Original Research

Borderline Forced Expiratory Volume in 1 Second to Forced Vital Capacity and Low Forced Expiratory Volume in 1 Second Predict Disease Progression in High-Risk Populations With COPD

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***Running Head*: Low FEV_1/FVC and FEV_1 Predict COPD Progression**

***Keywords*:** high risk population of COPD; disease progression; borderline ratio; PRISm; low FEV_1

Abbreviations:
COPD – Chronic obstructive pulmonary disease; FEV_1 – Forced expiratory volume in 1 second; FVC – Forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; PRISm – Preserved ratio impaired spirometry; UKB – UK Biobank; BMI – Body mass index; OR – Odds Ratio; CI – Confidence Interval; HR – Hazard Ratio; COVID-19 – Coronavirus disease 2019; AUC – Area under the curve; CT – Computed tomography; COPD-Q – Chronic Obstructive Pulmonary Disease Questionnaire; CAPTURE – Chronic Obstructive Pulmonary Disease Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk; VO – Variable obstruction; TFF2 – Trefoil factor 2;

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Abstract

Background and objectives: The ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC), and the proportion of predicted forced expiratory volume in one second (FEV_1 % predicted) are used to diagnose and determine the disease severity in chronic obstructive pulmonary disease (COPD). This study investigated the prognostic capabilities of borderline FEV_1/FVC and low FEV_1 on disease progression among a population at high risk for COPD.

Methods: This study utilized two-year follow-up data from the national COPD screening program. Participants were divided into four groups according to FEV_1/FVC and FEV_1: normal ratio with normal FEV_1, borderline ratio with normal FEV_1, normal ratio with low FEV_1, and borderline ratio with low FEV_1. The outcomes were FEV_1 decline and progression to airway obstruction.

Results: This study included a total of 2969 patients at high risk for COPD. Compared with the normal ratio with normal FEV_1 group, the borderline ratio with normal FEV_1 (adjusted odds ratio [OR]=1.81, 95% confidence interval [CI]: 1.34 to 2.44) and borderline ratio with low FEV_1 (adjusted OR=2.32, 95%CI: 1.46 to 3.69) groups showed higher risks of developing airway obstruction, while the normal ratio with low FEV_1 group showed no significant change in risk (adjusted OR=1.31, 95%CI: 0.83 to 2.07). Further, the findings also be proved in the general population with longer follow years by using data from UKB (the borderline ratio with normal FEV_1 group: adjusted hazard ratio [HR] = 2.92, 95% CI: 2.28 to 3.74; and borderline ratio with

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low FEV_1 group: adjusted HR = 4.53, 95% CI: 3.21 to 6.38).

Conclusion: Participants with borderline FEV_1/FVC had a higher risk of developing airway obstruction, regardless of a decline in FEV_1.

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Introduction

Chronic obstructive pulmonary disease (COPD) imposes a significant global disease burden and is a major cause of morbidity and mortality, particularly in China.[1,2] Lung damage often occurs before clinical symptoms or spirometry abnormalities are evident.[3,4] Therefore, early identification of high-risk individuals is important for timely interventions and potentially slowing disease progression.

The standard diagnostic criterion for COPD is based on spirometry, specifically a forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.7 in symptomatic individuals with relevant risk factors.[5] Individuals with an FEV_1/FVC ratio >0.8 have a low likelihood of progressing to airway obstruction.[6] In addition, several studies have proposed using an FEV_1/FVC threshold of 0.8 to better identify patients with obstructive abnormalities and reduce misclassification of restrictive pulmonary processes.[7-9]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends staging COPD based on the proportion of predicted forced expiratory volume in one second (FEV_1 % predicted), with GOLD stages 1–4 corresponding to ≥80%, 50–80%, 30–50%, and <30%, respectively.[10] Decline in FEV_1 is considered a marker of disease deterioration, distinct from the diagnostic criterion of FEV_1/FVC. However, patients not meeting COPD diagnostic thresholds may still exhibit decreased FEV_1, even below 80% of the FEV_1 %. This recognition has led to concepts such as preserved ratio impaired spirometry (PRISm). PRISm emphasizes smoking history and reduced FEV_1 or FVC despite a normal FEV_1/FVC ratio, but encompasses a

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heterogeneous group of complex lung conditions. By contrast, impaired FVC with a preserved FEV_1/FVC ratio defines a restrictive pattern.[11]

Spirometry, an objective and validated measurement, serves as a biomarker for disease progression, including measurements of FEV_1, FVC, FEV_1/FVC, peak expiratory flow, and diffusing capacity for carbon monoxide.[12-15] Given the complexity of spirometry, several studies have focused on the diagnostic relevance of a "normal but low" FEV_1/FVC ratio, which we called "borderline ratio" in current study. Meanwhile, reduced FEV_1 % predicted is often considered a feature of PRISm, yet has rarely been studied in combination with borderline FEV_1/FVC.

Therefore, the present study focused on a simple spirometry pattern defined by both FEV_1/FVC and FEV_1 % predicted in a population of patients at high risk for COPD. We examined the association between borderline ratio, PRISm (low FEV_1) with risk of developing airflow obstruction and FEV_1 decline, using data from the national COPD screening program in China. We then validated our findings in the general population using the UK Biobank (UKB).

Methods

Study design

In this study, we analyzed data from a high-risk COPD population in the National COPD Screening Program in China and validated our findings in the general population using the UK

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Biobank (UKB).

We included participants with normal lung function at baseline ($FEV_1/FVC \geq 0.7$) who had completed at least one follow-up assessment. For simplicity, we used the term 'low FEV_1' to represent FEV_1 % predicted <80%, instead of the PRISm classification. Based on the baseline lung function, participants were categorized into four subgroups: normal ratio with normal FEV_1 ($FEV_1/FVC \geq 0.8$, FEV_1 % predicted ≥80%), borderline ratio with normal FEV_1 ($0.7 \leq FEV_1/FVC < 0.8$, FEV_1 % predicted ≥80%), normal ratio with low FEV_1 ($FEV_1/FVC \geq 0.8$, FEV_1 % predicted <80%), and borderline ratio with low FEV_1 ($0.7 \leq FEV_1/FVC < 0.8$, FEV_1 % predicted ≥80%). The definitions of these subgroups are illustrated in Figure 1.

We also analyzed participants according to FEV_1/FVC or FEV_1 % predicted separately: FEV_1/FVC was categorized as normal ($FEV_1/FVC \geq 0.8$) and borderline ($0.7 \leq FEV_1/FVC < 0.8$), and FEV_1 was categorized as normal (FEV_1 % predicted ≥80%) or PRISm (also called "low FEV_1", FEV_1 % predicted <80%).

This study focused on the risk of FEV_1 decline and progression to airway obstruction in participants at high risk for COPD. FEV_1 decline was treated as both continuous and categorical variable. For the continuous variable, the value was defined as the follow-up FEV_1 minus the baseline FEV_1. Categorical of rapid FEV_1 decline was defined as an annual decrease of >50 mL, based on prior evidence showing a mean annual decline of ~50 mL in the general population.[16] Airway obstruction during follow-up was defined as post-bronchodilation $FEV_1/FVC < 0.7$.

Analyses were performed separately in the high-risk COPD cohort and the general population

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cohort to assess the consistency of findings across different populations.

The National COPD Screening Program in China

Data for this study were derived from the National COPD Screening Program in China, details of which have been described previously.[17] Briefly, residents aged 35–75 years from 160 districts or counties across 31 provinces in China participated in an online screening using the COPD Screening Questionnaire (COPD-SQ), which captures age, smoking history, body mass index (BMI), respiratory symptoms, biomass exposure, and family history.[18] Using a cut-off score of 16 points, the COPD-SQ correctly classifies 82.7% of patients, and is associated with a high area under the curve (AUC) of 0.829. Participants with a COPD-SQ score >16 were considered high-risk and invited to attend on-site screening, which included a detailed survey questionnaire and pre- and post-bronchodilation spirometry, followed by regular follow-ups. Data on relevant risk factors, symptoms, and pulmonary function were repeatedly collected during follow-up visits.

The National COPD Screening Program was officially launched in October 2021. However, due to disruptions caused by the coronavirus disease 2019 (COVID-19) pandemic, 3262 participants completed 2 years of follow-up, including full questionnaire responses and spirometry data, by July 2024. The present analysis included all participants who completed the 2-year follow-up and focused on individuals without COPD at baseline (Figure 2).

The program was approved by the Institutional Review Board of China–Japan Friendship

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Hospital (approval number: 2021-145-K103). All participants provided written informed consent.

UK Biobank

The UKB is a nationwide cohort of 502,394 participants aged 37–73 years, recruited between 2006 and 2010, with detailed baseline data collected via touchscreen questionnaires, nurse interviews, physical measurements, and biological samples, encompassing sociodemographic factors, lifestyle, diet, and reproductive history.

Ethical approval for the UKB study was obtained from the Northwest Multicenter Research Ethics Committee. All methods were performed following the relevant guidelines and regulations. This study was conducted using resources provided by the UK Biobank (application number 277441).

Data collection

The National COPD Screening Program in China used questionnaires to collect baseline information, including sex, age, annual income, education, marital status, employment, job type (indoor or outdoor), clean fuel use, smoking status, secondhand smoke exposure, family history of COPD, comorbidities, and respiratory symptoms. Anthropometric measurements, including height, weight, waist circumference, and hip circumference, were recorded on-site. BMI was

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calculated as body weight (kg)/height (m^2).

From the UKB database, data on participant, age, ethnicity, smoking status, and respiratory symptoms, height, weight, and BMI were collected.

All participants underwent spirometry according to the American Thoracic Society and European Respiratory Society guidelines.[19] Trained medical staff performed spirometry using portable pulmonary function measurement devices in primary care settings. The present analysis used pre-bronchodilator lung function in both datasets. Quality control was conducted by expert teams at provincial and national levels following guideline recommendations.[19] The predicted values of FEV_1 and FVC were calculated using the reference equations derived from the general Chinese population[20] for the National COPD Screening Program. The UKB used the race-neutral equations from the Global Lung Function Initiative (GLI Global).[21]

Statistics

Descriptive data are presented as means ± standard deviation for continuous variables and frequencies for categorical variables. Differences between groups were assessed using Student's t-test, Mann–Whitney U test, or one-way analysis of variance (ANOVA) for continuous variables, and χ^2 test for categorical variables. Comparisons were made between the borderline ratio and normal spirometry groups, as well as between the PRISm (low FEV_1) and normal spirometry groups. Changes in spirometry patterns from baseline to the 2-year follow-up were

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visualized using Sankey plots. Changes in lung function were measured as the difference between follow-up and baseline values, including FEV_1 change and FEV_1 % predicted change. In the National COPD Screening Program, lung function change over 2 years was directly calculated, whereas in the UKB, annual lung function changes were calculated instead due to variable follow-up times.

In the National COPD Screening Program, the follow-up times were consistent. Thus, logistic regression models were applied to analyze the risk of developing airflow obstruction and rapid FEV_1 decline, reported as odds ratios (ORs) and 95% confidence intervals (CIs). In the UKB, as the follow-up times differed, Cox regression models were used to measure the risk of disease progression, reported as hazard ratios (HRs) and 95% CIs. Sensitivity analyses were performed separately for the borderline ratio and PRISm (low FEV_1) groups. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for education level, income, ethnicity, BMI, smoking status, smoking pack years and other relevant factors. Further analysis of National COPD Screening Program data using univariable and multivariable logistic regression models identified risk factors for airway obstruction and rapid FEV_1 decline within the borderline ratio and PRISm (low FEV_1) groups. Sensitivity analyses were also performed using the GLI Global equations to calculate predicted FEV_1 and FVC in the National COPD Screening Program.

Statistical significance was defined as two-sided $p < 0.05$. All analyses were performed using R software (version 4.3.0).

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Results

Baseline characteristics of the enrolled high-risk population of COPD

This study analyzed a total of 2969 participants at high risk for COPD, including 1476 in the normal ratio with normal FEV_1 group, 981 in the borderline ratio with normal FEV_1 group, 321 in the normal ratio with low FEV_1 group, and 191 in the borderline ratio with low FEV_1 group. Table 1 shows their basic characteristics. The mean ages in the normal ratio with normal FEV_1, borderline ratio with normal FEV_1, normal ratio with low FEV_1, and borderline ratio with low FEV_1 groups were 60.77, 61.18, 60.25 and 62.31 years, respectively. The proportion of male participants was highest in the normal ratio with low FEV_1 group (78.5%). The normal ratio with low FEV_1 group showed the highest proportion of comorbidities (23.7%). The borderline ratio with low FEV_1 group showed the highest smoking exposure (40.29 pack-years) and the highest proportion of symptoms (46.1%). Supplementary Table 1 shows the characteristics of the participants stratified by borderline ratio and PRISm (low FEV_1), separately.

Changes in spirometry measurements over the 2-year follow-up revealed significant lung function decline in the borderline ratio with normal FEV_1 group (Supplementary Table 2). In contrast, lung function improved slightly in the normal spirometry and PRISm (low FEV_1) group but remained impaired in the borderline ratio group (Supplementary Table 3).

We also calculated the proportion of participants experiencing rapid FEV_1 decline and airway obstruction at the 2-year follow-up. The borderline ratio with normal FEV_1 group showed the

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highest proportion of participants with rapid FEV_1 rapid (47.6%), while the borderline ratio with low FEV_1 group showed the highest proportion of participants with airway obstruction (15.2%) (Supplementary Table 2) Figure 3 illustrates the changes in spirometry pattern from baseline to the 2-year follow-up, showing that most newly diagnosed cases of airway obstruction developed in patients in the borderline ratio group (43.1%).

Risk of progressing to airway obstruction

We explored the risk of progressing to airway obstruction in each group. Compared with the normal ratio with normal FEV_1 group, the borderline ratio with low FEV_1 group (adjusted OR = 2.32, 95% CI: 1.46 to 3.69) and borderline ratio with normal FEV_1 (adjusted OR = 1.81, 95% CI: 1.34 to 2.44) groups had higher risks of developing airway obstruction. By contrast, participants in the normal ratio with low FEV_1 group showed no significant risk of developing airway obstruction compared with the normal ratio with normal FEV_1 group (adjusted OR = 1.31, 95% CI: 0.83 to 2.07). Further, compared with individuals with normal spirometry, those with borderline ratio (adjusted OR = 1.97, 95% CI: 1.47 to 2.62) and PRISm (low FEV_1) (adjusted OR = 1.69, 95% CI: 1.17 to 2.44) had higher risks of developing airway obstruction (Table 2).

We further explored potential risk factors for airway obstruction within the borderline ratio group. Older age (adjusted OR = 1.07, 95% CI: 1.02 to 1.12) and secondhand smoke (adjusted OR = 2.38, 95% CI: 1.18 to 4.80) were identified as significant predictors, while female had the

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lower risk than male (adjusted OR = 0.23, 95% CI: 0.07 to 0.85) (Supplementary Table 4). In the PRISm (FEV_1) group, multivariable logistic analysis identified no significant risk factors for developing airway obstruction (Supplementary Table 5).

Risk of FEV_1 decline

For FEV_1 decline treated as the continuous variable, borderline ratio with normal FEV_1 group showed higher FEV_1 decline than normal ratio with normal FEV_1 group (adjusted β = -0.15, 95% CI: -0.21 to -0.10), while the borderline ratio with low FEV_1 (adjusted β = 0.62, 95% CI: 0.52 to 0.72) and normal ratio with low FEV_1 (adjusted β = 1.01, 95% CI: 0.93 to 1.09) groups showed less decline of FEV_1. Analysis of single spirometry parameter showed that borderline ratio group exhibited more decline of FEV_1 than normal spirometry group after adjusted for age and sex (adjusted β = -0.07, 95% CI: -0.13 to -0.02), but the results turned non-significant after adjusted for more other factors (adjusted β = -0.03, 95% CI: -0.09 to 0.02). PRISm (low FEV_1) group showed less decline of FEV_1 than normal group (adjusted β = 0.86, 95% CI: 0.79 to 0.93) (Table 3).

The borderline ratio with normal FEV_1 group showed an increased risk of rapid FEV_1 decline (adjusted OR = 1.26, 95% CI: 1.06 to 1.49). Conversely, the borderline ratio with low FEV_1 (adjusted OR = 0.18, 95% CI: 0.11 to 0.29) and normal ratio with low FEV_1 (adjusted OR = 0.08, 95% CI: 0.04 to 0.13) groups showed lower risks of rapid FEV1 decline compared with the

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normal ratio with normal FEV_1 group. Analysis by single spirometry patterns showed that participants in the borderline ratio group had a similar risk of rapid FEV_1 decline as the normal ratio group (adjusted OR = 1.01, 95% CI: 0.86 to 1.19), whereas participants with PRISm (low FEV_1) had a markedly lower risk (adjusted OR = 0.10, 95% CI: 0.07 to 0.15) (Table 3).

We further investigated the potential risk factors for FEV1 rapid decline in the borderline ratio and PRISm (low FEV_1) groups. In the borderline ratio group, multivariable logistic analysis indicated work indoor was the protective factor (adjusted OR = 0.45, 95% CI: 0.26 to 0.78). Current smokers also showed the lower risk of rapid FEV_1 decline (adjusted OR = 0.45, 95% CI: 0.21 to 0.96), which may be explained by the worse basic statement (Supplementary Table 6). In the PRISm (low FEV_1) group, no significant factors were found related to rapid FEV_1 decline (Supplementary Table 7).

Analysis in the general population based on UKB data

The analysis of the general population used data from 35,585 participants in the UKB without airway obstruction ($FEV_1/FVC \geq 0.7$), including 10,684 in the normal ratio with normal FEV_1 group, 23,108 in the borderline ratio with normal FEV_1 group, 313 in the normal ratio with low FEV_1 group, and 1,480 in the borderline ratio with low FEV_1 group. (Supplementary Figure 1) The basic characteristics of the general population were similar to those for the high-risk population (Supplementary Tables 8 and 9).

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Lung function changes over follow-up in each group were consistent with the findings in the high-risk COPD cohort (Supplementary Tables 10 and 11).

Regarding the risk of developing airway obstruction, the borderline ratio with normal FEV_1 (adjusted HR = 2.92, 95% CI: 2.28 to 3.74) and borderline ratio with low FEV_1 (adjusted HR = 4.53, 95% CI: 3.21 to 6.38) groups had significantly higher risks compared with the normal ratio with normal FEV_1 group. In contrast, the normal ratio with low FEV_1 group showed a non-significant increase in risk (adjusted HR = 0.60, 95% CI: 0.08 to 4.35) (Table 4).

Borderline ratio with normal FEV_1 group had the similar annual FEV_1 change with normal ratio with normal FEV_1 group (adjusted $\beta = 0.00$, 95% CI: 0.00 to 0.01), while normal ratio with low FEV_1 group (adjusted $\beta = 0.06$, 95% CI: 0.04 to 0.07) and borderline ratio with low FEV_1 (adjusted $\beta = 0.05$, 95% CI: 0.04 to 0.05) showed less decline. Regarding rapid FEV_1 decline, the borderline ratio with low FEV_1 group showed a higher risk than the normal ratio with normal FEV_1 group in the unadjusted model (HR = 1.09, 95%CI: 1.04-1.13). However, this association was not significant after adjusting for covariates (adjusted HR = 0.97, 95%CI: 0.88–1.07) (Table 5).

Sensitivity analysis using the GLI Global reference equations

We performed sensitivity analyses using the GLI Global reference equations to calculate predicted lung function values in the National COPD Screening Program. Among the 2,969 high-

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risk COPD participants, baseline characteristics were similar to those obtained using the Chinese reference equations (Supplementary Tables 12 and 13).

Lung function changes showed some differences. The highest proportion of rapid FEV_1 decline was observed in the borderline ratio with normal FEV_1 group (47.1%) (Supplementary Table 14). The normal and borderline FEV_1/FVC groups showed similar proportions of participants with rapid FEV_1 decline (39.2% vs. 40.7%, p=0.462) (Supplementary Table 15).

Regarding the risk of developing airway obstruction, the borderline ratio with low FEV_1 groups showed the highest risk among the three subgroups (adjusted OR = 2.66, 95% CI: 1.74 to 4.08) (Supplementary Table 16).

The findings regarding the FEV_1 decline were consistent with those using the Chinese reference equations. The borderline ratio with normal FEV_1 group showed more decline in FEV_1 (adjusted β = -0.15, 95% CI: -0.21 to -0.10) and higher risk of rapid FEV_1 decline (adjusted OR = 1.23, 95% CI: 1.04–1.46) than the normal spirometry groups (Supplementary Table 17).

Discussion

This study evaluated the risk of disease progression in a high-risk population for COPD, considering both borderline FEV_1/FVC (defined as $0.7 \leq FEV_1/FVC < 0.8$) and low FEV_1 (defined as FEV_1 % predicted ≤80%). Our results demonstrated that both measures are risk factors for disease progression, especially among participants with borderline ratio with low

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FEV_1 and borderline ratio with normal FEV_1. The findings were also observed among the general population.

In high-risk cohort, participants with borderline ratio with normal FEV_1 had the highest risk of rapid FEV_1 decline, while in UKB, the results turned non-significant. The UKB cohort had a substantially longer follow-up period (median 8 years) compared with the Chinese high-risk cohort (2 years). Longer follow-up inevitably captures more incident COPD events, yet the overall trends across subgroups remained directionally consistent. Importantly, lung function decline is not strictly linear; the rate of decline tends to diminish over time. This nonlinear pattern may explain why the association between borderline ratio and FEV1 decline was more pronounced in the Chinese high-risk cohort than UKB cohort. We should not overlook the fact that in high-risk populations, accelerated decline occurs predominantly in the early years—a clinically meaningful phenomenon that shorter-term studies are better positioned to capture.

Previous studies have emphasized the role of PRISm (low FEV_1) in early adulthood and suggested that accelerated FEV_1 decline is not a universal feature of COPD.[22,23] Our findings also support the importance of PRISm (low FEV_1), but not necessarily rapid FEV_1 decline, in predicting the risk of airway obstruction. The PRISm (low FEV_1) group in the present study showed increases in FEV_1, suggesting that the ratio decreased partly due to increased FVC. Some individuals in this group even reverted to normal lung function, consistent with earlier reports.[24,25] Baseline analysis also showed that individuals in the borderline ratio group had higher spirometry values, which may partially explain the observed “rapid decline,” reflecting a

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"more to lose" phenomenon described in different stages of COPD.[26,27] However, despite similar baseline lung function, individuals in the borderline ratio with normal FEV_1 group had a significantly higher risk of FEV_1 decline compared with those with normal spirometry, highlighting the need for greater clinical attention to this subgroup.

The concept of a pre-clinical stage of COPD, like pre-diabetes and pre-hypertension, has gained attention in recent years. Han and colleagues[28] proposed in 2021 that pre-clinical COPD should be defined by abnormalities in symptoms, structure, and function, with at least two criteria required.[28] However, this approach is limited: symptoms rely on subjective reporting, structural assessment usually requires computed tomography (CT) imaging, which is not widely available in primary care, and functional assessment depends on lung function trajectories. Thus, identifying pre-COPD individuals in the general population remains challenging. GOLD now recommends case-finding in high-risk populations using simple questionnaires such as the CAPTURE.[29]

Recent efforts have also highlighted the limitations of a spirometry-only diagnostic approach. In a large cohort study, a multidimensional diagnostic schema incorporating respiratory symptoms, quality of life, spirometry, and structural lung abnormalities assessed on chest CT reclassified a subset of individuals without airflow obstruction as having COPD.[30] While multidimensional approaches offer comprehensive risk assessment, their implementation in primary care is limited by the need for imaging and detailed questionnaires. In this context, simple objective spirometry-based markers such as borderline FEV_1/FVC may serve as a practical first-step screening tool to

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identify high-risk individuals who warrant further multidimensional evaluation.

Several spirometry-based definitions of "at-risk" for COPD have been proposed. One of the most well-known of these, PRISm, is characterized by a normal FEV_1/FVC ratio but reduced predicted FEV_1 or FVC among current or former smokers and is associated with a higher risk of developing COPD and increased mortality.[13,15,24,25,31] However, PRISm classification depends on predicted values, and therefore on reference equations. Similarly, defining high-risk status based on pre-bronchodilator FEV_1/FVC below the 10th percentile has been shown to predict COPD, but requires reference standards.[32] Buhr and colleagues introduced the concept of variable obstruction (VO), defined as pre-bronchodilation $FEV_1/FVC < 0.7$ and post-bronchodilation $FEV_1/FVC \geq 0.7$ to identify individuals at increased risk for developing COPD.[33] However, VO requires bronchodilation testing, which limits its applicability. In contrast, the current study showed that borderline FEV_1/FVC is a robust and easily applicable risk factor for airway obstruction, independent of reference equations or bronchodilation. Moreover, individuals in the borderline FEV_1/FVC but normal FEV_1 group were at risk of both obstruction and rapid decline—an at-risk subgroup not highlighted in prior studies. We suggest that an FEV_1/FVC ratio between 0.7 and 0.8 may represent a clinically meaningful threshold for risk stratification in primary care settings.

We also identified clinical factors that may further increase risk among individuals with borderline FEV_1/FVC or low FEV_1. However, most of these were self-reported and subject to bias. Previous studies have investigated biomarkers for identifying individuals at risk of rapid

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lung function decline, particularly in patients with asthma,[34,35] bronchiectasis,[36] and COPD.[37] A recent multi-cohort study of 6722 participants identified 15 proteins associated with FEV_1 decline, including elafin, leukocyte elastase inhibitor, and mucin-associated trefoil factor 2 (TFF2).[38]

Future research should involve larger cohorts with a longer follow-up period to validate the prognostic value of borderline FEV_1/FVC in China. Beyond spirometry, integrating clinical, imaging, and biomarker data may improve identification of individuals at the highest risk for COPD progression. Importantly, no effective interventions currently exist for individuals in the early stages to delay disease progression. Potential available strategies are predominantly non-pharmacological, including smoking cessation and pulmonary rehabilitation. One previous study on bronchodilator therapy in symptomatic smokers with preserved lung function have not demonstrated efficacy.[39] Several novel pharmacological agents have emerged, including ensifentrine[40] and dupilumab[41]. Therefore, further interventional research focusing on the early stages of the disease is warranted to identify more effective approaches to slow disease progression.

This study has several limitations. First, the follow-up period was limited to 2 years. Future studies with longer follow-up are needed to confirm the findings. Second, participants were selected from a high-risk population with positive COPD-SQ results, and those with normal spirometry were used as the reference. This design may underestimate risks among asymptomatic borderline FEV_1/FVC individuals with negative COPD-SQ scores. Third, not all

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high-risk individuals underwent lung function testing; thus, selection bias was possible. To address this, we validated the findings in the general population using UKB data, which showed similar results. Finally, imaging data were not available in the National COPD Screening Program. Future studies should evaluate the interplay between borderline FEV_1/FVC and structural abnormalities.

Conclusion

Individuals with borderline FEV_1/FVC were at increased risk of developing airway obstruction. Importantly, among high-risk populations for COPD, those with borderline FEV_1/FVC but preserved FEV_1 were most vulnerable to rapid FEV_1 decline, underscoring the need for close monitoring and timely intervention in this subgroup. Taken together, these findings demonstrate that this simple spirometry marker may be a practical tool for early risk stratification in primary care.

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Author contributions: XT designed the study, conducted the statistical analyses, and drafted the manuscript. WL, HN, MS, JY, YP, YC, TH, YL, JP, CZ, and CJ contributed to the data collection and program implementation. XC, TY, and KH supervised the study. KH is the guarantor of the current analysis. All authors approved the final version of the manuscript.

Declaration of interest:

All authors declare no competing interests.

Data availability statement

The raw and individual data are available upon reasonable request from the corresponding author (huangke_zryy@163.com)

Ethics statement

The program was approved by the Institutional Review Board of China–Japan Friendship Hospital (approval number: 2021-145-K103). All participants provided written informed consent.

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Tables

Table 1. Basic characteristics of enrolled participants.

	Normal ratio with normal FEV_1	Borderline ratio with normal FEV_1	Normal ratio with low FEV_1	Borderline ratio with low FEV_1
N	1476	981	321	191
Age (years, mean [SD])	60.77 (8.47)	61.18 (8.50)	60.25 (8.61)	62.31 (7.63)
Gender (n [%])				
Male	1037 (70.3)	692 (70.5)	252 (78.5)	141 (73.8)
Female	439 (29.7)	289 (29.5)	69 (21.5)	50 (26.2)
Income (ten thousand yuan/year, n [%])				
<2	558 (37.8)	379 (38.6)	110 (34.3)	79 (41.4)
2-5	622 (42.1)	312 (31.8)	165 (51.4)	73 (38.2)
≥5	296 (20.1)	290 (29.6)	46 (14.3)	39 (20.4)
Education (n [%])				

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Primary school and below	802 (54.3)	476 (48.5)	167 (52.0)	88 (46.1)
Middle and high school	641 (43.4)	462 (47.1)	149 (46.4)	98 (51.3)
College and above	33 (2.2)	43 (4.4)	5 (1.6)	5 (2.6)
Marriage (n [%])				
Single	14 (0.9)	9 (0.9)	4 (1.2)	2 (1.0)
Married	1405 (95.2)	939 (95.7)	312 (97.2)	186 (97.4)
Divorced	13 (0.9)	9 (0.9)	1 (0.3)	1 (0.5)
Widowed	44 (3.0)	24 (2.4)	4 (1.2)	2 (1.0)
Employment status (n [%])				
On work	298 (20.2)	263 (26.8)	37 (11.5)	34 (17.8)
Retire	95 (6.4)	146 (14.9)	21 (6.5)	33 (17.3)
Homework	1053 (71.3)	531 (54.1)	252 (78.5)	115 (60.2)
Unemployment	30 (2.0)	41 (4.2)	11 (3.4)	9 (4.7)
Job (n [%])				

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Indoor	197 (65.7)	175 (65.8)	24 (64.9)	26 (74.3)
Outdoor	71 (23.7)	71 (26.7)	7 (18.9)	7 (20.0)
Other	32 (10.7)	20 (7.5)	6 (16.2)	2 (5.7)
Fuel (n [%])				
Clean	565 (38.3)	486 (49.5)	127 (39.6)	91 (47.6)
Unclean	907 (61.4)	492 (50.2)	193 (60.1)	100 (52.4)
Unknown	4 (0.3)	3 (0.3)	1 (0.3)	0 (0.0)
Smoking status (n [%])				
Never	585 (39.6)	377 (38.4)	127 (39.6)	80 (41.9)
Former	179 (12.1)	139 (14.2)	48 (15.0)	29 (15.2)
Current	712 (48.2)	465 (47.4)	146 (45.5)	82 (42.9)
Smoking exposure (pack years, mean [SD])	27.11 (18.15)	30.90 (20.81)	33.56 (26.84)	40.29 (44.52)
Secondhand smoke (n [%])	358 (24.3)	263 (26.8)	62 (19.3)	48 (25.1)

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Cough before 14 years old (n [%])	95 (6.4)	68 (6.9)	23 (7.2)	9 (4.7)
Family history of COPD (n [%])	18 (1.2)	12 (1.2)	5 (1.6)	3 (1.6)
Comorbidities (n [%])	200 (13.6)	155 (15.8)	76 (23.7)	37 (19.4)
Symptoms (n [%])				
Cough	528 (35.8)	341 (34.8)	127 (39.6)	88 (46.1)
Breathlessness				
None	493 (33.4)	369 (37.6)	91 (28.3)	55 (28.8)
When walking	780 (52.8)	524 (53.4)	185 (57.6)	108 (56.5)
When climbing	203 (13.8)	88 (9.0)	45 (14.0)	28 (14.7)
Height (cm, mean [SD])	163.16 (7.76)	163.39 (7.59)	164.41 (7.36)	162.52 (7.46)
Weight (kg, mean [SD])	63.83 (10.75)	64.57 (10.77)	62.57 (9.52)	62.29 (10.75)
BMI (kg/m2, mean [SD])	23.93 (3.37)	24.13 (3.36)	23.14 (3.13)	23.54 (3.46)
Waist circumference (cm, mean [SD])	86.04 (9.10)	86.91 (9.73)	84.61 (8.80)	86.56 (8.87)
Hip circumference (cm, mean [SD])	94.38 (8.86)	95.14 (9.28)	92.67 (8.26)	94.23 (8.63)

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Lung function				
FEV_1 (L, mean [SD])	2.68 (0.56)	2.67 (0.57)	1.75 (0.43)	1.69 (0.44)
FEV_1 % predicted (%, mean [SD])	104.11 (16.35)	103.78 (16.76)	65.37 (12.54)	66.51 (12.91)
FVC (L, mean [SD])	3.04 (0.73)	3.53 (0.74)	1.89 (0.51)	2.28 (0.59)
FVC % predicted (%, mean [SD])	90.73 (17.62)	105.36 (17.06)	54.30 (11.97)	68.58 (13.50)
FEV_1/FVC (mean [SD])	0.89 (0.07)	0.76 (0.03)	0.93 (0.07)	0.74 (0.03)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Table 2. Risk of developing into airway obstruction during follow-up in high-risk population of COPD without airway obstruction at baseline.

	Univariable	Model 1	Model 2
Normal ratio with normal FEV_1	Ref	Ref	Ref
Borderline ratio with normal FEV_1	1.94 (1.45, 2.59)	1.90 (1.42, 2.55)	1.81 (1.34, 2.44)
Normal ratio with low FEV_1	1.38 (0.88, 2.16)	1.37 (0.87, 2.16)	1.31 (0.83, 2.07)
Borderline ratio with low FEV_1	2.69 (1.72, 4.21)	2.50 (1.59, 3.94)	2.32 (1.46, 3.69)
Normal ratio with normal FEV_1	Ref	Ref	Ref
Borderline ratio	2.06 (1.56, 2.71)	2.00 (1.51, 2.64)	1.97 (1.47, 2.62)
PRISm (Low FEV_1)	1.85 (1.30, 2.62)	1.81 (1.27, 2.58)	1.69 (1.17, 2.44)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

Logistic regression model was used, and results were showed using odds ratio (OR) and 95% confidence interval (CI).

Model 1: age and sex

Model 2: age, sex, education, income, marriage, employment, BMI, smoking and pack years.

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Table 3. Risk of FEV_1 decline during follow-up in high-risk population of COPD without airway obstruction at baseline.

	FEV_1 change in 2 years follow-up (continuous variable) β (95% CI)			FEV_1 rapid decline (categorical variable) OR (95%CI)		
	Univariable	Model 1	Model 2	Univariable	Model 1	Model 2
Normal ratio with normal FEV_1	Ref	Ref	Ref	Ref	Ref	Ref
Borderline ratio with normal FEV_1	-0.20 (-0.25, -0.14)	-0.20 (-0.26, -0.15)	-0.15 (-0.21, -0.10)	1.41 (1.20, 1.66)	1.42 (1.20, 1.67)	1.26 (1.06, 1.49)
Normal ratio with low FEV_1	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)	1.01 (0.93, 1.09)	0.07 (0.04, 0.13)	0.07 (0.04, 0.12)	0.08 (0.04, 0.13)
Borderline ratio with low FEV_1	0.60 (0.50, 0.70)	0.59 (0.49, 0.70)	0.62 (0.52, 0.72)	0.20 (0.13, 0.32)	0.20 (0.13, 0.32)	0.18 (0.11, 0.29)
Normal ratio with normal FEV_1	Ref	Ref	Ref	Ref	Ref	Ref
Borderline ratio	-0.07 (-0.12, -0.02)	-0.07 (-0.13, -0.02)	-0.03 (-0.09, 0.02)	1.11 (0.95, 1.30)	1.12 (0.96, 1.31)	1.01 (0.86, 1.19)

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PRISm (Low FEV_1)	0.87 (0.80, 0.94)	0.86 (0.79, 0.94)	0.86 (0.79, 0.93)	0.12 (0.08, 0.17)	0.12 (0.08, 0.17)	0.10 (0.07, 0.15)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

Linear model was used for analysis in FEV_1 change in 2 years follow-up (continuous variable), and results were showed using β and 95% confidence interval (CI). Logistic regression analysis was used for analysis in FEV_1 decline (categorical variable), and results were showed using odds ratio (OR) and 95% CI.

Model 1: age and sex

Model 2: age, sex, education, income, marriage, employment, BMI, smoking and pack years.

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Table 4. Risk of developing into airway obstruction during follow-up in general population without airway obstruction at baseline based on the data from UKB.

	Univariable	Model 1	Model 2
Normal ratio with normal FEV_1	Ref	Ref	Ref
Borderline ratio with normal FEV_1	2.71 (2.45, 3.00)	2.39 (2.16, 2.64)	2.92 (2.28, 3.74)
Normal ratio with low FEV_1	1.36 (0.84, 2.22)	1.42 (0.88, 2.31)	0.60 (0.08, 4.35)
Borderline ratio with low FEV_1	4.32 (3.69, 5.06)	3.93 (3.35, 4.60)	4.53 (3.21, 6.38)
Normal ratio with normal FEV_1	Ref	Ref	Ref
Borderline ratio	2.80 (2.53, 3.09)	2.47 (2.24, 2.74)	3.02 (2.36, 3.87)
PRISm (Low FEV_1)	3.77 (3.23, 4.40)	3.45 (2.96, 4.03)	3.93 (2.75, 5.62)

Abbreviations: UKB, United Kingdom Biobank; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

Cox regression analysis was used, and results were showed using hazard ratio (HR) and 95% confidence interval (CI).

Model 1: age and sex

Model 2: age, sex, BMI, ethic, smoking status, and pack years.

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Table 5. Risk of FEV_1 decline during follow-up in general population without airway obstruction at baseline based on the data from UKB.

	FEV_1 annual change (continuous variable) β (95% CI)			FEV_1 rapid decline (categorical variable) HR (95% CI)		
	Univariable	Model 1	Model 2	Univariable	Model 1	Model 2
Normal ratio with normal FEV_1	Ref	Ref	Ref	Ref	Ref	Ref
Borderline ratio with normal FEV_1	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.01)	1.09 (1.04, 1.13)	1.00 (0.96, 1.05)	0.97 (0.88, 1.07)
Normal ratio with low FEV_1	0.05 (0.05, 0.06)	0.05 (0.05, 0.06)	0.06 (0.04, 0.07)	0.26 (0.17, 0.39)	0.26 (0.17, 0.40)	0.19 (0.06, 0.60)
Borderline ratio with low FEV_1	0.05 (0.04, 0.05)	0.05 (0.04, 0.05)	0.05 (0.04, 0.05)	0.35 (0.30, 0.42)	0.34 (0.29, 0.40)	0.35 (0.25, 0.49)
Normal ratio with normal FEV_1	Ref	Ref	Ref	Ref	Ref	Ref
Borderline ratio	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.01 (0.00, 0.01)	1.04 (1.00, 1.09)	0.96 (0.92, 1.01)	0.93 (0.84, 1.02)

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PRISm (Low FEV_1)	0.05 (0.05, 0.05)	0.05 (0.05, 0.05)	0.05 (0.04, 0.05)	0.34 (0.29, 0.39)	0.33 (0.28, 0.38)	0.34 (0.24, 0.47)

Abbreviations: UKB, United Kingdom Biobank; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

Linear model was used for analysis in FEV_1 annual change (continuous variable), and results were showed using β and 95% confidence interval (CI). Cox regression analysis was used for analysis in FEV_1 rapid decline (categorical variable), and results were showed using hazard ratio (HR) and 95% CI.

Model 1: age and sex

Model 2: age, sex, BMI, ethic, smoking status, and pack years.

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Figure titles and legends

Figure 1. Definition of study groups based on borderline ratio and PRISm (low FEV_1).

Abbreviations: PRISm, preserved ratio impaired spirometry; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

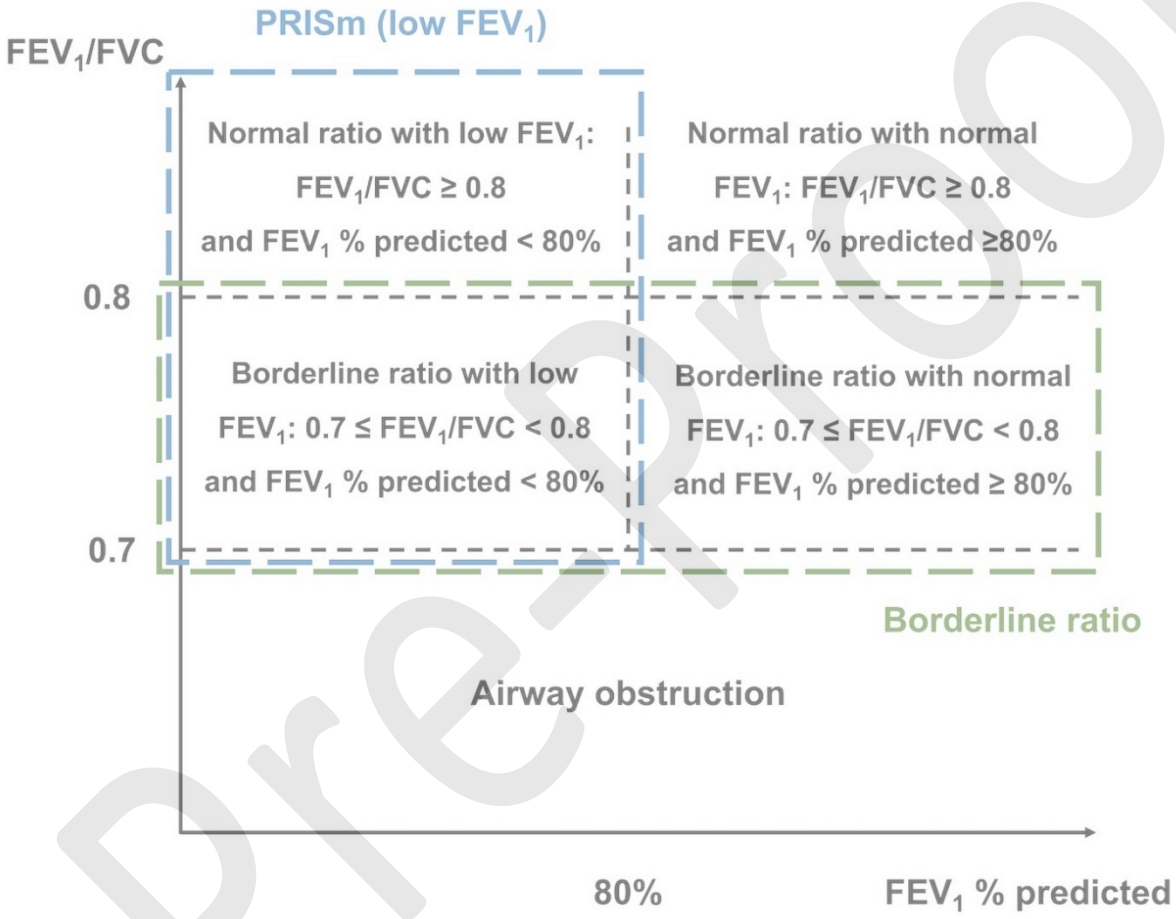

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Figure 2. Flow chart of the study.

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

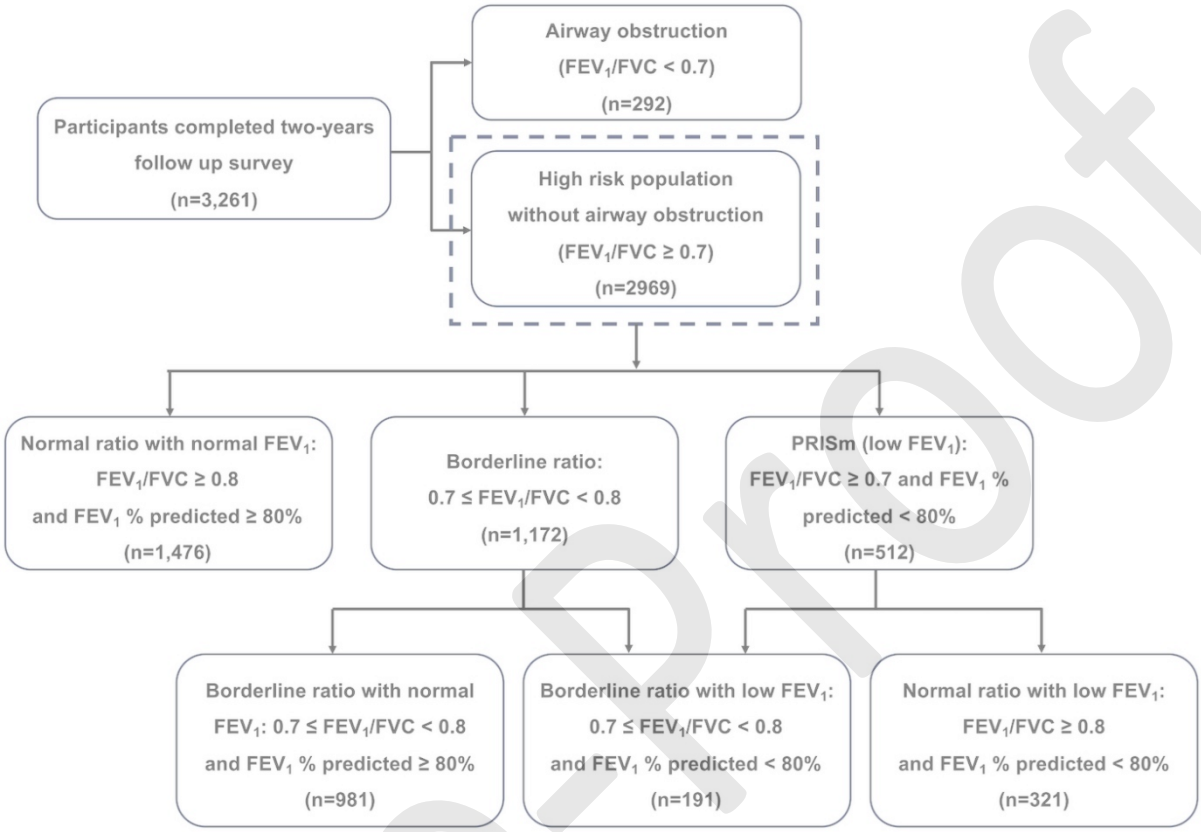

Figure 3. Sankey plot of lung function pattern changes in each group.

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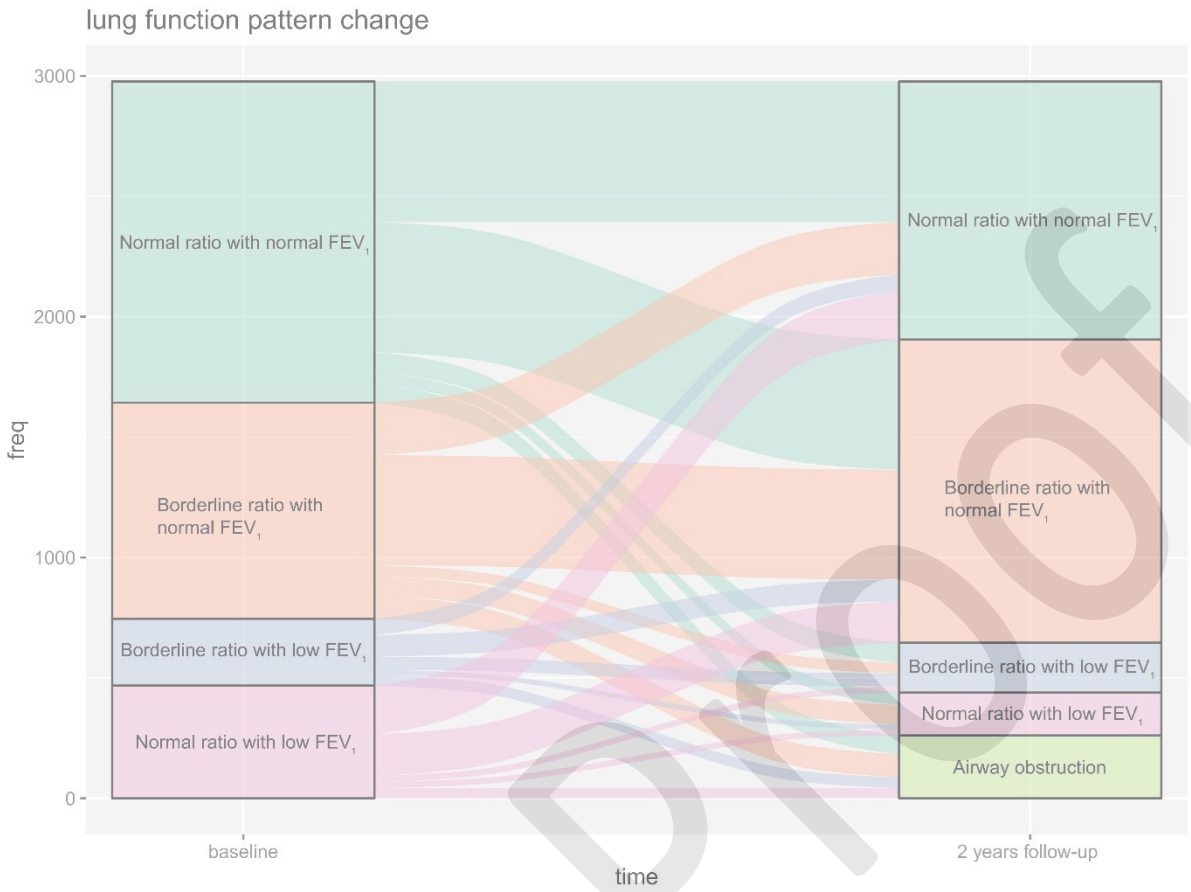
Abbreviations: FEV_1, forced expiratory volume in one second.



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Online Supplement

Supplement material I. Other analysis of using China equations to calculate the predicted value of FEV_1 and FVC

Supplement material II. Analysis among general participants based on the data from UK Biobank

Supplement material III. Sensitivity analysis of using the race-neutral Global Lung Function Initiative equations (GLI Global) to calculate the predicted value of FEV1 and FVC

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Supplement material I. Other analysis of using China equations to calculate the predicted value of FEV_1 and FVC

Supplement table 1. Basic characteristics of enrolled participants in borderline ratio and PRISm (low FEV_1) group.

	Normal ratio and normal FEV_1	Borderline ratio	PRISm (low FEV_1)	P value (borderline ratio vs normal spirometry)	P value (PRISm [low FEV_1] vs normal spirometry)
N	1476	1172	512		
Age (years, mean [SD])	60.77 (8.47)	61.36 (8.37)	61.02 (8.31)	0.072	0.565
Gender (n [%])				0.678	0.006
Male	1037 (70.3)	833 (71.1)	393 (76.8)		
Female	439 (29.7)	339 (28.9)	119 (23.2)		
Income (ten thousand yuan/year, n [%])				<0.001	0.129
<2	558 (37.8)	458 (39.1)	189 (36.9)		
2-5	622 (42.1)	385 (32.8)	238 (46.5)		
≥5	296 (20.1)	329 (28.1)	85 (16.6)		
Education (n [%])				0.001	0.167
Primary school and below	802 (54.3)	564 (48.1)	255 (49.8)		
Middle and high school	641 (43.4)	560 (47.8)	247 (48.2)		
College and above	33 (2.2)	48 (4.1)	10 (2.0)		
Marriage (n [%])				0.685	0.089
Single	14 (0.9)	11 (0.9)	6 (1.2)		
Married	1405 (95.2)	1125 (96.0)	498 (97.3)		
Divorced	13 (0.9)	10 (0.9)	2 (0.4)		
Widowed	44 (3.0)	26 (2.2)	6 (1.2)		
Employment status (n [%])				<0.001	<0.001
On work	298 (20.2)	297 (25.3)	71 (13.9)		
Retire	95 (6.4)	179 (15.3)	54 (10.5)		
Homework	1053 (71.3)	646 (55.1)	367 (71.7)		
Unemployment	30 (2.0)	50 (4.3)	20 (3.9)		
Job (n [%])				0.330	0.745
Indoor	197 (65.7)	201 (66.8)	50 (69.4)		
Outdoor	71 (23.7)	78 (25.9)	14 (19.4)		
Other	32 (10.7)	22 (7.3)	8 (11.1)		
Fuel (n [%])				<0.001	0.224
Clean	565 (38.3)	577 (49.2)	218 (42.6)		
Unclean	907 (61.4)	592 (50.5)	293 (57.2)		
Unknown	4 (0.3)	3 (0.3)	1 (0.2)		
Smoking status (n [%])				0.242	0.160

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Never	585 (39.6)	457 (39.0)	207 (40.4)		
Former	179 (12.1)	168 (14.3)	77 (15.0)		
Current	712 (48.2)	547 (46.7)	228 (44.5)		
Smoking exposure (pack years, mean [SD])	27.11 (18.15)	40.14 (43.13)	36.07 (34.38)	0.028	0.007
Secondhand smoke (n [%])	358 (24.3)	311 (26.5)	110 (21.5)	0.195	0.225
Cough before 14 years old (n [%])	95 (6.4)	77 (6.6)	32 (6.2)	0.953	0.965
Family history of COPD (n [%])	18 (1.2)	15 (1.3)	8 (1.6)	>0.999	0.717
Comorbidities (n [%])	200 (13.6)	192 (16.4)	113 (22.1)	0.047	<0.001
Symptoms (n [%])					
Cough	528 (35.8)	429 (36.6)	215 (42.0)	0.688	0.014
Breathlessness				0.008	0.120
None	493 (33.4)	424 (36.2)	146 (28.5)		
When walking	780 (52.8)	632 (53.9)	293 (57.2)		
When climbing	203 (13.8)	116 (9.9)	73 (14.3)		
Height (cm, mean [SD])	163.16 (7.76)	163.25 (7.58)	163.71 (7.45)	0.776	0.166
Weight (kg, mean [SD])	63.83 (10.75)	64.20 (10.79)	62.47 (9.99)	0.378	0.012
BMI (kg/m^2, mean [SD])	23.93 (3.37)	24.04 (3.38)	23.29 (3.26)	0.415	<0.001
Waist circumference (cm, mean [SD])	86.04 (9.10)	86.86 (9.59)	85.34 (8.87)	0.025	0.130
Hip circumference (cm, mean [SD])	94.38 (8.86)	94.99 (9.18)	93.25 (8.42)	0.084	0.012
Lung function					
FEV_1 (L, mean [SD])	2.68 (0.56)	2.51 (0.66)	1.73 (0.43)	<0.001	<0.001
FEV_1 % predicted (%, mean [SD])	104.11 (16.35)	97.70 (21.25)	65.79 (12.68)	<0.001	<0.001
FVC (L, mean [SD])	3.04 (0.73)	3.33 (0.86)	2.03 (0.57)	<0.001	<0.001
FVC % predicted (%, mean [SD])	90.73 (17.62)	99.37 (21.40)	59.63 (14.32)	<0.001	<0.001
FEV_1/FVC (mean [SD])	0.89 (0.07)	0.75 (0.03)	0.86 (0.11)	<0.001	<0.001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 2. Lung function change and disease progression during 2 years follows up.

	Normal ratio with normal FEV_1	Borderline ratio with normal FEV_1	Normal ratio with low FEV_1	Borderline ratio with low FEV_1
FEV_1 change in 2 years follow-up (L, mean [SD])	0.06 (0.70)	-0.13 (0.61)	1.09 (0.70)	0.66 (0.77)
FEV_1 % predicted change in 2 years follow-up (%, mean [SD])	5.40 (28.96)	-2.72 (24.61)	43.85 (27.98)	28.71 (31.11)
FEV_1 rapid decline in 2 years follow-up (n [%])	571 (38.7)	467 (47.6)	14 (4.4)	22 (11.5)
Airway obstruction in 2 years follow-up (n [%])	92 (6.2)	112 (11.4)	27 (8.4)	29 (15.2)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

Supplement table 3. Lung function change and disease progression in borderline ratio and PRISm (low FEV_1) group during 2 years follow up.

	Normal ratio and normal FEV_1	Borderline ratio	PRISm (low FEV_1)	P value (borderline ratio vs normal spirometry)	P value (PRISm [low FEV_1] vs normal spirometry)
FEV_1 change in 2 years follow-up (L, mean [SD])	0.06 (0.70)	0.00 (0.70)	0.93 (0.76)	<0.001	<0.001
FEV_1 % predicted change in 2 years follow-up (%, mean [SD])	5.40 (28.96)	2.40 (28.26)	38.21 (30.06)	0.007	<0.001
FEV_1 rapid decline in 2 years follow-up (n [%])	571 (38.7)	489 (41.7)	36 (7.0)	0.122	<0.001
Airway obstruction in 2 years follow-up (n [%])	92 (6.2)	141 (12.0)	56 (10.9)	<0.001	0.001

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 4. Risk factors of developing into airway obstruction in high-risk population of COPD with borderline ratio.

	Univariable	multivariable
Age	1.06 (1.03, 1.09)	1.07 (1.02, 1.12)
Gender		
Male	Ref	Ref
Female	0.47 (0.29, 0.74)	0.23 (0.07, 0.85)
Income (ten thousand yuan/year)		
<2	Ref	Ref
2-5	0.79 (0.52, 1.21)	2.48 (0.94, 6.57)
≥5	0.92 (0.60, 1.41)	2.63 (0.93, 7.40)
Education		
Primary school and below	Ref	Ref
Middle and high school	1.13 (0.79, 1.62)	1.07 (0.51, 2.27)
College and above	0.70 (0.24, 2.00)	1.32 (0.29, 6.06)
Marriage		
Single	Ref	Ref
Married	1.40 (0.18, 11.01)	/
Divorced	/	/
Widowed	0.83 (0.07, 10.27)	/
Employment status		
On work	Ref	Ref
Retire	1.10 (0.63, 1.94)	0.68 (0.32, 1.48)
Homework	0.92 (0.60, 1.42)	/
Unemployment	2.36 (1.13, 4.95)	/
Job		
Outdoor	Ref	Ref
Indoor	0.54 (0.26, 1.12)	0.49 (0.19, 1.25)
Other	1.06 (0.47, 2.41)	1.12 (0.42, 3.01)
Biofuel use	0.94 (0.66, 1.34)	1.15 (0.56, 2.35)
Smoking status		
Never	Ref	Ref
Former	1.60 (0.94, 2.74)	1.21 (0.40, 3.68)
Current	1.51 (1.01, 2.24)	0.73 (0.23, 2.34)
Smoking pack years	1.01 (1.00, 1.01)	1.00 (0.98, 1.02)
Secondhand smoke	1.20 (0.82, 1.77)	2.38 (1.18, 4.80)
Cough before 14 years old	1.38 (0.73, 2.63)	0.59 (0.19, 1.84)
Family history of COPD	1.85 (0.51, 6.62)	4.87 (0.74, 32.22)
Height	1.01 (0.98, 1.03)	1.38 (0.98-1.95)
Weight	0.99 (0.97, 1.00)	0.65 (0.42-1.01)
BMI	0.94 (0.88, 0.99)	3.00 (0.95-9.43)
Waist line	0.98 (0.97, 1.00)	0.94 (0.88-1.00)
Hip line	1.00 (0.98, 1.02)	1.05 (1.00-1.11)

Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV_1, forced expiratory

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volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC

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Supplement table 5. Risk factors of developing into airway obstruction in high-risk population of COPD with PRISm (low FEV_1).

	Univariable	multivariable
Age	1.06 (1.02, 1.11)	1.10 (0.98, 1.23)
Gender		
Male	Ref	Ref
Female	0.89 (0.45, 1.75)	0.10 (0.01, 1.33)
Income (ten thousand yuan/year)		
<2	Ref	Ref
2-5	0.60 (0.32, 1.13)	0.96 (0.14, 6.32)
≥5	1.24 (0.60, 2.57)	0.82 (0.11, 6.29)
Education		
Primary school and below	Ref	Ref
Middle and high school	0.81 (0.46, 1.42)	0.97 (0.22, 4.21)
College and above	1.87 (0.38, 9.25)	2.04 (0.10, 40.30)
Marriage		
Single	Ref	Ref
Married	/	/
Divorced	/	/
Widowed	/	/
Employment status		
On work	Ref	Ref
Retire	1.09 (0.42, 2.85)	0.35 (0.05, 2.61)
Homework	0.43 (0.20, 0.92)	/
Unemployment	4.46 (1.50, 13.28)	/
Job		
Outdoor	Ref	Ref
Indoor	1.79 (0.64, 4.98)	1.04 (0.20, 5.59)
Other	1.34 (0.26, 7.03)	1.60 (0.18, 14.12)
Biofuel use	0.40 (0.23, 0.72)	0.38 (0.07, 2.02)
Smoking status		
Never	Ref	Ref
Former	1.31 (0.57, 3.03)	0.86 (0.09, 8.44)
Current	1.39 (0.75, 2.56)	0.16 (0.01, 2.21)
Smoking pack years	1.01 (1.00, 1.02)	1.02 (0.99, 1.06)
Secondhand smoke	2.47 (1.37, 4.46)	5.51 (0.99, 30.48)
Cough before 14 years old	0.83 (0.25, 2.83)	0.28 (0.02, 3.89)
Family history of COPD	5.11 (1.19, 21.97)	1.61 (0.04, 61.00)
Height	0.98 (0.94, 1.02)	1.55 (0.92-2.62)
Weight	0.97 (0.94, 1.00)	0.50 (0.25-1.01)
BMI	0.95 (0.87, 1.04)	4.73 (0.76-29.66)
Waist line	1.01 (0.98, 1.04)	0.99 (0.89-1.11)
Hip line	1.03 (1.00, 1.06)	1.01 (0.88-1.15)

Abbreviations: COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry; BMI, body mass index; FEV_1, forced expiratory volume in one second; FEV_1 % predicted, proportion of predicted FEV_1

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Supplement table 6. Risk factors of FEV_1 rapid decline in high-risk population of COPD with borderline ratio.

	Univariable	multivariable
Age	0.99 (0.97, 1.00)	0.97 (0.95, 1.00)
Gender		
Male	Ref	Ref
Female	0.80 (0.62, 1.04)	0.95 (0.46, 1.96)
Income (ten thousand yuan/year)		
<2	Ref	Ref
2-5	0.86 (0.65, 1.14)	1.06 (0.59, 1.90)
≥5	1.20 (0.90, 1.59)	1.55 (0.84, 2.87)
Education		
Primary school and below	Ref	Ref
Middle and high school	1.18 (0.93, 1.50)	0.65 (0.40, 1.06)
College and above	1.13 (0.62, 2.06)	0.85 (0.34, 2.14)
Marriage		
Single	Ref	Ref
Married	0.81 (0.25, 2.68)	0.19 (0.02, 2.29)
Divorced	0.51 (0.09, 3.11)	0.17 (0.01, 5.30)
Widowed	1.64 (0.40, 6.76)	0.46 (0.02, 8.61)
Employment status		
On work	Ref	Ref
Retire	0.64 (0.44, 0.94)	0.83 (0.50, 1.38)
Homework	0.64 (0.49, 0.85)	0.61 (0.05, 7.34)
Unemployment	0.64 (0.35, 1.19)	/
Job		
Outdoor	Ref	Ref
Indoor	0.51 (0.33, 0.79)	0.45 (0.26, 0.78)
Other	1.05 (0.59, 1.86)	1.15 (0.60, 2.20)
Biofuel use	0.96 (0.76, 1.22)	1.23 (0.79, 1.92)
Smoking status		
Never	Ref	Ref
Former	1.15 (0.80, 1.66)	0.81 (0.38, 1.73)
Current	1.26 (0.98, 1.62)	0.45 (0.21, 0.96)
Smoking pack years	1.00 (1.00, 1.00)	1.01 (1.00, 1.03)
Secondhand smoke	1.04 (0.80, 1.36)	1.14 (0.72, 1.79)
Cough before 14 years old	1.10 (0.69, 1.75)	0.86 (0.43, 1.73)
Family history of COPD	0.73 (0.25, 2.14)	1.23 (0.25, 6.02)
Height	1.01 (1.00, 1.03)	1.09 (0.90-1.32)
Weight	1.01 (1.00, 1.02)	0.89 (0.70-1.13)
BMI	1.01 (0.98, 1.05)	1.30 (0.69-2.42)
Waist line	1.00 (0.99, 1.01)	1.00 (0.96-1.04)
Hip line	1.01 (1.00, 1.02)	1.03 (0.99-1.07)

Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV_1, forced expiratory

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volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC.

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Supplement table 7. Risk factors of FEV_1 rapid decline in high-risk population of COPD with PRISm (low FEV_1).

	Univariable	multivariable
Age	0.98 (0.94, 1.02)	0.94 (0.86, 1.03)
Gender		
Male	Ref	Ref
Female	0.29 (0.09, 0.97)	1.17 (0.07, 20.87)
Income (ten thousand yuan/year)		
<2	Ref	Ref
2-5	0.86 (0.37, 1.99)	1.47 (0.21, 10.23)
≥5	2.66 (1.12, 6.30)	1.62 (0.21, 12.34)
Education		
Primary school and below	Ref	Ref
Middle and high school	1.26 (0.62, 2.55)	0.84 (0.20, 3.54)
College and above	4.00 (0.78, 20.52)	5.72 (0.34, 96.82)
Marriage		
Single	Ref	Ref
Married	/	/
Divorced	/	/
Widowed	/	/
Employment status		
On work	Ref	Ref
Retire	1.01 (0.41, 2.53)	2.59 (0.54, 12.38)
Homework	0.14 (0.06, 0.32)	/
Unemployment	0.23 (0.03, 1.92)	/
Job		
Outdoor	Ref	Ref
Indoor	0.33 (0.09, 1.20)	0.10 (0.01, 0.77)
Other	1.91 (0.51, 7.14)	2.53 (0.39, 16.27)
Biofuel use	0.68 (0.34, 1.36)	0.74 (0.19, 2.84)
Smoking status		
Never	Ref	Ref
Former	1.57 (0.45, 5.50)	6.34 (0.31, 128.27)
Current	3.36 (1.42, 7.98)	5.71 (0.37, 87.52)
Smoking pack years	1.01 (1.00, 1.03)	1.03 (0.99, 1.06)
Secondhand smoke	1.51 (0.70, 3.24)	1.37 (0.30, 6.20)
Cough before 14 years old	1.45 (0.42, 5.01)	0.10 (0.01, 1.27)
Family history of COPD	/	/
Height	1.04 (0.99, 1.09)	1.20 (0.69-2.08)
Weight	1.02 (0.99, 1.16)	0.77 (0.39-1.55)
BMI	1.02 (0.92, 1.13)	1.48 (0.22-9.78)
Waist line	1.03 (0.99, 1.07)	1.12 (0.97-1.30)
Hip line	1.02 (0.98, 1.06)	0.98 (0.85-1.12)

Abbreviations: COPD, chronic obstructive pulmonary disease; PRISm, preserved ratio impaired spirometry; BMI, body mass index; FEV_1, forced expiratory volume in one second; FEV_1 % predicted, proportion of predicted FEV_1

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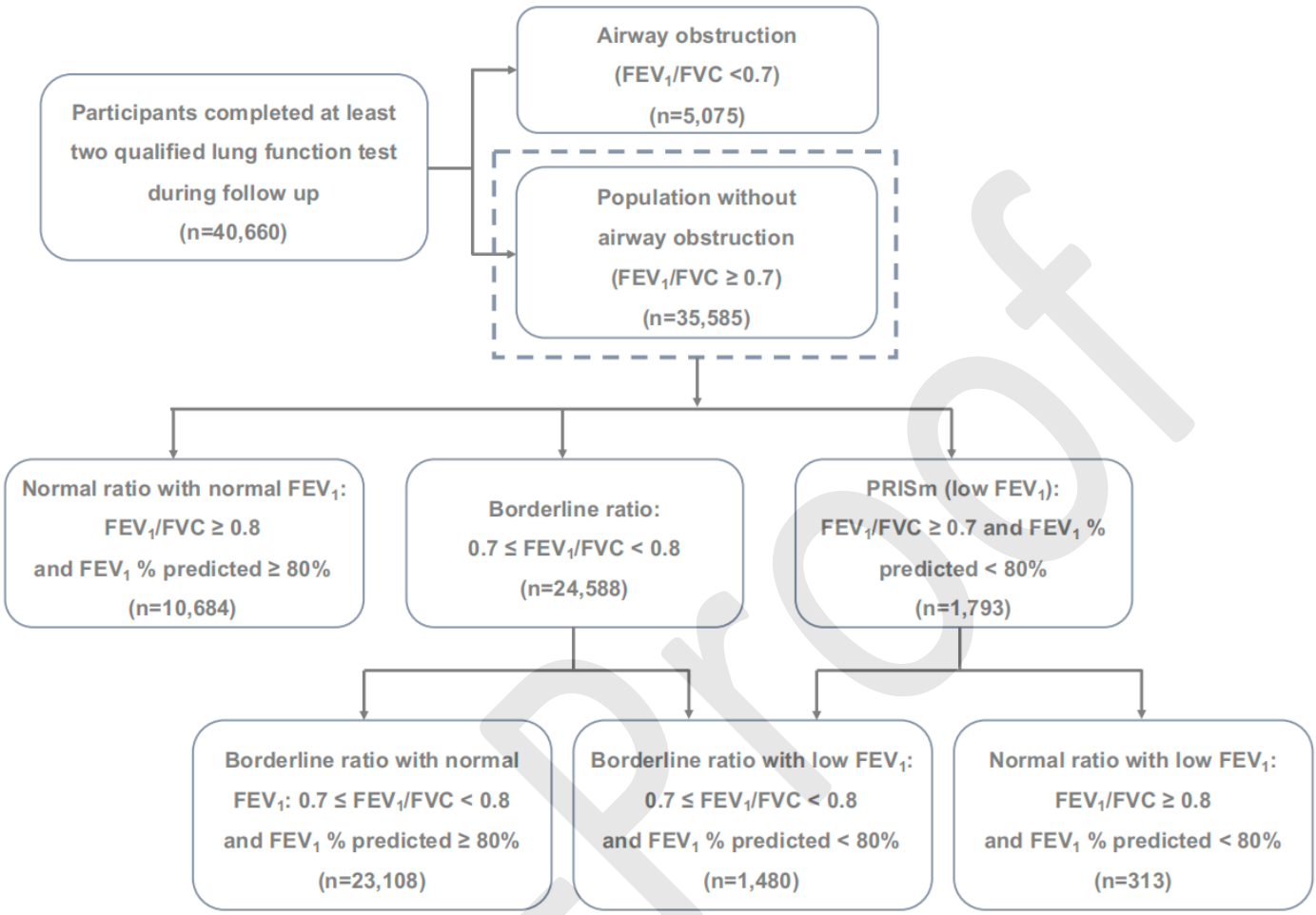
Supplement material II. Analysis among general participants based on the data from UK Biobank

Supplement figure 1. Flow chart based on the data from UKB.



Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV1 % predicted, proportion of predicted FEV_1 value.

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Supplement table 8. Basic characteristics of enrolled general participants based on the data from UKB.

	Normal ratio with normal FEV_1	Borderline ratio with normal FEV_1	Normal ratio with low FEV_1	Borderline ratio with low FEV_1
N	10684	23108	313	1480
Age (years, mean [SD])	53.25 (7.55)	56.02 (7.35)	53.19 (7.59)	55.57 (7.47)
Gender (n [%])				
Male	4331 (40.5)	10329 (44.7)	113 (36.1)	570 (38.5)
Female	6353 (59.5)	12779 (55.3)	200 (63.9)	910 (61.5)
Ethic (n [%])				
Asia	375 (3.5)	645 (2.8)	14 (4.5)	43 (2.9)
White	9985 (93.5)	21916 (94.8)	284 (90.7)	1390 (93.9)
Mix	324 (3.0)	547 (2.4)	15 (4.8)	47 (3.2)
Smoking status (n [%])				
Never	6980 (65.3)	13795 (59.7)	206 (65.8)	826 (55.8)
Former	3213 (30.1)	7961 (34.5)	82 (26.2)	524 (35.4)
Current	491 (4.6)	1352 (5.9)	25 (8.0)	130 (8.8)
Smoking exposure (pack years, mean [SD])	16.10 (13.04)	17.97 (14.47)	23.73 (29.24)	24.94 (17.41)
Symptoms (n [%])				
Dyspnea	194 (5.3)	318 (4.5)	15 (21.1)	46 (11.8)
Wheeze	1188 (11.3)	3071 (13.4)	62 (20.1)	358 (24.6)
Chest pain	1295 (12.2)	2768 (12.1)	62 (20.0)	264 (18.1)
Height (cm, mean [SD])	76.98 (15.59)	75.52 (14.35)	83.56 (20.44)	80.41 (17.03)
Weight (kg, mean [SD])	167.83 (8.95)	169.27 (9.00)	167.58 (9.49)	168.67 (8.90)
BMI (kg/m^2, mean [SD])	27.23 (4.70)	26.26 (4.07)	29.70 (6.71)	28.14 (5.39)
Lung function				
FEV_1 (L, mean [SD])	3.15 (0.72)	3.03 (0.69)	2.14 (0.51)	2.13 (0.47)
FEV_1 % predicted (%, mean [SD])	107.27 (13.15)	103.30 (12.79)	73.19 (7.37)	73.33 (6.62)
FVC (L, mean [SD])	3.81 (0.87)	4.01 (0.92)	2.59 (0.63)	2.86 (0.64)
FVC % predicted (%, mean [SD])	104.20 (12.92)	108.56 (13.36)	71.06 (7.74)	78.50 (7.68)
FEV_1/FVC (mean [SD])	0.83 (0.02)	0.76 (0.03)	0.83 (0.03)	0.75 (0.03)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 9. Basic characteristics of enrolled participants in borderline ratio and PRISm (low FEV_1) group based on the data from UKB.

	Normal ratio and normal FEV_1	Borderline ratio	PRISm (low FEV_1)	P value (borderline ratio vs normal spirometry)	P value (PRISm [low FEV_1] vs normal spirometry)
N	10684	24588	1793		
Age (years, mean [SD])	53.25 (7.55)	56.00 (7.36)	55.15 (7.54)	<0.001	<0.001
Gender (n [%])				<0.001	0.054
Male	4331 (40.5)	10899 (44.3)	683 (38.1)		
Female	6353 (59.5)	13689 (55.7)	1110 (61.9)		
Ethic (n [%])				<0.001	0.500
Asia	375 (3.5)	688 (2.8)	57 (3.2)		
White	9985 (93.5)	23306 (94.8)	1674 (93.4)		
Mix	324 (3.0)	594 (2.4)	62 (3.5)		
Smoking status (n [%])				<0.001	<0.001
Never	6980 (65.3)	14621 (59.5)	1032 (57.6)		
Former	3213 (30.1)	8485 (34.5)	606 (33.8)		
Current	491 (4.6)	1482 (6.0)	155 (8.6)		
Smoking exposure (pack years, mean [SD])	16.10 (13.04)	18.46 (14.80)	24.80 (19.10)	<0.001	<0.001
Symptoms (n [%])					
Dyspnea	194 (5.3)	364 (4.8)	61 (13.3)	0.314	<0.001
Wheeze	1188 (11.3)	3429 (14.1)	420 (23.9)	<0.001	<0.001
Chest pain	1295 (12.2)	3032 (12.4)	326 (18.4)	0.596	<0.001
Height (cm, mean [SD])	76.98 (15.59)	75.81 (14.57)	80.96 (17.71)	<0.001	<0.001
Weight (kg, mean [SD])	167.83 (8.95)	169.23 (9.00)	168.48 (9.01)	<0.001	0.005
BMI (kg/m^2, mean [SD])	27.23 (4.70)	26.37 (4.19)	28.41 (5.67)	<0.001	<0.001
Lung function					
FEV_1 (L, mean [SD])	3.15 (0.72)	2.98 (0.71)	2.13 (0.48)	<0.001	<0.001
FEV_1 % predicted (%, mean [SD])	107.27 (13.15)	101.49 (14.39)	73.31 (6.76)	<0.001	<0.001
FVC (L, mean [SD])	3.81 (0.87)	3.94 (0.94)	2.81 (0.65)	<0.001	<0.001
FVC % predicted (%, mean [SD])	104.20 (12.92)	106.75 (14.92)	77.20 (8.19)	<0.001	<0.001
FEV_1/FVC (mean [SD])	0.83 (0.02)	0.76 (0.03)	0.76 (0.04)	<0.001	<0.001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 10. Lung function change and disease progression during follow-up based on the data from UKB.

	Normal ratio with normal FEV_1	Borderline ratio with normal FEV_1	Normal ratio with low FEV_1	Borderline ratio with low FEV_1
Follow up years (years, mean [SD])	8.21 (2.51)	8.15 (2.59)	8.00 (2.58)	7.89 (2.61)
FEV_1 annual change (L, mean [SD])	-0.04 (0.05)	-0.04 (0.05)	0.02 (0.06)	0.01 (0.06)
FEV_1 % predicted annual change (%, mean [SD])	-0.21 (1.91)	-0.25 (1.98)	1.46 (2.28)	1.20 (2.26)
FEV_1 rapid decline during follow-up (n [%])	2943 (27.5)	6870 (29.7)	22 (7.0)	138 (9.3)
Airway obstruction during follow-up (n [%])	441 (4.1)	2548 (11.0)	17 (5.4)	238 (16.1)

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

Supplement table 11. Lung function change and disease progression in borderline ratio and PRISm (low FEV_1) group during follow up based on the data from UKB.

	Normal ratio and normal FEV_1	Borderline ratio	PRISm (low FEV_1)	P value (borderline ratio vs normal spirometry)	P value (PRISm [low FEV_1] vs normal spirometry)
Follow up years (years, mean [SD])	8.21 (2.51)	8.13 (2.59)	7.91 (2.60)	0.018	<0.001
FEV_1 annual change (L, mean [SD])	-0.04 (0.05)	-0.03 (0.06)	0.01 (0.06)	0.006	<0.001
FEV_1 % predicted annual change (%, mean [SD])	-0.21 (1.91)	-0.16 (2.02)	1.24 (2.27)	0.043	<0.001
FEV_1 rapid decline during follow-up (n [%])	2943 (27.5)	7008 (28.5)	160 (8.9)	0.069	<0.001
Airway obstruction during follow-up (n [%])	441 (4.1)	2786 (11.3)	255 (14.2)	<0.001	<0.001

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement material III. Sensitivity analysis of using the race-neutral Global Lung Function Initiative equations (GLI Global) to calculate the predicted value of FEV1 and FVC

Supplement table 12. Basic characteristics of enrolled participants based on GLI Global.

	Normal ratio with normal FEV_1	Borderline ratio with normal FEV_1	Normal ratio with low FEV_1	Borderline ratio with low FEV_1
N	1426	945	371	227
Age (years, mean [SD])	60.80 (8.41)	61.12 (8.50)	60.20 (8.83)	62.37 (7.74)
Gender (n [%])				
Male	997 (69.9)	668 (70.7)	292 (78.7)	165 (72.7)
Female	429 (30.1)	277 (29.3)	79 (21.3)	62 (27.3)
Income (ten thousand yuan/year, n [%])				
<2	539 (37.8)	363 (38.4)	129 (34.8)	95 (41.9)
2-5	600 (42.1)	306 (32.4)	187 (50.4)	79 (34.8)
≥5	287 (20.1)	276 (29.2)	55 (14.8)	53 (23.3)
Education (n [%])				
Primary school and below	780 (54.7)	454 (48.0)	189 (50.9)	110 (48.5)
Middle and high school	615 (43.1)	451 (47.7)	175 (47.2)	109 (48.0)
College and above	31 (2.2)	40 (4.2)	7 (1.9)	8 (3.5)
Marriage (n [%])				
Single	14 (1.0)	9 (1.0)	4 (1.1)	2 (0.9)
Married	1358 (95.2)	904 (95.7)	359 (96.8)	221 (97.4)
Divorced	13 (0.9)	8 (0.8)	1 (0.3)	2 (0.9)
Widowed	41 (2.9)	24 (2.5)	7 (1.9)	2 (0.9)
Employment status (n [%])				
On work	289 (20.3)	253 (26.8)	46 (12.4)	44 (19.4)
Retire	94 (6.6)	140 (14.8)	22 (5.9)	39 (17.2)
Homework	1015 (71.2)	512 (54.2)	290 (78.2)	134 (59.0)
Unemployment	28 (2.0)	40 (4.2)	13 (3.5)	10 (4.4)
Job (n [%])				
Indoor	228 (59.4)	241 (61.2)	36 (52.2)	54 (63.5)
Outdoor	100 (26.0)	103 (26.1)	24 (34.8)	25 (29.4)
Other	56 (14.6)	50 (12.7)	9 (13.0)	6 (7.1)
Fuel (n [%])				
Clean	540 (37.9)	468 (49.5)	152 (41.0)	109 (48.0)
Unclean	882 (61.9)	474 (50.2)	218 (58.8)	118 (52.0)
Unknown	4 (0.3)	3 (0.3)	1 (0.3)	0 (0.0)
Smoking status (n [%])				
Never	571 (40.0)	362 (38.3)	141 (38.0)	95 (41.9)
Former	169 (11.9)	135 (14.3)	58 (15.6)	33 (14.5)
Current	686 (48.1)	448 (47.4)	172 (46.4)	99 (43.6)
Smoking exposure (pack years, mean [SD])	21.67 (24.10)	24.93 (41.14)	21.30 (22.55)	22.67 (28.11)
Secondhand smoke (n [%])	349 (24.5)	252 (26.7)	71 (19.1)	59 (26.0)

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Cough before 14 years old (n [%])	95 (6.7)	67 (7.1)	23 (6.2)	10 (4.4)
Family history of COPD (n [%])	18 (1.3)	11 (1.2)	5 (1.3)	4 (1.8)
Comorbidities (n [%])	196 (13.7)	148 (15.7)	80 (21.6)	44 (19.4)
Symptoms (n [%])				
Cough	506 (35.5)	328 (34.7)	149 (40.2)	101 (44.5)
Breathlessness				
None	484 (33.9)	357 (37.8)	100 (27.0)	67 (29.5)
When walking	744 (52.2)	503 (53.2)	221 (59.6)	129 (56.8)
When climbing	198 (13.9)	85 (9.0)	50 (13.5)	31 (13.7)
Height (cm, mean [SD])	162.92 (7.68)	163.22 (7.59)	165.19 (7.53)	163.39 (7.54)
Weight (kg, mean [SD])	63.58 (10.61)	64.47 (10.79)	63.69 (10.33)	63.08 (10.77)
BMI (kg/m^2, mean [SD])	23.91 (3.32)	24.15 (3.37)	23.33 (3.40)	23.58 (3.40)
Waist circumference (cm, mean [SD])	85.96 (9.07)	86.94 (9.76)	85.10 (9.02)	86.50 (8.87)
Hip circumference (cm, mean [SD])	94.36 (8.84)	95.23 (9.32)	92.98 (8.45)	93.96 (8.51)
Lung function				
FEV_1 (L, mean [SD])	2.69 (0.56)	2.69 (0.56)	1.83 (0.49)	1.77 (0.46)
FEV_1 % predicted (%, mean [SD])	102.80 (15.76)	102.48 (16.44)	65.95 (12.53)	67.43 (12.64)
FVC (L, mean [SD])	3.05 (0.73)	3.56 (0.74)	1.99 (0.58)	2.37 (0.62)
FVC % predicted (%, mean [SD])	92.51 (17.48)	107.44 (17.32)	56.80 (12.45)	71.61 (13.59)
FEV_1/FVC (mean [SD])	0.89 (0.07)	0.76 (0.03)	0.93 (0.07)	0.74 (0.03)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 13. Basic characteristics of enrolled participants in borderline ratio and PRISm (low FEV_1) group based on GLI Global.

	Normal ratio and normal FEV_1	Borderline ratio	PRISm (low FEV_1)	P value (borderline ratio vs normal spirometry)	P value (PRISm [low FEV_1] vs normal spirometry)
N	1426	1172	598		
Age (years, mean [SD])	60.80 (8.41)	61.36 (8.37)	61.03 (8.49)	0.088	0.579
Gender (n [%])				0.548	0.004
Male	997 (69.9)	833 (71.1)	457 (76.4)		
Female	429 (30.1)	339 (28.9)	141 (23.6)		
Income (ten thousand yuan/year, n [%])				<0.001	0.471
<2	539 (37.8)	458 (39.1)	224 (37.5)		
2-5	600 (42.1)	385 (32.8)	266 (44.5)		
≥5	287 (20.1)	329 (28.1)	108 (18.1)		
Education (n [%])				<0.001	0.153
Primary school and below	780 (54.7)	564 (48.1)	299 (50.0)		
Middle and high school	615 (43.1)	560 (47.8)	284 (47.5)		
College and above	31 (2.2)	48 (4.1)	15 (2.5)		
Marriage (n [%])				0.765	0.237
Single	14 (1.0)	11 (0.9)	6 (1.0)		
Married	1358 (95.2)	1125 (96.0)	580 (97.0)		
Divorced	13 (0.9)	10 (0.9)	3 (0.5)		
Widowed	41 (2.9)	26 (2.2)	9 (1.5)		
Employment status (n [%])				<0.001	<0.001
On work	289 (20.3)	297 (25.3)	90 (15.1)		
Retire	94 (6.6)	179 (15.3)	61 (10.2)		
Homework	1015 (71.2)	646 (55.1)	424 (70.9)		
Unemployment	28 (2.0)	50 (4.3)	23 (3.8)		
Job (n [%])				0.453	0.193
Indoor	228 (59.4)	295 (61.6)	90 (58.4)		
Outdoor	100 (26.0)	128 (26.7)	49 (31.8)		
Other	56 (14.6)	56 (11.7)	15 (9.7)		
Fuel (n [%])				<0.001	0.049
Clean	540 (37.9)	577 (49.2)	261 (43.6)		
Unclean	882 (61.9)	592 (50.5)	336 (56.2)		
Unknown	4 (0.3)	3 (0.3)	1 (0.2)		
Smoking status (n [%])				0.172	0.108
Never	571 (40.0)	457 (39.0)	236 (39.5)		
Former	169 (11.9)	168 (14.3)	91 (15.2)		
Current	686 (48.1)	547 (46.7)	271 (45.3)		
Smoking exposure (pack	21.67 (24.10)	24.49 (38.96)	21.82 (24.80)	0.024	0.899

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years, mean [SD])					
Secondhand smoke (n [%])	349 (24.5)	311 (26.5)	130 (21.7)	0.248	0.206
Cough before 14 years old (n [%])	95 (6.7)	77 (6.6)	33 (5.5)	0.988	0.387
Family history of COPD (n [%])	18 (1.3)	15 (1.3)	9 (1.5)	>0.999	0.824
Comorbidities (n [%])	196 (13.7)	192 (16.4)	124 (20.7)	0.069	<0.001
Symptoms (n [%])					
Cough	506 (35.5)	429 (36.6)	250 (41.8)	0.582	0.008
Breathlessness				0.008	0.019
None	484 (33.9)	424 (36.2)	167 (27.9)		
When walking	744 (52.2)	632 (53.9)	350 (58.5)		
When climbing	198 (13.9)	116 (9.9)	81 (13.5)		
Height (cm, mean [SD])	162.92 (7.68)	163.25 (7.58)	164.50 (7.58)	0.272	<0.001
Weight (kg, mean [SD])	63.58 (10.61)	64.20 (10.79)	63.46 (10.49)	0.143	0.808
BMI (kg/m^2, mean [SD])	23.91 (3.32)	24.04 (3.38)	23.42 (3.40)	0.327	0.003
Waist circumference (cm, mean [SD])	85.96 (9.07)	86.86 (9.59)	85.63 (8.98)	0.015	0.454
Hip circumference (cm, mean [SD])	94.36 (8.84)	94.99 (9.18)	93.36 (8.48)	0.076	0.019
Lung function					
FEV_1 (L, mean [SD])	2.69 (0.56)	2.51 (0.66)	1.80 (0.48)	<0.001	<0.001
FEV_1 % predicted (%, mean [SD])	102.80 (15.76)	95.70 (20.99)	66.51 (12.58)	<0.001	<0.001
FVC (L, mean [SD])	3.05 (0.73)	3.33 (0.86)	2.13 (0.62)	<0.001	<0.001
FVC % predicted (%, mean [SD])	92.51 (17.48)	100.50 (21.87)	62.42 (14.76)	<0.001	<0.001
FEV_1/FVC (mean [SD])	0.89 (0.07)	0.75 (0.03)	0.86 (0.11)	<0.001	<0.001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 14. Lung function change and disease progression during 2 years follow up based on GLI Global.

	Normal ratio with normal FEV_1	Borderline ratio with normal FEV_1	Normal ratio with low FEV_1	Borderline ratio with low FEV_1
FEV_1 change in 2 years follow-up (L, mean [SD])	0.05 (0.69)	-0.15 (0.60)	1.02 (0.72)	0.61 (0.75)
FEV_1 % predicted change in 2 years follow-up (%, mean [SD])	5.28 (29.92)	-3.30 (24.22)	40.70 (28.32)	25.57 (29.51)
FEV_1 rapid decline in 2 years follow-up (n [%])	559 (39.2)	445 (47.1)	18 (4.9)	32 (14.1)
Airway obstruction in 2 years follow-up (n [%])	88 (6.2)	103 (10.9)	31 (8.4)	38 (16.7)

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

Supplement table 15. Lung function change and disease progression in borderline ratio and PRISm (low FEV_1) group during 2 years follow up based on GLI Global.

	Normal ratio and normal FEV_1	Borderline ratio	PRISm (low FEV_1)	P value (borderline ratio vs normal spirometry)	P value (PRISm [low FEV_1] vs normal spirometry)
FEV_1 change in 2 years follow-up (L, mean [SD])	0.05 (0.69)	0.00 (0.70)	0.86 (0.76)	0.063	<0.001
FEV_1 % predicted change in 2 years follow-up (%, mean [SD])	5.28 (29.92)	2.29 (27.77)	34.96 (29.67)	0.009	<0.001
FEV_1 rapid decline in 2 years follow-up (n [%])	559 (39.2)	477 (40.7)	50 (8.4)	0.462	<0.001
Airway obstruction in 2 years follow-up (n [%])	88 (6.2)	141 (12.0)	69 (11.5)	<0.001	<0.001

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV1 % predicted, proportion of predicted FEV_1 value; FVC % predicted, proportion of predicted FVC value.

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Supplement table 16. Risk of developing into airway obstruction during follow-up in high-risk population of COPD without airway obstruction at baseline based on GLI Global.

	Univariable	Model 1	Model 2
Normal ratio with normal FEV_1	Ref	Ref	Ref
Borderline ratio with normal FEV_1	1.86 (1.38, 2.50)	1.83 (1.35, 2.47)	1.73 (1.27, 2.35)
Normal ratio with low FEV_1	1.39 (0.91, 2.12)	1.38 (0.89, 2.12)	1.31 (0.85, 2.03)
Borderline ratio with low FEV_1	3.06 (2.03, 4.61)	2.84 (1.87, 4.30)	2.66 (1.74, 4.08)
Normal ratio with normal FEV_1	Ref	Ref	Ref
Borderline ratio	2.08 (1.57, 2.75)	2.02 (1.52, 2.68)	1.98 (1.48, 2.65)
PRISm (Low FEV_1)	1.98 (1.42, 2.76)	1.95 (1.39, 2.72)	1.81 (1.28, 2.55)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

Logistic regression model was used, and results were showed using odds ratio (OR) and 95% confidence interval (CI).

Model 1: age and sex

Model 2: age, sex, education, income, marriage, employment, BMI, smoking and pack years.

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Supplement table 17. Risk of FEV_1 rapid decline during follow-up in high-risk population of COPD patients without airway obstruction at baseline based on GLI Global.

	FEV_1 change in 2 years follow-up (continuous variable)			FEV_1 rapid decline (categorical variable)		
	Univariable	Model 1	Model 2	Univariable	Model 1	Model 2
Normal ratio with normal FEV_1	Ref	Ref	Ref	Ref	Ref	Ref
Borderline ratio with normal FEV_1	-0.20 (-0.25 to -0.14)	-0.20 (-0.25 to -0.14)	-0.15 (-0.21 to -0.10)	1.38 (1.17, 1.63)	1.39 (1.17, 1.64)	1.23 (1.04, 1.46)
Normal ratio with low FEV_1	0.98 (0.90 to 1.05)	0.98 (0.90 to 1.06)	0.96 (0.88 to 1.03)	0.08 (0.05, 0.13)	0.08 (0.05, 0.12)	0.08 (0.05, 0.13)
Borderline ratio with low FEV_1	0.56 (0.47 to 0.65)	0.55 (0.46 to 0.65)	0.58 (0.49 to 0.68)	0.25 (0.17, 0.38)	0.26 (0.17, 0.38*	0.23 (0.15, 0.34)
Normal ratio with normal FEV_1	Ref	Ref	Ref	Ref	Ref	Ref
Borderline ratio	-0.05 (-0.10, 0.00)	-0.05 (-0.11, 0.00)	-0.01 (-0.07, 0.04)	1.06 (0.91, 1.25)	1.07 (0.92, 1.26)	0.96 (0.82, 1.14)
PRISm (Low FEV_1)	0.82 (0.75, 0.89)	0.81 (0.75, 0.88)	0.81 (0.75, 0.88)	0.14 (0.10, 0.19)	0.14 (0.10, 0.19)	0.12 (0.09, 0.17)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of FEV_1/FVC; FEV_1 % predicted, proportion of predicted FEV_1 value.

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Linear model was used for analysis in FEV_1 change in 2 years follow-up (continuous variable), and results were showed using β and 95% confidence interval (CI). Logistic regression analysis was used for analysis in FEV_1 decline (categorical variable), and results were showed using odds ratio (OR) and 95% CI.

Model 1: age and sex

Model 2: age, sex, education, income, marriage, employment, BMI, smoking and pack years.

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