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ORIGINAL RESEARCH

Reduced FEV_3/FVC as an Early Indicator of COPD in Individuals with Normal Spirometry: A Prospective Analysis from the ECOPD Study

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Purpose: This study aimed to evaluate the association between the forced expiratory volume in 3 s (FEV_3) to forced vital capacity (FVC) and computed tomography (CT)-defined abnormalities, and to assess its potential value in predicting incident chronic obstructive pulmonary disease (COPD) over a 3-year period.

Participants and Methods: This 3-year community-based cohort study enrolled participants with normal lung function (post-bronchodilator FEV_1/FVC ≥ 0.70 and FEV_1 ≥ 80% predicted). Baseline assessments included questionnaires, spirometry, CT scans, and impulse oscillometry. Participants were stratified by post-bronchodilator FEV_3/FVC tertiles. Outcomes included acute respiratory events, annual lung function decline, and COPD incidence. Data were analyzed using mixed-effects models, log-binomial regression, and zero-inflated negative binomial models.

Results: Of the 981 participants with normal baseline lung function stratified by post-bronchodilator FEV_3/FVC tertiles (high: ≥95.5%, medium: 91.9–95.4%, low: ≤91.8%), 807 completed the 3-year follow-up. Compared to the high-FEV_3/FVC group, participants in the low-FEV_3/FVC group tended to be older (60.5 vs 55.7 years) and included more males (80.4% vs 38.8%) and smokers. The low-FEV_3/FVC group also demonstrated a lower baseline post-bronchodilator FEV_1/FVC (74.0% vs 85.1%) and higher prevalence of emphysema (53.5% vs 18.3%). Longitudinal analysis revealed a greater annual post-bronchodilator FEV_1 decline in the low-FEV_3/FVC group (adjusted mean difference: 10 mL, 95% confidence interval [CI]: 0 to 21mL; p = 0.043) and an increased risk of developing COPD (19.4% versus 1.9%; adjusted relative risk: 4.96, 95% CI: 1.96–12.51; p = 0.001) than the high-FEV_3/FVC group, with no difference in acute respiratory events.

Conclusion: A reduced FEV_3/FVC ratio was associated with an increased risk of accelerated lung function decline and progression to COPD in individuals with normal spirometry. As a readily accessible measure derived from routine spirometry, FEV_3/FVC may have a role in early COPD detection.

Keywords: forced expiratory volume in 3 s, forced vital capacity, small airway dysfunction, lung function decline, pre-COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is defined by persistent respiratory symptoms and irreversible airflow limitation.[1] Existing international standards require a post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio under 0.70 for diagnosis.[1] However, growing evidence shows that this spirometric

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criterion does not identify early-stage disease, especially in asymptomatic individuals who exhibit preserved FEV_1/FVC.[2,3] This diagnostic gap highlights a necessity for more sensitive strategies to detect early pathological changes before they develop into an irreversible airflow limitation.

The term "pre-COPD" describes a high-risk condition in which individuals do not meet spirometric criteria for COPD but exhibit respiratory symptoms or objective biomarkers of early disease.[2,3] A nationally representative survey in China (2012–2015) reported a pre-COPD prevalence of 7.2%,[4] underscoring the substantial size of this at-risk population. Early detection of pre-COPD is critical for implementing preventive strategies. Current common useful approaches for identifying at-risk individuals include preserved ratio impaired spirometry (PRISm),[5,6] longitudinal tracking of FEV_1 decline,[7] computed tomography (CT) indicators (such as the percentage of the low-attenuation area [LAA] below −856 Hounsfield units on full-expiration CT [LAA_{-856}] and parametric response mapping of functional small airway disease) and diffusing capacity for carbon monoxide (DL_{CO}).[3,8,9] However, these methods face limitations in broad clinical application: PRISm defines a heterogeneous group with variable outcomes,[5] FEV_1 decline requires repeated measurements over time,[7] and both CT and DL_{CO} require specialized equipment.[8,9] These constraints highlight the need for a more accessible and integrated physiological indicator capable of capturing early disease signals.

Small airway dysfunction (SAD) is widely recognized as a key pathophysiological feature in early COPD.[10,11] The ratio of forced expiratory volume in 3 s (FEV_3) to FVC has recently emerged as a promising composite measure of airflow limitation.[12,13] Physiologically, the FEV_3/FVC ratio serves as a composite measure that integrates airflow from both the early expiratory phase (captured by FEV_1/FVC) and the mid-to-late phase, which is particularly sensitive to SAD.[14,15] This terminal portion of the expiratory curve is sensitive to SAD because the obstruction in small airways leads to delayed emptying, resulting in air trapping and heterogeneous ventilation distribution.[15–17] Therefore, a reduced FEV_3/FVC ratio reflects these pathophysiological hallmarks of SAD and correlates with radiographic abnormalities and impaired gas exchange.[12,14,18] As a continuous variable derived from routine spirometry, FEV_3/FVC may offer a more stable and practical tool than PRISm,[5] enable risk assessment at a single timepoint unlike tracking FEV_1 decline,[7] and avoid the need for specialized equipment required for CT or DL_{CO}.[8] Although previous cross-sectional studies, such as that by Lam et al[13] support its potential in detecting high-risk smokers, the prognostic value of FEV_3/FVC for predicting lung function decline and incident COPD remains to be established.

This prospective community-based cohort study explored the association between a reduced FEV_3/FVC ratio and the risk of developing COPD. We hypothesized that this ratio, which captures mid-to-late expiratory flow, might signal early functional decline. For this purpose, the study assessed its correlation with CT-defined abnormalities and its prognostic value for 3-year incident COPD.

Methods

Study Participants and Design

This research used data from the Early Chronic Obstructive Pulmonary Disease (ECOPD) study, a prospective cohort investigation conducted in Guangdong, China, from 2019 to 2024. The study protocol was previously described.[19] The study enrolled adults aged 40–80 years with normal lung function (post-bronchodilator FEV_1/FVC ≥ 0.70 and FEV_1 ≥ 80% predicted).[19,20] Participants were required to complete a standardized questionnaire and undergo both lung function testing and CT scanning. Exclusion criteria were: recent respiratory infection (<4 weeks); major cardiac events (<3 months); prior lobectomy; active malignancy; or significant non-asthmatic lung disease. Participants with incomplete baseline assessment were excluded from the study, while the remainder underwent annual assessments at 12, 24, and 36 months, including anthropometry, medical history updates, respiratory questionnaires, and lung function testing. Incident COPD was identified by a post-bronchodilator FEV_1/FVC ratio below 0.70 at the third year of follow-up, based on the standard Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criterion.[1] This follow-up scheme is detailed in the study protocol.[19]

Data Collection and Measurements

The participants completed out a standardized questionnaire that was previously used in a Chinese study on COPD.[21] The questionnaire was administered by trained researchers and was used to collect sociodemographic and self-reported health data. Data included risk factors, medical history, and acute exacerbations of respiratory symptoms over the previous year. The COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scale were used to measure chronic respiratory symptoms.[22]

Spirometry was performed by physicians using a portable spirometer, both before and after the administration of 400 μg of salbutamol, in accordance with American Thoracic Society and European Respiratory Society standards.[23] The predicted values were derived using global race-neutral reference equations.[20] SAD was defined as having at least two of three post-bronchodilator metrics (forced expiratory flow (FEF) 50%, FEF75%, or FEF_{25-75}%) below 65% of predicted value.[17]

Chest CT images were obtained using 128-slice scanners (Siemens Definition AS Plus and United-imaging uCT 760). All participants underwent standardized breathing training prior to the scan. Subsequently, the images were interpreted by two radiologists blinded to the lung function results.[19] Chest CT images were analyzed using a chest imaging platform during the full inhalation and exhalation phases.[24] Inspiratory LAA_{-950} was used to quantify emphysema, and expiratory LAA_{-856} was used to assess air trapping.[25] Emphysema and air trapping were identified by an inspiratory LAA_{-950} beyond 0.5% and an expiratory LAA_{-856} surpassing 15%, respectively.

Following the exclusion of non-respiratory etiologies, an acute respiratory episode was defined as the onset or exacerbation of ≥2 of 5 key symptoms (cough, expectoration, purulent sputum, wheeze, dyspnea) lasting >48 hours, and was graded as mild (self-managed at home), moderate (requiring outpatient), or severe (requiring hospitalization).[26] All reported incidents were recorded and evaluated by investigators based on established criteria.[19]

Ethical Statement

The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2018–53) approved this study. Each participant provided written informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

In the absence of validated reference standards for FEV_3/FVC in the Chinese population, tertile-based categorization was employed for analytical purposes. Participants were assigned to high-, medium-, and low-FEV_3/FVC groups based on their post-bronchodilator FEV_3/FVC ratios. We applied the following statistical models: mixed-effects regression for the longitudinal deterioration of lung function; log-binomial regression for incident COPD risk to obtain relative risks; and zero-inflated negative binomial regression for over-dispersed count data on acute respiratory events. All models, without adjustment for FEV_1/FVC, were adjusted for a pre-defined set of baseline confounders, including age, sex, body mass index, smoking status, smoking index, occupational exposure, biomass exposure, and family history of respiratory disease.[19] The data in this study meet all the requirements for multivariable linear regression analysis. This study included only participants with follow-up data in the prognostic analysis and no data imputation was performed. Because this was an exploratory study, we did not perform multiple comparison adjustment.[27] Statistical processing was conducted using the SAS 9.4, SPSS 25.0, and R 4.2.2 software packages. The alpha level for significance testing was established at 0.05.

Results

Study Recruitment

Among the 2200 enrolled participants, 981 with normal lung function at baseline met the study's inclusion criteria, with 327 participants each in the high-, medium-, and low-FEV_3/FVC groups, defined based on post-bronchodilator FEV_3/FVC ratios of ≥95.5%, 91.9–95.4%, and ≤91.8%, respectively (Figure 1).

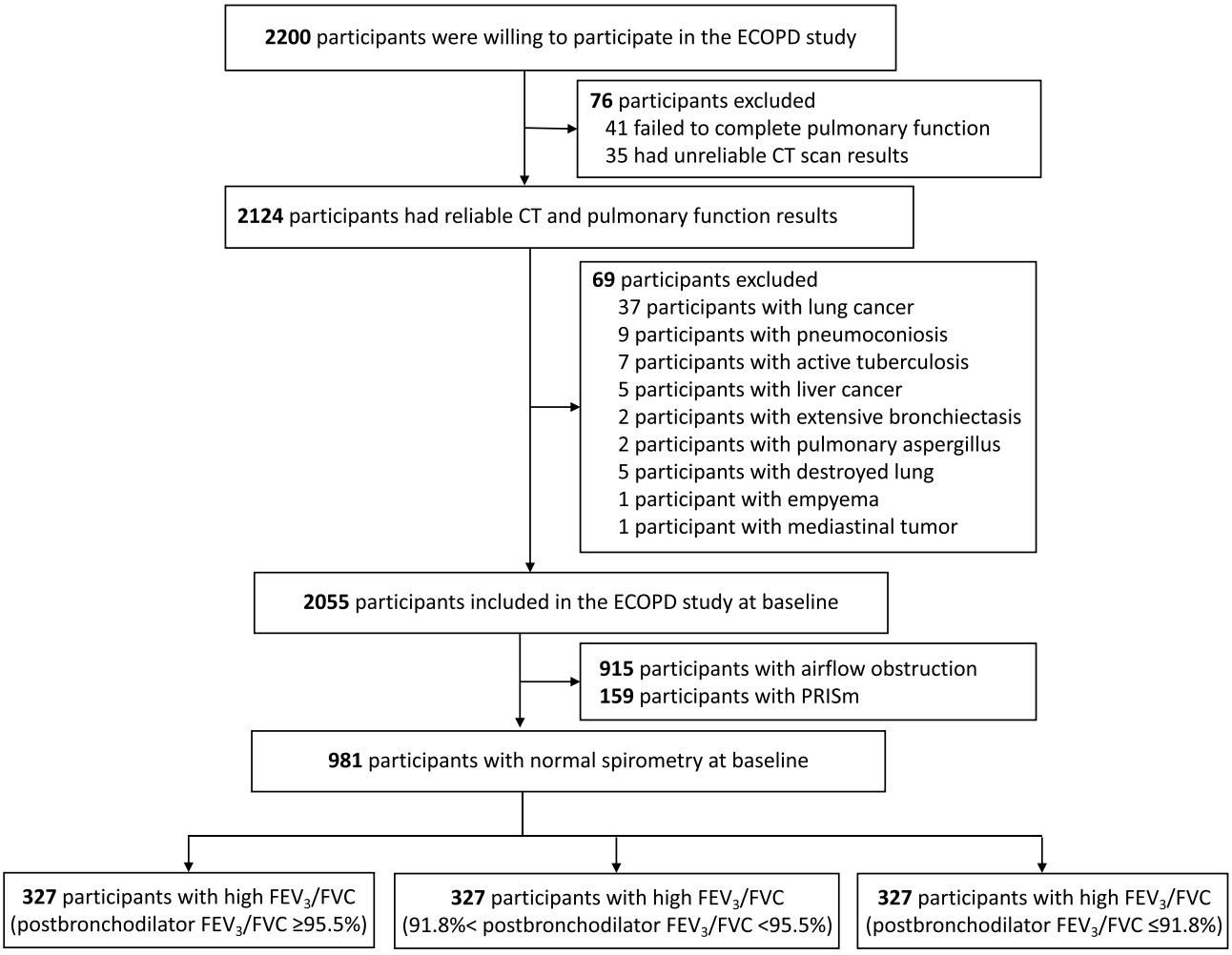

Figure 1 Participant enrollment flowchart. The diagram outlines the screening process for the ECOPD study and the final classification of participants. The normal spirometry group was divided into high-, medium-, and low-FEV_3/FVC tertiles.
Abbreviations: CT, computed tomography; ECOPD, Early Chronic Obstructive Pulmonary Disease study; FEV_3, forced expiratory volume in 3s; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry.

Participant Characteristics

Table 1 shows participant demographics and clinical features by FEV_3/FVC tertiles. Participants in the low-FEV_3/FVC group were older (60.5, 58.7, and 55.7 years; $p < 0.001$) and had a greater male percentage (80.4%, 59.0%, and 38.8%; $p < 0.001$) compared to medium and high groups. Smoking exposure was greater in the low-FEV_3/FVC group, with higher rates of current/former smoking and cumulative smoking index. The prevalence of comorbidities, including hypertension, diabetes, coronary heart disease, and asthma, did not differ significantly across groups. Prior respiratory medication use was 11.3%, 10.7%, and 8.6% from low to high-FEV_3/FVC groups, respectively. Self-reported COPD

Table 1 Baseline Participant Characteristics According to FEV_3/FVC Tertile

Characteristic	Low FEV_3/FVC (n = 327)	Medium FEV_3/FVC (n = 327)	High FEV_3/FVC (n = 327)	P value
Age (years), mean ± SD	60.5 ± 7.2	58.7 ± 7.5	55.7±8.0	<0.001
Male sex, n (%)	263 (80.4)	193 (59.0)	127 (38.8)	<0.001
BMI (kg/m^2), mean ± SD	23.3 ± 2.9	23.5 ± 3.3	23.4 ± 3.2	0.833

(*Continued*)

Table 1 (Continued).

Characteristic	Low FEV_3/FVC (n = 327)	Medium FEV_3/FVC (n = 327)	High FEV_3/FVC (n = 327)	P value
Smoking status, n (%)				<0.001
Never smoked	105 (32.1)	177 (54.1)	244 (74.6)	
Former smoker	57 (17.4)	43 (13.1)	25 (7.6)	
Current smoker	165 (50.5)	107 (32.7)	58 (17.7)	
Smoking index (pack-years), mean ± SD	28.0 ± 31.3	18.2 ± 27.4	9.7 ± 22.1	<0.001
Biomass exposure, n (%)	104 (31.8)	125 (38.2)	106 (32.4)	0.161
Occupational exposure, n (%)	61 (18.7)	47 (14.4)	47 (14.4)	0.223
Family history of respiratory disease, n (%)	30 (9.2)	27 (8.3)	29 (8.9)	0.915
Prior use of respiratory medication, n (%)	37 (11.3)	35 (10.7)	28 (8.6)	0.474
Previous diagnosis of COPD, n (%)	11 (3.4)	2 (0.6)	0 (0.0)	<0.001
Comorbidity, n (%)				
Hypertension	60 (18.3)	68 (20.8)	51 (15.6)	0.227
Diabetes	17 (5.2)	17 (5.2)	16 (4.9)	0.979
Coronary heart disease	9 (2.8)	9 (2.8)	10 (3.1)	0.964
Asthma	3 (0.9)	1 (0.3)	0 (0.0)	0.173
Respiratory symptoms, n (%)				
Dyspnea	63 (19.3)	69 (21.1)	67 (20.5)	0.838
Chronic cough	65 (19.9)	50 (15.3)	53 (16.2)	0.257
Chronic phlegm	89 (27.2)	82 (25.1)	71 (21.7)	0.258
Wheeze	13 (4.0)	23 (7.0)	13 (4.0)	0.117
Post-bronchodilator spirometry				
FEV_1 (L), mean ± SD	2.59 ± 0.47	2.50 ± 0.52	2.43 ± 0.59	0.001
FEV_1% of predicted, mean ± SD	98.0 ± 10.9	98.4 ± 11.3	99.4 ± 11.7	0.272
FEV_3 (L), mean ± SD	3.12 ± 0.56	2.97 ± 0.61	2.79 ± 0.67	<0.001
FVC (L), mean ± SD	3.50 ± 0.64	3.18 ± 0.66	2.86 ± 0.69	<0.001
FVC % of predicted, mean ± SD	105.4 ± 11.6	100.4 ± 11.5	94.9 ± 11.4	<0.001
FEV_1/FVC %, mean ± SD	74.0 ± 2.5	78.7 ± 3.5	85.1 ± 4.1	<0.001
FEV_3/FVC %, mean ± SD	89.2 ± 2.0	93.6 ± 1.1	97.6 ± 1.3	<0.001

Note: Data are mean ± standard deviation (SD) or n (%).
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1s; FEV_3, forced expiratory volume in 3s; FVC, forced vital capacity.

prevalence was considerably greater in the low-FEV_3/FVC group (3.4%) compared to the medium (0.6%) and high (0.0%) groups ($p < 0.001$). Post-bronchodilator spirometry parameters differed significantly across groups. FEV_1/FVC ratios were 74.0±2.5%, 78.7±3.5%, and 85.1±4.1% ($p < 0.001$); FEV_1 values were 2.59±0.47, 2.50±0.52, and 2.43±0.59 L ($p = 0.001$); FEV_3 values were 3.12±0.56, 2.97±0.61, and 2.79±0.67 L ($p < 0.001$) across decreasing FEV_3/FVC groups (Table 1).

Impulse Oscillometry and Computed Tomography

The occurrence of chronic respiratory symptoms, measured using the CAT symptom score and the mMRC dyspnea scale, showed no significant differences across the groups (Table 2). The percentage of individuals who experienced acute respiratory incidents in the previous year was 4.0%, 8.0%, and 6.4% among the low-, medium-, and high-FEV_3/FVC groups, respectively. The medium-FEV_3/FVC group showed an elevated rate relative to the high-FEV_3/FVC group ($p = 0.040$). IOS data were available for most participants and demonstrated no notable differences across the groups.

The prevalence of emphysema (inspiratory LAA_{-950} >0.5%) varied across FEV_3/FVC groups, with rates of 53.5%, 33.9%, and 18.3% in the low-, medium-, and high-groups, respectively. Participants in the low-FEV_3/FVC group had an elevated risk of emphysema when compared to the high group (OR=2.87, 95% confidence interval [CI]: 1.90–4.34, $p < 0.001$). The medium-FEV_3/FVC group also demonstrated elevated odds relative to the high-group (OR=1.69, 95% CI: 1.12–2.55, p =

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Table 2 Measures of Respiratory Symptoms and Respiratory Function Variable Outcomes According to FEV_3/FVC Tertile

Variable	Low FEV_3/FVC	Medium FEV_3/FVC	High FEV_3/FVC	Low vs High		Medium vs High	
				Adjusted Difference (95% CI)†	Adjusted p value	Adjusted Difference (95% CI)†	Adjusted p value
Respiratory symptoms	n=327	n=327	n=327				
mMRC dyspnea scale	0.22 ± 0.48	0.24 ± 0.50	0.24 ± 0.51	−0.02 (−0.07 to 0.02)	0.311	−0.01 (−0.09 to 0.07)	0.739
mMRC dyspnea scale grade 2+*	7 (2.1)	11 (3.4)	9 (2.8)	0.74 (0.24 to 2.28)	0.600	1.08 (0.43 to 2.77)	0.863
CAT score	2.87 ± 3.48	3.36 ± 4.08	3.05 ± 3.92	−0.21 (−0.54 to 0.12)	0.218	0.13 (−0.51 to 0.78)	0.683
CAT score ≥10*	18 (5.5)	28 (8.6)	23 (7.0)	0.71 (0.35 to 1.42)	0.330	1.12 (0.62 to 2.04)	0.707
Acute exacerbations in the previous year*	13 (4.0)	26 (8.0)	21 (6.4)	1.68 (0.78 to 3.64)	0.185	2.10 (1.04 to 4.27)	0.040
Impulse oscillometry	n=305	n=293	n=296				
R5 (kPa/L/s)	0.31 ± 0.08	0.32 ± 0.09	0.33 ± 0.09	0.00 (0.00 to 0.01)	0.209	0.01 (−0.01 to 0.02)	0.417
R20 (kPa/L/s)	0.26 ± 0.06	0.27 ± 0.07	0.29 ± 0.07	0.00 (0.00 to 0.01)	0.291	0.00 (−0.01 to 0.01)	0.629
R5–R20 (kPa/L/s)	0.045 ± 0.037	0.044 ± 0.038	0.044 ± 0.038	0.00 (0.00 to 0.01)	0.450	0.00 (0.00 to 0.01)	0.453
R5–R20 >0.07 kPa/L/s*	52 (17.0)	54 (18.4)	48 (16.2)	1.49 (0.90 to 2.46)	0.120	1.35 (0.85 to 2.15)	0.210
X5 (kPa/L/s)	−0.10 ± 0.04	−0.09 ± 0.04	−0.10 ± 0.04	0.00 (0.00 to 0.00)	0.640	0.00 (−0.01 to 0.01)	0.634
AX (kPa/L)	0.36 ± 0.31	0.34 ± 0.28	0.35 ± 0.26	0.01 (−0.02 to 0.03)	0.520	0.01 (−0.03 to 0.05)	0.582
Fres (Hz)	12.9 ± 3.7	12.7 ± 3.5	12.5 ± 3.3	0.16 (−0.16 to 0.47)	0.323	0.26 (−0.28 to 0.80)	0.347
Computed tomography	n=327	n=327	n=327				
Inspiratory LAA_{-950} (%)	1.0 ± 1.3	0.7 ± 1.3	0.5 ± 1.1	0.06 (−0.04 to 0.16)	0.241	0.07 (−0.11 to 0.26)	0.426
Inspiratory LAA_{-950} > 0.5%*	175 (53.5)	111 (33.9)	60 (18.3)	2.87 (1.90 to 4.34)	<0.001	1.69 (1.12 to 2.55)	0.012
Expiratory LAA_{-856} (%)	8.5 ± 10.3	7.7 ± 12.2	4.6 ± 7.6	0.96 (0.21 to 1.71)	0.013	1.75 (0.23 to 3.26)	0.024
Expiratory LAA_{-856} > 15%*	52 (15.9)	44 (13.5)	28 (8.6)	1.27 (0.72 to 2.21)	0.410	1.21 (0.70 to 2.11)	0.493
Inspiratory Pi10 (mm)	3.48 ± 0.62	3.61 ± 0.69	3.57 ± 0.69	0.03 (−0.03 to 0.08)	0.308	0.10 (2.05 to 3.15)	<0.001
Spirometry-defined SAD*	257 (78.6)	140 (42.8)	64 (19.6)	19.64 (12.60 to 30.61)	<0.001	3.43 (2.35 to 5.01)	<0.001

Notes: Data are mean ± standard deviation (SD) or n (%). Adjusted differences are β coefficients unless otherwise noted. † Adjusted for age, sex, body mass index, smoking status, smoking index, occupational exposure, biomass exposure, and family history of respiratory disease. *Odds ratio.

Abbreviations: Ax, reactance area; CAT, COPD Assessment Test; CI, confidence interval; Fres, resonant frequency in Hz; LAA_{-856}, % of the low-attenuation area < −856 HU on full-expiration computed tomography; LAA_{-950}, % of the low-attenuation area < −950 HU on full-inspiration computed tomography; mMRC, modified Medical Research Council; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5–R20, resistance at 5 and 20 Hz; SAD, small airway dysfunction; X5, reactance at 5 Hz.

0.012). Expiratory LAA_{-856} levels were elevated in both low-and medium-FEV_3/FVC groups compared to the high-group (8.5±10.3% and 7.7±12.2% vs 4.6±7.6%, p = 0.013 and p = 0.024, respectively). The medium-FEV_3/FVC group demonstrated higher Pi10 values than the high-group (3.61±0.69 mm vs 3.57±0.69 mm, difference =0.10 mm, 95% CI: 2.05–3.15, p < 0.001). The prevalence of spirometry-defined SAD was 78.6% in the low-, 42.8% in the medium-, and 19.6% in the high-FEV_3/FVC groups. Odds for SAD were greater in the low-group relative to the high-group (OR=19.64, 95% CI: 12.60–30.61, p<0.001), as did the medium group (OR=3.43, 95% CI: 2.35–5.01, p<0.001) (Table 2).

Annual Reduction in Lung Function

Figure 2 presents the annual lung function decline across the FEV_3/FVC groups.

The longitudinal analysis, which employed mixed-effects regression models adjusted for potential confounders, revealed greater annual declines in the low- versus high-FEV_3/FVC group for pre-bronchodilator FEV_1 (adjusted mean difference: 15 mL, 95% CI: 6 to 25 mL; p = 0.002), FEV_1% (adjusted mean difference: 0.6, 95% CI: 0.2 to 1.1; p = 0.002), FVC (adjusted mean difference: 39 mL, 95% CI:23 to 55 mL; p < 0.001), and FVC% (adjusted mean difference: 1.4, 95% CI: 0.8 to 1.9; p < 0.001). Comparing the high-FEV_3/FVC group, the medium-FEV_3/FVC group showed a greater annual decline in FVC (adjusted mean difference: 22 mL, 95% CI: 6 to 39 mL; p = 0.007) and FVC%. Post-bronchodilator spirometry showed the low-FEV_3/FVC group had lower FEV_1, FVC, and FVC% than the high-FEV_3 /FVC group. The participants in the medium-FEV_3/FVC group also had reduced post-bronchodilator FVC and FVC% compared to those in the high-FEV_3/FVC group (Figure 2).

Risk of Airflow Limitation

Figure 3 shows the proportion of participants with airflow limitation (post-bronchodilator FEV_1/FVC < 0.70) in each FEV_3/FVC group at the three-year follow-up. Compared with the high-FEV_3/FVC group, the low-FEV_3/FVC group had a elevated risk of airway limitation (19.4% [53/273] vs 1.9% [5/258]; adjusted relative risk (RR): 4.96, 95% CI: 1.96–12.51; p = 0.001), based on an adjusted log-binomial regression model adjusted for key demographic and exposure factors (Figure 3A). Among non-SAD individuals, the low-FEV_3/FVC group demonstrated a greater risk of developing airflow limitation than the high-FEV_3/FVC group (Figure 3B).

Acute Respiratory Events

Zero-inflated negative binomial regression revealed no significant difference in rates of acute respiratory events across FEV_3/FVC groups during the 3-year follow-up (Figure 4).

Discussion

This prospective community-based cohort study evaluated the utility of the FEV_3/FVC ratio for early COPD detection. CT imaging at baseline demonstrated that lower FEV_3/FVC ratios were associated with more severe emphysema. Over the 3-year follow-up, individuals in the lowest FEV_3/FVC tertile experienced accelerated lung function decline and an approximately fivefold higher risk of COPD incidence compared to those in the highest tertile.

Our findings appear to align with the "pre-COPD" concept,[3] and suggest that the FEV_3/FVC ratio may provide a supplement to current early detection methods. When considered alongside other proposed early detection approaches, FEV_3/FVC appears to offer some practical advantages. For example, unlike PRISm, which defines a heterogeneous group with variable outcomes, FEV_3/FVC provides a continuous measure.[5,28] Also, while tracking FEV_1 decline rate requires repeated testing over years, FEV_3/FVC enables risk assessment from a single test.[7] Moreover, unlike CT and DL_{CO} measurements that require specialized equipment, the FEV_3/FVC ratio is derived from routine spirometry without the need for additional testing.[8,9] While conventional metrics such as FEF_{25-75}% are widely used to assess SAD, their reproducibility and sensitivity can be limited due to FVC dependence.[17,23] Obtained from routine spirometry without additional maneuvers, the FEV_3/FVC ratio may better capture airflow limitation in distal airways and could offer advantages for detecting early COPD changes.

Notably, individuals with reduced FEV_3/FVC demonstrated lung function decline in the absence of increased exacerbations or oscillometric abnormalities, indicating an early, clinically silent phase of disease. The observed lack

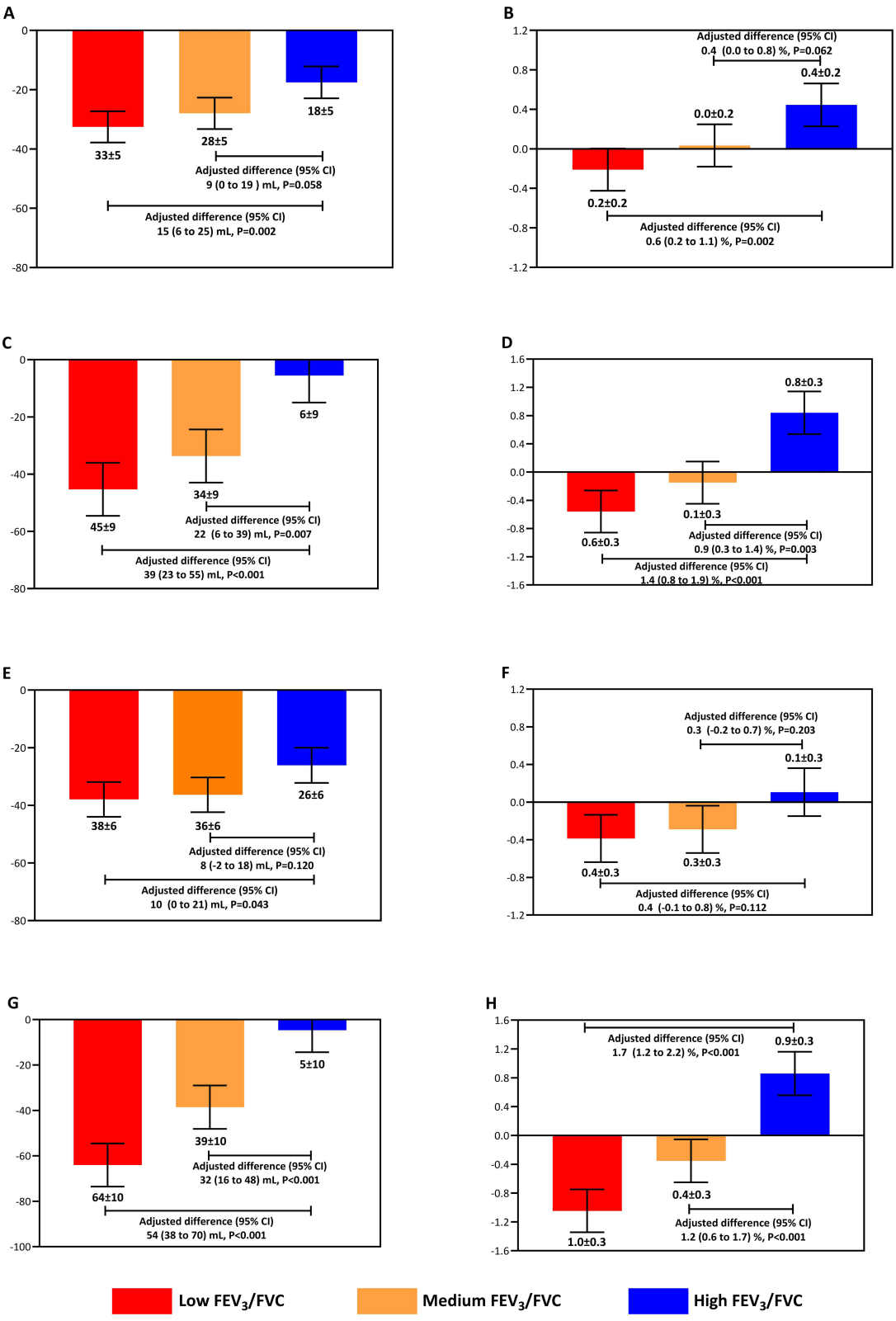

Figure 2 Annual rate of decline in lung function during the 3-year follow-up: (**A**) pre-bronchodilator FEV_1; (**B**) pre-bronchodilator FEV_1% of predicted; (**C**) pre-bronchodilator FVC; (**D**) pre-bronchodilator FVC % of predicted; (**E**) post-bronchodilator FEV_1; (**F**) post-bronchodilator FEV_1% of predicted; (**G**) post-bronchodilator FVC; (**H**) post-bronchodilator FVC % of predicted. Data are presented as mean ± standard deviation. Adjusted differences (95% CI) between groups (Low vs Medium, Low vs High) were calculated using linear mixed-effects models, adjusted for key covariates (eg, age and sex).

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1s; FEV_3, forced expiratory volume in 3s; FVC, forced vital capacity.

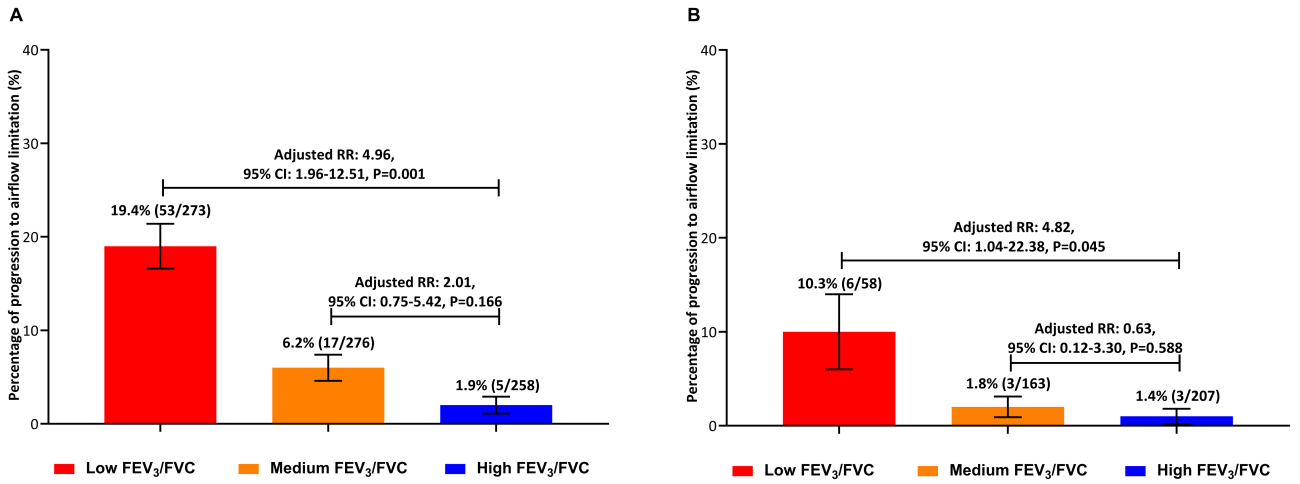

Figure 3 Risk of airflow limitation at the third year of follow-up: (**A**) between different groups and (**B**) between different groups of non-SAD participants. Bars show the cumulative incidence (n/N).
Abbreviations: CI, confidence interval; FEV_3, forced expiratory volume in 3s; FVC, forced vital capacity; RR, relative risk.

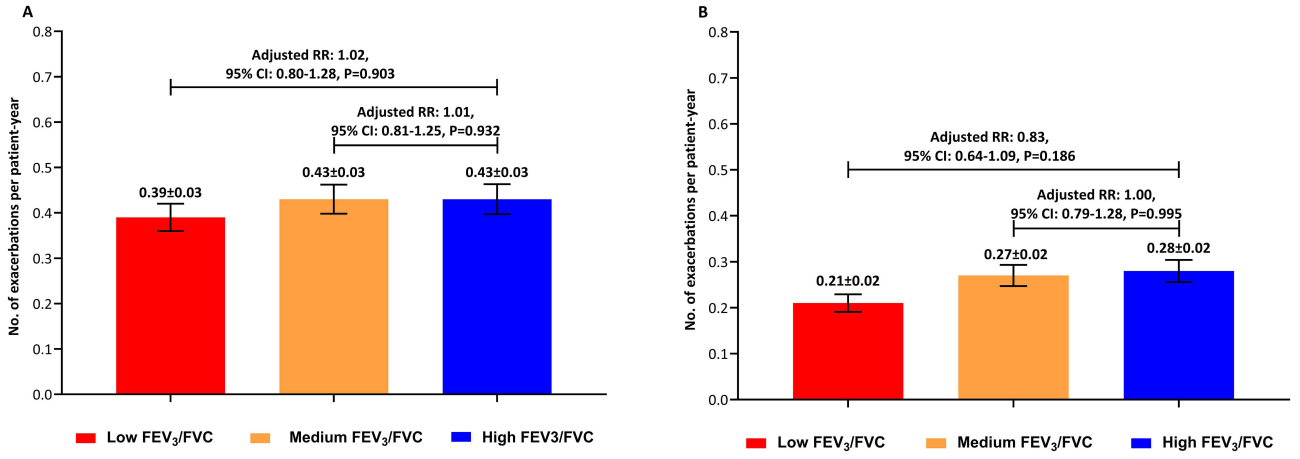

Figure 4 Risk of acute respiratory events during the 3-year follow-up: (**A**) total acute exacerbation; (**B**) moderate-to-severe acute exacerbation.
Abbreviations: CI, confidence interval; FEV_3, forced expiratory volume in 3s; FVC, forced vital capacity; RR, relative risk.

of correlation between FEV_3/FVC and IOS parameters likely reflects fundamental differences in their underlying physiological targets. Specifically, FEV_3/FVC appears more sensitive to air trapping during forced expiration, whereas IOS primarily captures airway resistance during quiet breathing.[12,29] Furthermore, it is possible that although the FEV_3 /FVC values of individuals with normal lung function in this study were categorized as "low", they remained substantially higher than those observed in patients with established COPD. As a result, the corresponding R5–R20 values in this subgroup may not have exhibited significant changes. This interpretation is consistent with our team's prior research, which found only minimal agreement between spirometric, IOS, and CT-based indicators of SAD.[30] The correlation between reduced FEV_3/FVC and emphysema on CT in our findings also suggests that this functional abnormality emerges early in the disease process, before a measurable increase in airway resistance occurs. Consistent with this observation, the observed concurrent decline in FEV_1 and FVC further suggests the involvement of both airway and parenchymal compartments. Specifically, the FEV_1 reduction could relate to increased airway resistance, while the FVC decline may reflect contributions from parenchymal compliance changes and air trapping.[16,31,32] This pattern is consistent with the complex pathophysiology of COPD,[33,34] and supports further investigation of FEV_3/FVC as a composite measure of SAD.

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From a clinical perspective, the principal utility of the FEV_3/FVC ratio lies in its practicality. It is derived from conventional spirometry without requiring additional testing, cost, or patient effort.[23,35] As an efficient and low-cost supplementary tool, it may holds practical value for risk stratification, especially by identifying those with preserved FEV_1/FVC who would otherwise not be identified. In our cohort, individuals in the lowest FEV_3/FVC tertile experienced accelerated lung function decline and an approximately fivefold higher risk of COPD incidence compared to those in the highest tertile over the 3-year follow-up. Furthermore, participants in the medium FEV_3/FVC tertile, who exhibited accelerated lung function decline without a significant increase in COPD incidence, may represent an intermediate group in a preclinical stage of disease. Taken together, these findings suggest that FEV_3/FVC may contribute to early-warning assessments by helping to identify individuals experiencing accelerated lung function decline, before they meet formal diagnostic criteria. The identified risk strata hold potential value for informing clinical management. Based on the risk strata defined by FEV_3/FVC in this study, we tentatively suggest that individuals in the low group could be reasonably prioritized for enhanced interventions, such as supported smoking cessation. Furthermore, for the intermediate group, we suggest more frequent lung function monitoring to detect progression risks. Nevertheless, the observed association between low FEV_3/FVC and disease progression requires consideration of local population characteristics. In general, for individuals with relatively low FEV_3/FVC, we need to implement more intensive risk factor interventions, follow up, and manage their relatively low FEV_3/FVC in order to identify them as early as possible if they progress to COPD. Given the unique risk profiles (eg, smoking patterns, biomass exposure) in our rural Chinese cohort, the notably high incidence suggests that FEV_3/FVC risk thresholds are likely population-specific.[36,37] Therefore, future large-scale studies are needed to establish population-specific reference values and refine the clinical utility of FEV_3/FVC.

Our study has several limitations. Firstly, the absence of a applicable lower limit of normal for FEV_3/FVC in Chinese populations means that the tertile thresholds derived from our cohort require external validation. We acknowledge that this study is only a preliminary finding and that further cohort studies with longer follow-up periods are needed to clarify the findings. Secondly, without histological data, we cannot confirm that reduced FEV_3/FVC reflects structural small airway pathology. Additionally, the 3-year follow-up period is relatively short for defining the natural history of COPD.[1] Finally, a limitation of this study is the attrition of 174 participants (17.7%) over the 3-year follow-up period. While this rate is consistent with, or even lower than, that reported in other long-term COPD cohort studies,[28,38] it may still introduce potential bias. Nevertheless, our follow-up rate of over 80% is generally considered acceptable in epidemiological research to maintain the validity of the findings.[39]

Conclusion

These findings suggest that the FEV_3/FVC ratio could serve as a useful composite marker for early COPD risk assessment. As a simple measure derived from routine spirometry, it may help identify individuals with imaging abnormalities and accelerated lung function decline. The ratio shows potential for primary care screening, though further studies are needed to establish population-specific thresholds and confirm its clinical utility in COPD prevention strategies.

Abbreviations

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEF50%, forced expiratory flow at 50% of forced vital capacity; FEF75%, forced expiratory flow at 75% of forced vital capacity; FEF25–75%, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1s; FEV_3, forced expiratory volume in 3s; FVC, forced vital capacity; LAA, low-attenuation area; mMRC, Modified Medical Research Council; SAD, small airway dysfunction.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding authors, Pixin Ran or Yumin Zhou, upon reasonable request.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2018-53). All participants provided written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors disclose no conflicts of interest.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of chronic obstructive pulmonary disease 2025. 2025. Available from: https://goldcopd.org/2025-gold-report/. Accessed May 13, 2025.
2. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*. 2002;166(3):329–332. doi:10.1164/rccm.2112048
3. Han MK, Agusti A, Celli BR, et al. From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med*. 2021;203(4):414–423. doi:10.1164/rccm.202008-3328PP
4. Lei J, Huang K, Wu S, et al. Heterogeneities and impact profiles of early chronic obstructive pulmonary disease status: findings from the China pulmonary health study. *Lancet Reg Health West Pac*. 2024;45:101021. doi:10.1016/j.lanwpc.2024.101021
5. Wijnant SRA, De Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam study. *Eur Respir J*. 2020;55(1):1901217. doi:10.1183/13993003.01217-2019
6. Robertson NM, Centner CS, Tejwani V, et al. Preserved ratio impaired spirometry prevalence, risk factors, and outcomes: a systematic review and meta-analysis. *Chest*. 2025;167(6):1591–1614. doi:10.1016/j.chest.2024.12.025
7. Petersen H, Sood A, Polverino F, et al. The course of lung function in middle-aged heavy smokers: incidence and time to early onset of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(11):1449–1451. doi:10.1164/rccm.201805-0861LE
8. Sharma M, Kirby M, McCormack DG, Parraga G. Machine learning and CT texture features in ex-smokers with no CT evidence of emphysema and mildly abnormal diffusing capacity. *Acad Radiol*. 2024;31(6):2567–2578. doi:10.1016/j.acra.2023.11.022
9. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49(1):1600016. doi:10.1183/13993003.00016-2016
10. Higham A, Quinn AM, Cançado JED, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. *Respir Res*. 2019;20(1):49. doi:10.1186/s12931-019-1017-y
11. Xiao D, Chen Z, Wu S, et al. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. *Lancet Respir Med*. 2020;8(11):1081–1093. doi:10.1016/s2213-2600(20)30155-7
12. Morris ZQ, Coz A, Starosta D. An isolated reduction of the FEV3/FVC ratio is an indicator of mild lung injury. *Chest*. 2013;144(4):1117–1123. doi:10.1378/chest.12-2816
13. Lam DC, Fong DY, Yu WC, et al. FEV3, FEV6 and their derivatives for detecting airflow obstruction in adult Chinese. *Int J Tuberc Lung Dis*. 2012;16(5):681–686. doi:10.5588/ijtld.11.0283
14. Hansen JE, Sun XG, Wasserman K. Discriminating measures and normal values for expiratory obstruction. *Chest*. 2006;129(2):369–377. doi:10.1378/chest.129.2.369
15. Hoesterey D, Das N, Janssens W, et al. Spirometric indices of early airflow impairment in individuals at risk of developing COPD: spirometry beyond FEV(1)/FVC. *Respir Med*. 2019;156:58–68. doi:10.1016/j.rmed.2019.08.004
16. Hogg JC, Paré PD, Hackett TL. The contribution of small airway obstruction to the pathogenesis of chronic obstructive pulmonary disease. *Physiol Rev*. 2017;97(2):529–552. doi:10.1152/physrev.00025.2015
17. Li Y, Li XY, Yuan LR, Wang HL, Pang M. Evaluation of small airway function and its application in patients with chronic obstructive pulmonary disease (Review). *Exp Ther Med*. 2021;22(6):1386. doi:10.3892/etm.2021.10822
18. Knox-Brown B, Mulhern O, Feary J, Amaral AFS. Spirometry parameters used to define small airways obstruction in population-based studies: systematic review. *Respir Res*. 2022;23(1):67. doi:10.1186/s12931-022-01990-2
19. Wu F, Zhou Y, Peng J, et al. Rationale and design of the early chronic obstructive pulmonary disease (ECOPD) study in Guangdong, China: a prospective observational cohort study. *J Thorac Dis*. 2021;13(12):6924–6935. doi:10.21037/jtd-21-1379

20. Bowerman C, Bhakta NR, Brazzale D, et al. A race-neutral approach to the interpretation of lung function measurements. *Am J Respir Crit Care Med*. 2023;207(6):768–774. doi:10.1164/rccm.202205-0963OC
21. Zhong N, Wang C, Yao W, et al. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. *Am J Respir Crit Care Med*. 2007;176(8):753–760. doi:10.1164/rccm.200612-1749OC
22. Kim S, Oh J, Kim YI, et al. Differences in classification of COPD group using COPD assessment test (CAT) or modified medical research council (mMRC) dyspnea scores: a cross-sectional analyses. *BMC Pulm Med*. 2013;13(1):35. doi:10.1186/1471-2466-13-35
23. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. an official american thoracic society and european respiratory society technical statement. *Am J Respir Crit Care Med*. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
24. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the quantitative imaging network. *Magn Reson Imaging*. 2012;30(9):1323–1341. doi:10.1016/j.mri.2012.05.001
25. Labaki WW, Martinez CH, Martinez FJ, et al. The role of chest computed tomography in the evaluation and management of the patient with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;196(11):1372–1379. doi:10.1164/rccm.201703-0451PP
26. Dransfield MT, Kunisaki KM, Strand MJ, et al. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(3):324–330. doi:10.1164/rccm.201605-1014OC
27. Wu F, Huang S, Zhou K, et al. Clinical validation of a multidimensional diagnostic approach for chronic obstructive pulmonary disease in Chinese. *Chest*. 2025. doi:10.1016/j.chest.2025.10.002
28. Perez-Padilla R, Montes de Oca M, Thirion-Romero I, et al. Trajectories of spirometric patterns, obstructive and PRISm, in a population-based cohort in Latin America. *Int J Chron Obstruct Pulmon Dis*. 2023;18:1277–1285. doi:10.2147/copd.S406208
29. Kolsum U, Borrill Z, Roy K, et al. Impulse oscillometry in COPD: identification of measurements related to airway obstruction, airway conductance and lung volumes. *Respir Med*. 2009;103(1):136–143. doi:10.1016/j.rmed.2008.07.014
30. Huang S, Wu F, Deng Z, et al. Comparing spirometry, impulse oscillometry with computed tomography for assessing small airway dysfunction in subjects with and without chronic obstructive pulmonary disease. *BMC Pulm Med*. 2025;25(1):45. doi:10.1186/s12890-025-03507-1
31. Burgel PR, Bourdin A, Chanez P, et al. Update on the roles of distal airways in COPD. *Eur Respir Rev*. 2011;20(119):7–22. doi:10.1183/09059180.10010610
32. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet*. 2004;364(9435):709–721. doi:10.1016/s0140-6736(04)16900-6
33. Yoo S, Takikawa S, Geraghty P, et al. Integrative analysis of DNA methylation and gene expression data identifies EPAS1 as a key regulator of COPD. *PLoS Genet*. 2015;11(1):e1004898. doi:10.1371/journal.pgen.1004898
34. Sood A, Petersen H, Blanchette CM, et al. Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers. *Am J Respir Crit Care Med*. 2010;182(9):1098–1104. doi:10.1164/rccm.201002-0222OC
35. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. ;2022;60(1):2101499. doi:10.1183/13993003.01499-2021
36. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet*. 2018;391(10131):1706–1717. doi:10.1016/s0140-6736(18)30841-9
37. Zhou Y, Zou Y, Li X, et al. Lung function and incidence of chronic obstructive pulmonary disease after improved cooking fuels and kitchen ventilation: a 9-year prospective cohort study. *PLoS Med*. 2014;11(3):e1001621. doi:10.1371/journal.pmed.1001621
38. Yohannes AM, Müllerová H, Hanania NA, et al. Long-term course of depression trajectories in patients with COPD: a 3-year follow-up analysis of the evaluation of COPD longitudinally to identify predictive surrogate endpoints cohort. *Chest*. 2016;149(4):916–926. doi:10.1016/j.chest.2015.10.081
39. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology*. 2006;17(4):413–418. doi:10.1097/01.ede.0000220549.14177.60