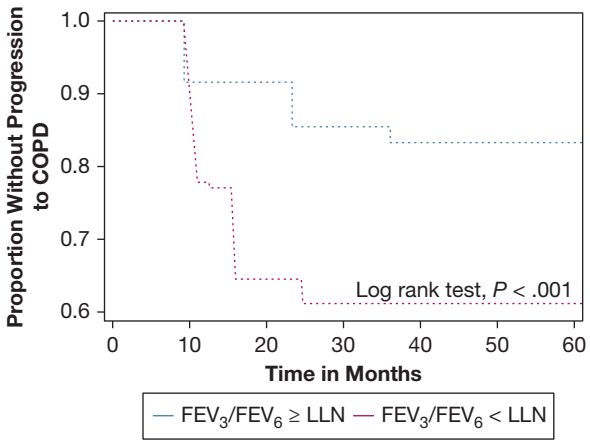

Figure 2 – *Cumulative incidence of percent progression to COPD with interval censoring in ever-smokers (≥ 20 pack-years) without COPD (post-bronchodilator FEV1/FVC ≥ 0.7 at baseline) stratified according to pre-bronchodilator FEV_3/FEV_6. FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal.*

Although we found that pre-bronchodilator FEV_3/FEV_6 was associated with several clinical outcomes, it is important to acknowledge the potential contribution from pre-bronchodilator measurements compared with post-bronchodilator measurements. From a practical standpoint, individuals without evidence of obstruction on routine pre-bronchodilator spirometry may not undergo post-bronchodilator testing. However, although pre-bronchodilator values may overestimate airflow obstruction, debate remains on whether post-bronchodilator spirometry results are clearly superior to pre-bronchodilator measurements in predicting outcomes and mortality.[39-41] Our study used LLN values for FEV_3/FEV_6 derived from the National Health and Nutrition Examination Survey III in which only pre-bronchodilator values were obtained.[13,17] In a supplemental analysis using post-bronchodilator measures (with pre-bronchodilator reference cutoffs for LLN), only 43 (5.2%) of ever-smokers without COPD would have a reduced FEV_3/FEV_6 (e-Table 2). Unfortunately, the small sample size limited the ability to obtain reliable estimates from adjusted models.

Another consideration is the value of pre-bronchodilator FEV_3/FEV_6 over the more familiar FEV_1/FVC with bronchodilator reversibility (pre-bronchodilator $FEV_1/FVC < 0.7$ and post-bronchodilator $FEV_1/FVC \geq 0.7$) given the correlation between FEV_1 and FEV_3.[42] Participants with baseline reduced pre-bronchodilator FEV_1/FVC and normal post-bronchodilator FEV_1/FVC had increased risk of progression to COPD but were not noted to be at increased risk for respiratory exacerbations or decreased time to first exacerbation (e-Table 6). Given these limitations and considerations, we evaluated pre-bronchodilator FEV_3/FEV_6 measurements and believe this metric has clinical utility regarding progression to COPD outcomes, particularly with exacerbations.

Given the often progressive nature of COPD with associated significant functional limitations, symptoms, and mortality in addition to the overall burden on health-care systems, early identification of individuals at risk for respiratory exacerbations and development of COPD remains important.[30,43] FEV_3 and FEV_6, although not widely reported, are available on routine spirometry, and population-based reference values for defining the LLN of pre-bronchodilator FEV_3/FEV_6 are available.[17] Identification of individuals at high risk of progression to COPD with FEV_3/FEV_6 presents an opportunity to further target interventions, including early smoking cessation (which has known benefit).[44] Prior studies have shown that diagnosis of airflow limitation according to spirometry results has been associated with increased motivation to quit smoking.[45,46] It is possible that knowledge of an increased risk of progression to COPD may also provide further motivation for smoking cessation. This remains an area for future research along with evaluation of possible pharmacologic therapies for early airflow obstruction in the clinical trial setting.

This study has several limitations. SPIROMICS did not enroll a random sample, and as a result, the findings may not be fully generalizable to the entire population. COPD was defined with a fixed cutoff of post-bronchodilator $FEV_1/FVC < 0.7$ based on GOLD criteria, which potentially underdiagnoses COPD in younger participants and overdiagnoses it in older participants.[47] Diagnosis of COPD in SPIROMICS was established on a single baseline assessment of post-bronchodilator FEV_1 and FVC, which may not be sufficient in individuals with borderline FEV_1/FVC ratio, although reproducibility analysis in the SPIROMICS cohort showed excellent agreement for FEV_1/FVC on repeated testing.[48] SPIROMICS did not include individuals with preserved ratio impaired spirometry, and thus the significance of FEV_3/FEV_6 in this population could not be assessed.[49] Finally, our analysis is based on a relatively short follow-up period, and an extended follow-up period may provide better insight into the full potential of this metric to help predict related clinical outcomes in populations at risk.

Several strengths of this study merit emphasis. This analysis was based on data from a large cohort of ever-

smokers with and without COPD whose clinical characteristics were well described at baseline and longitudinally, allowing for adequate assessment of the association of FEV_3/FEV_6 with multiple clinical outcomes. To our knowledge, this study is the first to both evaluate the utility and significance of FEV_3/FEV_6 in subjects at risk of developing COPD without airflow obstruction at baseline ($FEV_1/FVC \geq 0.7$) and to investigate the relationship of this metric with longitudinal outcomes in this population.

Interpretation

A reduced FEV_3/FEV_6 in current and former smokers without COPD identifies individuals who are at risk of experiencing respiratory exacerbations and developing COPD. It is a simple, routinely available, and reproducible metric with potential to aid with early identification and timely intervention in people at risk for COPD. The study data suggest that interpretation of spirometry results beyond FEV_1 and FVC can offer additional relevant clinical insights in this population.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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