Original Research

Clinical Significance of Reduced Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 Seconds in Adults

Siman Liao, MD[1*] Juncheng Liang, MD[1*] Jie Ou, MD[2] Ranxi Peng, MD[3] Shiyu Zhang, MD[4] Leheng Tang, MD[4] Qiaorui Zhou, MD[4] Yingtong Chen, MD[4] Xiaozi Guo, MD[1] Jingxian Chen, MD[1] Qi Wan, MD[5] Zihui Wang, MD, PhD[5] Zhishan Deng, MD, PhD[5] Yumin Zhou, MD, PhD[5,6] Fan Wu, MD, PhD[5]

[1]The Second Clinical College, Guangzhou Medical University, Guangzhou, China

[2]State Key Laboratory of Respiratory Disease, Guangzhou Chest Hospital, Guangzhou, China

[3]The Third Clinical College, Guangzhou Medical University, Guangzhou, China

[4]The First Clinical College, Guangzhou Medical University, Guangzhou, China

[5]State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease & National Center for Respiratory Medicine & Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[6]Guangzhou National Laboratory, Guangzhou, China

** Theses authors contributed equally to this work.*

Address correspondence to:
Fan Wu, MD, PhD
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou, China
Email: wu.fan@vip.163.com.

Yumin Zhou, MD, PhD
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou National Laboratory
Guangzhou, China
Email: zhouyumin410@126.com

Running Head: **Clinical Significance of Reduced FEV_3/FEV_6**

Keywords: COPD; forced expiratory volume in 3 seconds; forced expiratory volume in 6 seconds; small airway disease; all-cause mortality

Abbreviations:

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Funding Support: This work was supported by the Foundation of Guangzhou National Laboratory (No. SRPG22-016 and SRPG22-018), the Clinical and Epidemiological Research Project of State Key Laboratory of Respiratory Disease (No. SKLRD-L-202402), the Plan on Enhancing Scientific Research in Guangzhou Medical University (No. GMUCR2024-01012), and the Zhongnanshan Medical Foundation of Guangdong Province·(ZNSXS-20250019).

Date of Acceptance: March 3,2026 | ***Published Online Date***: March 31, 2026

Citation: Liao S, Liang J, Ou J, et al. Clinical significance of reduced forced expiratory volume in 3 seconds to forced expiratory volume in 6 seconds in adults. *Chronic Obstr Pulm Dis*. 2026; Published online March 31, 2026.
https://doi.org/10.15326/jcopdf.2025.0649

This article has an online supplement.

Abstract

Background: The forced expiratory volume (FEV) in 3 seconds (FEV_3) to FEV_6 ratio (FEV_3/FEV_6) is a novel spirometry measure that identifies early airflow abnormalities, but its long-term prognosis value in the general population remains unclear. We aim to evaluated the long-term all-cause mortality risk among participants with reduced FEV_3/FEV_6.

Methods: Data were obtained from the National Health and Nutrition Examination Survey cycles 1988–1994 and 2007–2012 Reduced FEV_3/FEV_6 was defined as FEV_3/FEV_6 less than the lower limit of normal. Multivariable logistic regression was used to assess the relationship of reduced FEV_3/FEV_6 with comorbidities and chronic respiratory symptoms. The relationship between reduced FEV_3/FEV_6 and all-cause mortality was evaluated using Cox regression models. The non-linear relationship between FEV_3/FEV_6 and all-cause mortality was assessed using restricted cubic splines. Subgroup analyses and sensitivity analyses were conducted to validate the robustness of the relationship.

Results: Overall, 25,159 participants were enrolled in the 308-month median follow-up analysis, of whom 8.8% (2,225/25,159) had reduced FEV_3/FEV_6 Participants with reduced FEV_3/FEV_6 exhibited increased risks of congestive heart failure, asthma, chronic bronchitis, emphysema, respiratory symptoms, and all-cause mortality risk (hazard ratio=1.23, 95% confidence interval: 1.13–1.34, $P<0.001$). The findings remained consistent across subgroups. A non-linear U-shaped association was observed between FEV_3/FEV_6 and all-cause mortality, with the turning point at 1.04, and sensitivity analyses confirmed the robustness of this relationship.

Conclusions: Participants with reduced FEV_3/FEV_6 had worse respiratory health outcomes, suggesting that FEV_3/FEV_6 can be used as prognostic spirometry indicator.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Introduction

Spirometry is an essential diagnostic tool for identifying obstructive lung disease and monitoring its progression. However, traditional spirometry such as forced expiratory volume in 1 second (FEV_1) mainly reflects large airway obstruction, and lacks the sensitivity to detect small airway abnormalities in the early stage of chronic airway disease [1-3]. Therefore, a spirometry indicator that could accurately reflect early small airway abnormalities is needed.

The forced expiratory volume (FEV) in 3 seconds (FEV_3) to FEV_6 ratio (FEV_3/FEV_6) is a routinely available and repeatable spirometry index that can detect early airway abnormalities [4,5]. A national cross-sectional study conducted in China revealed that the overall predicted prevalence of small airway dysfunction (SAD) was 52.4% usingFEV_3/FEV_6 less than the lower limit of normal (LLN) as the diagnostic indicator [6]. FEV_3/FEV_6 <LLN in individuals with a normal FEV_1/forced vital capacity (FVC) ratio is significantly associated with impaired computed tomography measurements, shorter 6-minute walking distance, increased dyspnea, and lower quality of life, suggesting that FEV_3/FEV_6 reflects mild pulmonary structural, functional, and clinical abnormalities [7]. The SPIROMICS study of current and former smokers without chronic obstructive pulmonary disease (COPD) found that FEV_3/FEV_6 <LLN was associated with an increased risk of severe respiratory exacerbations and a shorter time to first exacerbation, and these patients were more likely to progress to COPD [5]. The UK Biobank Study, which used FEV_3/FEV_6 <LLN to define SAD, indicated that participants with SAD are at an increased risk of all-cause, cardiovascular, respiratory, and neoplasm mortality [8]. However, the clinical utility of FEV_3/FEV_6 in the general population remains limited, particularly its potential non-linear relationship with all-cause mortality and long-term prognosis require further investigations.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

In this study, we aim to explore the clinical characteristics and long-term prognosis of participants with FEV_3/FEV_6 <LLN based on the general population analyzed in the National Health and Nutrition Examination Survey (NHANES). We also aim to explore whether participants with reduced FEV_3/FEV_6 have an elevated risk of all-cause death, both overall and after subgroup stratification. This study also sought to explore the potential non-linear relationship between FEV_3/FEV_6 and all-cause mortality.

Methods

Study population

We conducted a retrospective cohort study by performing a secondary analysis of data from the NHANES, a nationally representative study conducted by the Centers for Disease Control and Prevention and the National Centers for Health Statistics (NCHS) in the US. The NHANES uses a rigorous stratified, multistage probability sampling design to ensure representativeness. The NCHS Research Ethics Review Board approved the NHANES protocols, and written informed consent was obtained from all participants. Data were sourced from the NHANES website [9].

This study included 50,492 participants from the NHANES database, encompassing two time periods with available spirometry data: 1988–1994 and 2007–2012. The exclusion criteria were (1) age <20 years; (2) missing spirometry data; (3) spirometry data of unacceptable quality; (4) pregnancy; (5) incomplete physical data; and (6) missing data on smoking status. Of the eligible participants, those with missing mortality data or without FEV_3/FEV_6 data were further excluded.

Spirometry testing

The postbronchodilator spirometry data were absent for the majority of participants enrolled in the NHANES cycles 1988–1994 and 2007–2012, whereas prebronchodilator spirometry data were

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

more comprehensive. Therefore, we used prebronchodilator spirometry data. Prebronchodilator spirometry was conducted using Ohio 822/827 dry-rolling volume seal spirometers. For the 1988–1994 cycle, reproducible FEV_1 and FVC measurements from ≥2 acceptable trials were required, whereas the 2007–2012 period mandated quality scores of grade B or higher according to the American Thoracic Society standards [10,11].

In this study, FEV_3/FEV_6 <LLN was defined as reduced FEV_3/FEV_6. The LLN for prebronchodilator FEV_3/FEV_6 was calculated according to the linear iterative equation redefined by Hansen et al., using age, sex, and ethnicity [4]. Owing to limited sample sizes and difficulty in classification, the study by Hansen et al. lacked linear iterative equations for other races (including other Hispanics, Asians, and Native Americans). Consequently, we referred to the SPIROMICS cohort study and used the reference equation for the Latin population (Mexican–American) to calculate the LLN of FEV_3/FEV_6 for the other races included in the dataset [5].

Mortality ascertainment

The study endpoint was all-cause mortality (death from any cause). The National Death Index death certificate records provided by the NCHS provided mortality data, with follow-up through December 31, 2019.

Assessment of covariates

Standardized in-home interviews captured demographic, socioeconomic, health condition, and behavioral data, while mobile examination centers with quality-controlled procedures obtained physical measurements and laboratory test results. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and grouped into four categories: underweight (<18.5 kg/m^2), normal (≥18.5 kg/m^2 to <25 kg/m^2), overweight (≥25.0 kg/m^2 to <30.0 kg/m^2), and obese (≥30.0 kg/m^2). The following formula was used to calculate body surface area

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

(BSA): BSA (m^2) = (body weight [kg])$^{0.425}$ × (height [cm])$^{0.725}$ × 0.007184 [12]. Race was categorized as non-Hispanic White, non-Hispanic Black, Mexican–American, or other race. The level of education of adults aged >20 years was categorized as less than 9th grade, 9th–12th grade, or above 12th grade. Poverty-to-income (PIR) ratio was grouped into low-income (<1.3), middle-income (1.3 to <3.5), and high-income (≥3.5). Smoking status was classified based on self-reported questionnaire responses into three categories: never smoker (<100 cigarettes in the entire lifetime), former smoker (≥100 cigarettes but current cessation), and current smoker (≥100 cigarettes with persistent smoking). Data on the presence of comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes mellitus, and hypertension) were obtained through a questionnaire in which participants were asked to indicate whether they had ever been informed by a medical practitioner or other health professional that they had been diagnosed with a specific disease. Chronic cough and chronic phlegm were defined as daily coughing or sputum persisting for ≥3 consecutive months per year. Wheezing was defined by audible whistling or wheezing from the chest within the past year. Shortness of breath was defined as an occurrence of awakening caused by trouble breathing or shortness of breath other than when they had a cold.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation, while categorical variables are expressed as frequency (percentage). Baseline characteristics were compared using the independent-samples t-test for continuous variables and Pearson's chi-square test for categorical variables. Logistic regression models adjusted for age, sex, race, BMI, and smoking status were employed to assess the relationship between chronic respiratory symptoms and comorbidities and reduced FEV_3/FEV_6. Five Cox regression models were constructed to evaluate the association

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

between all-cause mortality and reduced FEV_3/FEV_6. The crude model was unadjusted, while Model 1 was adjusted for age, sex, BSA, race, and BMI. Model 2 was additionally adjusted for smoking status, PIR, and level of education. Model 3 was additionally adjusted for comorbidities, including congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension. Model 4 was adjusted for all previously mentioned covariates plus percent predicted FEV_1.

Based on the crude Cox regression model and Model 3, we performed subgroup analyses to assess the association between reduced FEV_3/FEV_6 and all-cause mortality in different subgroups stratified by sex, age, BMI, race, and smoking status. We included FEV_3/FEV_6 and subgroup variables as interaction terms in the model analyses to test for potential interaction effects. To investigate whether there was a non-linear relationship between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality, we used restricted cubic spline (RCS) analysis with five knots in both the univariable model (crude model) and multivariable model (Model 3) using the "plotRCS" package of R software [13 ,14].

Sensitivity analyses were performed to confirm the validity of our findings: (1) participants with FVC<80% of the predicted value were exclude; (2) age was used as a categorial variable (20-40, 41-60, 61-80); (3) comorbidity including congestive heart failure, asthma, chronic bronchitis, emphysema were used as a categorial variable; (4) the relationship between FEV_3/FEV_6 as a standalone variable and all-cause mortality was examined; (5) age was used as the time axis in survival analyses [15]. Statistical significance was set at $P <0.05$ (two-tailed). All analyses R, version 4.3.2, and SPSS, version 27.0.

Results

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Participants' baseline characteristics

Overall, 50,492 participants were enrolled in the NHANES cycles 1988–1994 and 2007–2012. Participants aged <20 years (n=13,954), without spirometry data (n=7,782), with unacceptable spirometry (n=3,043), with pregnancy (n=262), without complete physical measurements (n=58), and without data on smoking status (n=7) were excluded. Of the remaining 25,386 participants, 227 were excluded owing to missing follow-up time for death at baseline (n=29) or incorrect FEV_3 or FEV_6 data (n=198). Finally, 25,159 participants were enrolled, among whom 8.8% (2,225/25,159) exhibited reduced FEV_3/FEV_6 (**Figure 1**).

The baseline characteristics of the normal FEV_3/FEV_6 and reduced FEV_3/FEV_6 groups are presented in **Table 1**. The mean age of the participants in the reduced FEV_3/FEV_6 group was 53.2±17.4 years, and 54.8% were male. Compared with the normal FEV_3/FEV_6 group, the majority of participants with reduced FEV_3/FEV_6 were non-Hispanic White (59.2%), current smokers (43.8%), and had a lower level of education and a lower PIR. The reduced FEV_3/FEV_6 group also had significantly lower prebronchodilator FEV_1, FVC, percent predicted FEV_1, and percent predicted FVC values.

Risk of chronic respiratory symptoms and comorbidities

Table 2 shows the association between reduced FEV_3/FEV_6 and chronic respiratory symptoms and comorbidities. The reduced FEV_3/FEV_6 group had a higher risk of a self-reported diagnosis of congestive heart failure (adjusted odds ratio [OR] 1.31, 95% confidence interval [CI] 1.03–1.67, P=0.026), asthma (adjusted OR 3.23, 95% CI 2.87–3.63, P<0.001), chronic bronchitis (adjusted OR 2.47, 95% CI 2.13–2.88, P<0.001), and emphysema (adjusted OR 5.39, 95% CI 4.28–6.78, P<0.001). Meanwhile, the FEV_3/FEV_6 group was significantly more likely to suffer from chronic respiratory symptoms, including chronic cough (adjusted OR 1.92, 95% CI 1.68–2.20, P<0.001),

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

chronic phlegm (adjusted OR 1.93, 95% CI 1.69–2.21, P<0.001), wheezing (adjusted OR 2.64, 95% CI 2.38–2.93, P<0.001), and shortness of breath (adjusted OR 2.12, 95% CI 1.87–2.41, P<0.001) than the normal FEV_3/FEV_6 group.

Association of reduced FEV_3/FEV_6 with all-cause mortality

During the median follow-up period of 308 months, 6,393 participants (25.4%) died, of which 45.3% (1,008/2,225) had reduced FEV_3/FEV_6 and 23.0% (5,285/22,934) had normal FEV_3/FEV_6. The all-cause mortality risk curves in the normal and reduced FEV_3/FEV_6 groups are shown in **Figure 1**. The analyses demonstrated that participants in the reduced FEV_3/FEV_6 group exhibited significantly higher all-cause mortality than those in the normal FEV_3/FEV_6 group (log-rank P<0.001).

Table 3 shows the five Cox regression models. Compared with the normal FEV_3/FEV_6 group, the reduced FEV_3/FEV_6 group exhibited a significantly increased risk of all-cause mortality in the crude model (hazard ratio [HR] 2.45, 95% CI 2.29–2.62, P<0.001). The reduced FEV_3/FEV_6 group still exhibited an increased risk of all-cause mortality in the multivariable analysis controlled for sociodemographic factors (Model 1: HR 1.68, 95% CI 1.57–1.80, P<0.001). The association between reduced FEV_3/FEV_6 and all-cause mortality was not attenuated by adjustment for smoking status, PIR, and level of education (Model 2: HR 1.45, 95% CI 1.35–1.57, P<0.001). Further adjustment for comorbidities (Model 3: HR 1.43, 95% CI 1.33–1.55, P<0.001) and spirometry only slightly weakened the association (Model 4: HR 1.23, 95% CI 1.13–1.34, P<0.001).

Subgroup analyses

As demonstrated in **Figure 2**, subgroup analyses were performed to evaluate the association between FEV_3/FEV_6 and all-cause mortality according to sex, age, BMI, race, and smoking status.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

In the univariable model, reduced FEV_3/FEV_6 was associated with higher all-cause mortality in all subgroups, revealing significant interactions between FEV_3/FEV_6 and each subgroup. In the multivariable model adjusted for sex, age, BSA, BMI, race, smoking status, level of education, PIR, congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension, significant interactions were observed between FEV_3/FEV_6 and race and smoking status only.

Non-linear relationship between the ratio of FEV_3/FEV_6 to LLN and mortality

Figure 3 illustrates the RCS analysis curves prior to and following adjustment for aforementioned covariates, revealing a consistent U-shaped association between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality with an inflection point at 1.04 (all $P_{non\text{-}linearity} < 0.001$). Below and above the inflection point, an inverse trend in mortality risk was observed. On the left side of the inflection point, a reduced FEV_3/FEV_6 ratio was negatively associated with all-cause mortality, while an abnormally elevated ratio on the right was positively associated. A L-shaped nonlinear association was observed between the continuous FEV_3/FEV_6 ratio and all-cause mortality.

Sensitivity analyses

Figure S1 and **Figure S2** reveal that the U-shaped nonlinear relationship between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality remained stable in sensitivity analyses, which excluded participants with FVC<80% predicted value or treated comorbidity as categorical variable. Stratified analysis in **Figure S3** shows this robust relationship in the 41-60 and 61-80 age groups, with no significant association observed in the 20-40 age group. An L-shaped nonlinear association was observed between the continuous FEV_3/FEV_6 ratio and all-cause mortality in **Figure S4**. When age was used as the survival analysis time scale, the all-cause mortality risk curves in **Figure S5** revealed a striking divergence after age 60, with a steep increase in risk specifically for the

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

reduced FEV_3/FEV_6 group. The pattern aligns with the Cox regression models in **Table S1**, which remained consistent with the primary analysis.

Discussion

This study revealed that participants with reduced FEV_3/FEV_6 had an increased risk of comorbidities, chronic respiratory symptoms, and all-cause mortality compared with participants with normal FEV_3/FEV_6, and the above results were consistent across the subgroup analyses. Furthermore, a non-linear U-shaped relationship between FEV_3/FEV_6 and all-cause mortality risk was identified.

To our knowledge, this study has the longest follow-up of the current studies that have evaluated the relationship between reduced FEV_3/FEV_6 and all-cause mortality. Concurrently, it is the first study to explore the non-linear relationship between FEV_3/FEV_6 and all-cause mortality risk. These findings suggest that FEV_3/FEV_6 can serve not only as a biomarker to evaluate the risk of developing chronic multimorbidity, but also as an independent prognostic marker of lung function in clinical practice.

Reduced FEV_3/FEV_6 serves as an early indicator of SAD [5]. The small airways are defined as those with a luminal diameter of <2 mm [16]. SAD may develop through multiple pathological mechanisms, including luminal occlusion by mucus, reduction in luminal diameter from inflammatory infiltrates, smooth muscle hypertrophy, or airway wall thickening. Furthermore, loss of structural airway support can increase the collapsibility of the airways [2]. Yee et al. (SPIROMICS study) and Dilektasli et al. (COPDGene cohort) demonstrated associations between FEV_3/FEV_6 <LLN and respiratory deterioration and dyspnea [5,7]. Additionally, Ben et al. found that chronic cough, chronic phlegm, wheezing, and shortness of breath were associated with isolated small airway obstruction, consistent with the results of the present study. Participants with

reduced FEV_3/FEV_6 were more likely to have chronic respiratory symptoms owing to characteristic pathological changes and small airway obstruction [17]. In addition, chronic exposure to inhalant irritants that damage the walls of the small airways may also lead to respiratory symptoms in these participants because particles can more easily collide with the narrower small airway surfaces [17,18].

A previous study also used the FEV_3/FEV_6 ratio to define small airway obstruction, showing that participants with small airway obstruction were at an increased risk of all-cause, respiratory, cardiovascular, and neoplasm-related mortality, similar to our findings [8]. Our study demonstrated that participants with reduced FEV_3/FEV_6 had an increased risk of chronic bronchitis, asthma, emphysema, and congestive heart failure. The ATLANTIS study demonstrated a SAD prevalence of up to 91% among patients with asthma [19]. Furthermore, the severity of small airway dysfunction is markedly associated with an increased risk of asthma exacerbation, and its presence adversely affects asthma symptom control [20]. The small airways play a pivotal role in the pathophysiology of obstructive lung diseases, including asthma and COPD. The characteristic of airway inflammation, mucus hypersecretion, and structural remodeling in these conditions contributes to respiratory diseases, cardiometabolic complications, and reduced quality of life [21-23]. Also, SAD may be a precursor to emphysema, and loss of alveolar attachments may be the underlying mechanism [18,24]. It has also been found that patients with isolated small airway obstruction are more likely to be diagnosed with cardiovascular disease, even without coexisting airflow obstruction, possibly mediated through spirometry small airway obstruction upregulated inflammatory processes [16]. However, no significant association was observed between participants with reduced FEV_3/FEV_6 and cancer, which may be related to the insufficiency of the cancer data included.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

This study revealed a non-linear U-shaped relationship between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality risk. Reduced FEV_3/FEV_6 may increase all-cause mortality through a combination of mechanisms, including small airway remodeling, mucous plugging, immune cell infiltration and systemic inflammation [2, 25]. In patients with comorbid chronic airway disease, reduced FEV_3/FEV_6 is associated with frequent exacerbations, a heightened symptom burden, and diminished quality of life [5,7,17,26]. These findings demonstrate a biologically plausible association between reduced FEV_3/FEV_6 and increased all-cause mortality. Notably, excessive FEV_3/FEV_6 ratio paradoxically predicts a higher risk of all-cause mortality. Sensitivity analyses that excluded participants with FVC <80% predicted or categorized comorbidities (congestive heart failure, asthma, chronic bronchitis, emphysema) consistently demonstrated a robust U-shaped association, suggesting that restrictive ventilatory impairment and comorbidities may not be the primary drivers of the rightward shift in the curve beyond the inflection point. In previous studies, we observed that the nonlinear relationship between FEV_1/FVC and all-cause mortality shifted from an L-shaped curve to a U-shaped curve after adjusting for confounders, and Tang. et.al. suggested that age may be a key factor driving this change, though the precise mechanism remains unclear [27]. In our study, the U-shaped curve was specific to individuals aged above 41, suggesting that the paradoxical rise in FEV_3/FEV_6 might be related to age-dependent respiratory muscle weakness [28]. Furthermore, since respiratory muscle strength is closely tied to nutritional status and cardiac index, participants with respiratory muscle weakness may often present with underlying conditions such as malnutrition or compensatory heart failure. These compounding factors may collectively explain the elevated risk observed on the right side of the curve [29] However, these hypotheses require further validation through targeted investigations.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

The association between reduced FEV_3/FEV_6 and all-cause mortality remained consistent across the subgroup analyses. Despite significant interaction terms being observed only for race and smoking status, the association between reduced FEV_3/FEV_6 and increased mortality showed a consistent effect direction across all subgroups, underscoring the robustness of the finding. Previous cohort studies and clinical practices have been conducted only in the population of smokers, ignoring the role of reduced FEV_3/FEV_6 in never-smokers [5,7,30]. Our study found that reduced FEV_3/FEV_6 remained significantly associated with increased all-cause mortality among never-smokers, which not only remedies the scarcity of studies involving never-smokers, but it also demonstrates the good generalizability of FEV_3/FEV_6 as a lung function indicator.

This study has several important strengths that merit emphasis. First, the data were obtained from the NHANES, which boasts a substantial sample size and comprehensive data coverage, thereby facilitating more precise generalizations to the general population and enabling a comprehensive assessment of the relationship between FEV_3/FEV_6 and all-cause mortality. Second, our study used five Cox proportional-hazards models and incorporated extensive adjustment for confounders to verify the robustness and credibility of the findings. Furthermore, subgroup analyses were conducted based on the univariable and multivariable models, the results of which were consistent with the main analysis, further enhancing the robustness of the results. Finally, we fitted RCS curves, both unadjusted and adjusted for confounders. The findings revealed an independent relationship between FEV_3/FEV_6 and all-cause mortality.

Our study also has several limitations. First, even after adjustment for a wide range of potential confounding factors through the multivariable models, the relationship between FEV_3/FEV_6 and all-cause mortality might have still been affected by unmeasured factors, such as occupational exposure and air pollution due to limitations in data availability. Second,

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

prebronchodilator spirometry data were used owing to constrained postbronchodilator spirometry data availability. Although previous studies have shown that postbronchodilator spirometry is a more accurate predictor of mortality than prebronchodilator spirometry, the difference between the two is relatively minor [31,32]. Third, due to the unavailability of specific all-cause death data for participants during the 1988-1994 period, we were unable to exclude the external causes such as accidents that may have diluted the true association between FEV_3/FEV_6 and all-cause mortality. Finally, the data comprised two components of spirometry that used different quality control criteria and operational standards, which has the potential to influence the accuracy of FEV_3/FEV_6 measurements.

Conclusion

In summary, this analysis of data from the NHANES showed that participants with reduced FEV_3/FEV_6 had a higher risk of chronic respiratory symptoms, comorbidities, and all-cause mortality. Moreover, we observed a non-linear U-shaped relationship between FEV_3/FEV_6 and all-cause mortality risk. These results suggest that FEV_3/FEV_6 could be a sensitive prognostic spirometry indicator in the general population.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Acknowledgements

We thank all participants who volunteered as part of the National Health and Nutrition Examination Survey. We thank Emily Woodhouse, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Authorship contributions

S.L. and. F.W. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design – S.L., J.L., and F.W. Acquisition, analysis or interpretation of data – S.L., J.L., J.O., R.P., S.Z., L.T., Q.Z., Y.C., X.G., J.C., Q.W., Z.W., Z.D., Y.Z., F.W. Statistical analysis – S.L., J.L., and. F.W. Drafting of the manuscript – S.L., J.L., and. F.W. Study guarantor – S.L. and. F.W. Critical revision of the manuscript – all authors.

Declarations

Ethics statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the institutional review board of the National Center for Health Statistic (NCHS). Written informed consent was obtained from all participants.

Disclosure of Interest

The authors declare that they have no conflicts of interest.

References

1 Hoesterey D, Das N, Janssens W, et al. Spirometric indices of early airflow impairment in individuals at risk of developing COPD: spirometry beyond FEV1/FVC. Respir Med. 2019; 156:58-68.

2 McNulty W, Usmani OS. Techniques of assessing small airways dysfunction. Eur Clin Respir J. 2014; 1:10.3402.

3 Hansen JE, Sun XG, Wasserman K. Discriminating measures and normal values for expiratory obstruction. Chest. 2006;129(2):369-377.

4 Hansen JE, Porszasz J, Casaburi R, Stringer WW. Re-Defining Lower Limit of Normal for FEV1/FEV6, FEV1/FVC, FEV3/FEV6 and FEV3/FVC to Improve Detection of Airway Obstruction. Chronic Obstr Pulm Dis. 2015;2(2):94-102.

5 Yee N, Markovic D, Buhr RG, et al. Significance of FEV3/FEV6 in Recognition of Early Airway Disease in Smokers at Risk of Development of COPD: Analysis of the SPIROMICS Cohort. Chest. 2022;161(4):949-959.

6 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.

7 Dilektasli AG, Porszasz J, Casaburi R, et al. A Novel Spirometric Measure Identifies Mild COPD Unidentified by Standard Criteria. Chest. 2016;150(5):1080-1090.

8 Quintero Santofimio V, Knox-Brown B, Potts J, Bartlett-Pestell S, Feary J, Amaral AFS. Small Airways Obstruction and Mortality: Findings From the UK Biobank. Chest. 2024;166(4):712-720.

9 National Center for Health Statistic. About the National Health and Nutrition Examination

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Survey. 2019. Available: National Center for Health Statistics. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed: 5 June 2025.

10 Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis. 1991;144(5):1202-1218.

11 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.

12 Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.

13 Harrell FE Jr. Regression Modeling Strategies. 2nd ed. New York, NY: Springer-Verlag; 2015

14 Huo R. plotRCS: Plot Restricted Cubic Splines Curves. Version 0.1.5. 2024. .

15 Thiébaut AC, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med. 2004;23(24):3803-3820.

16 Macklem PT. The physiology of small airways. Am J Respir Crit Care Med. 1998;157(5 Pt 2):S181-S183,

17 Knox-Brown B, Patel J, Potts J, et al. The association of spirometric small airways obstruction with respiratory symptoms, cardiometabolic diseases, and quality of life: results from the Burden of Obstructive Lung Disease (BOLD) study. Respir Res. 2023;24(1):137.

18 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

19 Postma DS, Brightling C, Baldi S, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study Lancet Respir Med. 2019;7(5):402-416.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

20 Abdo M, Trinkmann F, Kirsten AM, et al. The Relevance of Small Airway Dysfunction in Asthma with Nocturnal Symptoms. J Asthma Allergy. 2021;14:897-905. Published 2021 Jul 13. doi:10.2147/JAA.S313572

21 Kraft M, Richardson M, Hallmark B, et al. The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. Lancet Respir Med. 2022;10(7):661-668.

22 Crisafulli E, Pisi R, Aiello M, et al. Prevalence of Small-Airway Dysfunction among COPD Patients with Different GOLD Stages and Its Role in the Impact of Disease. Respiration. 2017;93(1):32-41.

23 Schneider C, Bothner U, Jick SS, Meier CR. Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. Eur J Epidemiol. 2010;25(4):253-260.

24 Janssen R, Wouters EFM. Loss of Alveolar Attachments as a Pathomechanistic Link between Small Airway Disease and Emphysema. Am J Respir Crit Care Med. 2020;201(7):878-879.

25 Kapellos TS, Baßler K, Fujii W, et al. Systemic alterations in neutrophils and their precursors in early-stage chronic obstructive pulmonary disease. Cell Rep. 2023;42(6):112525.

26 Tang L, Wu F, Zhang S, et al. Association between FEV1/FVC levels and all-cause mortality in the general population. BMC Pulm Med. 2025;25(1):108

27 Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. Eur Respir J. 1999;13(1):197-205.

28 Hamazaki N, Kamiya K, Nozaki K, et al. Correlation between respiratory muscle weakness and frailty status as risk markers for poor outcomes in patients with cardiovascular disease. Eur J Cardiovasc Nurs. 2022;21(8):782-790.

29 Day K, Ostridge K, Conway J, et al. Interrelationships Among Small Airways Dysfunction,

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Neutrophilic Inflammation, and Exacerbation Frequency in COPD. Chest. 2021;159(4):1391-1399

30 Tenin K, Aurélien S, Daniela M, Denis C, Frédéric C. Prevalence of a decreased FEV3/FEV6 ratio in symptomatic smokers with preserved lung function. *Respir Med Res*. 2022;81:100891.

31 Bhatta L, Leivseth L, Carslake D, et al. Comparison of pre- and post-bronchodilator lung function as predictors of mortality: The HUNT Study. Respirology. 2020;25(4):401-409.

32 Mannino DM, Diaz-Guzman E, Buist S. Pre- and post-bronchodilator lung function as predictors of mortality in the Lung Health Study. Respir Res. 2011;12(1):136.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Table 1. Baseline characteristics in patients stratified according to pre-bronchodilator FEV_3/FEV_6.

Variable	FEV_3/FEV_6 <LLN (n=2225)	FEV_3/FEV_6 ≥LLN (n=22934)	P Value
Age, years	53.2 ± 17.4	45.6 ± 17.0	<0.001
Male sex, n (%)	1219 (54.8)	11058 (48.2)	<0.001
Race, n (%)			<0.001
Non-Hispanic White	1317 (59.2)	9510 (41.5)	
Non-Hispanic Black	497 (22.3)	5591 (24.4)	
Mexican American	256 (11.5)	5335 (23.3)	
Other race	155 (7.0)	2498 (10.9)	
Body mass index, kg/m^2	26.4 ± 5.9	28.2 ± 6.3	<0.001
Smoking status, n (%)			<0.001
Never	586 (26.3)	12256 (53.4)	
Current	975 (43.8)	5357 (23.4)	
Former	664 (29.8)	5321 (23.2)	
Education Level, n (%)			<0.001
<9th Grade	425 (19.2)	3557 (15.6)	
9-12th Grade	1070 (48.4)	9838 (43.0)	
>12th Grade	717 (32.4)	9460 (41.4)	
Poverty income ratio, n (%)			<0.001
Low	699 (34.0)	6364 (30.3)	
Middle	842 (40.9)	8611 (41.0)	
High	517 (25.1)	6012 (28.6)	
Pre-bronchodilator spirometry			
FEV_1, L	2.30 ± 0.84	3.11 ± 0.88	<0.001
FEV_1 % of predicted, %	75.5 ± 19.0	99.6 ± 14.5	<0.001
FVC, L	3.69 ± 1.12	3.89 ± 1.07	<0.001
FVC % of predicted, %	95.6 ± 18.2	100.2 ± 14.2	<0.001
FEV_3, L	3.03 ± 1.04	3.62 ± 1.03	<0.001
FEV_6, L	3.37 ± 1.09	3.78 ± 1.05	<0.001
FEV_1/FVC, %	61.6 ± 9.9	80.0 ± 6.7	<0.001
FEV_3/FEV_6, %	89.0 ± 4.0	95.6 ± 2.3	<0.001

Data are expressed as mean ± standard deviation or n (%).

Abbreviations: FEV_1 = forced expiratory volume in 1 s; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Table 2. The risk of chronic respiratory symptoms and comorbidity in participants with reduced FEV_3/FEV_6

Variable	FEV_3/FEV_6 <LLN (n=2225)	FEV_3/FEV_6 ≥LLN (n=22934)	Unadjusted		Adjusted *	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Chronic respiratory symptoms						
Chronic cough	368 / 2012	1427 / 19680	2.86 (2.53-3.25)	<0.001	1.92 (1.68-2.20)	<0.001
Chronic phlegm	354 / 2010	1435 / 19676	2.72 (2.39-3.08)	<0.001	1.93 (1.69-2.21)	<0.001
Wheezing	680 / 2225	2880 / 22925	3.06 (2.78-3.38)	<0.001	2.64 (2.38-2.93)	<0.001
Shortness of breath	554 / 1326	2817 / 12580	2.49 (2.21-2.80)	<0.001	2.12 (1.87-2.41)	<0.001
Comorbidity						
Congestive heart failure	97 / 2216	506 / 22903	2.03 (1.62-2.53)	<0.001	1.31 (1.03-1.67)	0.026
Stroke	66 / 2222	466 / 22922	1.48 (1.14-1.92)	0.004	0.82 (0.63-1.09)	0.172
Asthma	485 /2223	2006 /22926	2.91 (2.60-3.25)	<0.001	3.23 (2.87-3.63)	<0.001
Chronic bronchitis	281 /2220	1013 /22922	3.13 (2.73-3.61)	<0.001	2.47 (2.13-2.88)	<0.001
Emphysema	194 / 2221	172 /22923	12.66 (10.26-15.62)	<0.001	5.39 (4.28-6.78)	<0.001
Cancer	262 / 2224	1513 / 22923	1.89 (1.64-2.17)	<0.001	1.12 (0.96-1.31)	0.143
Diabetes	187 / 2223	1974 / 22911	0.97 (0.83-1.14)	0.743	0.90 (0.76-1.06)	0.197
Hypertension	717 / 2214	6370 / 22824	1.24 (1.13-1.36)	<0.001	1.01 (0.90-1.12)	0.917

Data are n (%).

* Models were adjusted for sex, age, race, body mass index, and smoking status using logistic regression models.

Abbreviations: FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal; OR= odds ratio; CI = confidence interval.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Table3. Risk of death in participants with reduced FEV_3/FEV_6

Models	FEV_3/FEV_6 ⩾LLN		FEV_3/FEV_6 <LLN		FEV_3/FEV_6 <LLN vs. FEV_3/FEV_6	
	Total	Death	Total	Death	hazard ratio (95%	P value
Crude model	22934	5285 (23.0%)	2225	1008 (45.3%)	2.45 (2.29-2.62)	<0.001
Model 1*	22934	5285 (23.0%)	2225	1008 (23.0%)	1.68 (1.57-1.80)	<0.001
Model 2†	20933	4732 (22.6%)	2047	918 (44.8%)	1.45 (1.35-1.57)	<0.001
Model 3‡	20760	4689 (22.6%)	2012	905 (45.0%)	1.43 (1.33-1.55)	<0.001
Model 4§	20760	4689 (22.6%)	2012	905 (45.0%)	1.23 (1.13-1.34)	<0.001

*Model 1 was adjusted for age, sex, race, body mass index, and body surface area.

†Moder 2 was further adjusted for smoke status, poverty income ratio, and education level.

‡Model 3 was further adjusted for comorbidity (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension) on the basis of model 2.

§Model 4 was adjusted for pre-bronchodilator FEV_1 % of predicted in addition to the variables in model 3.

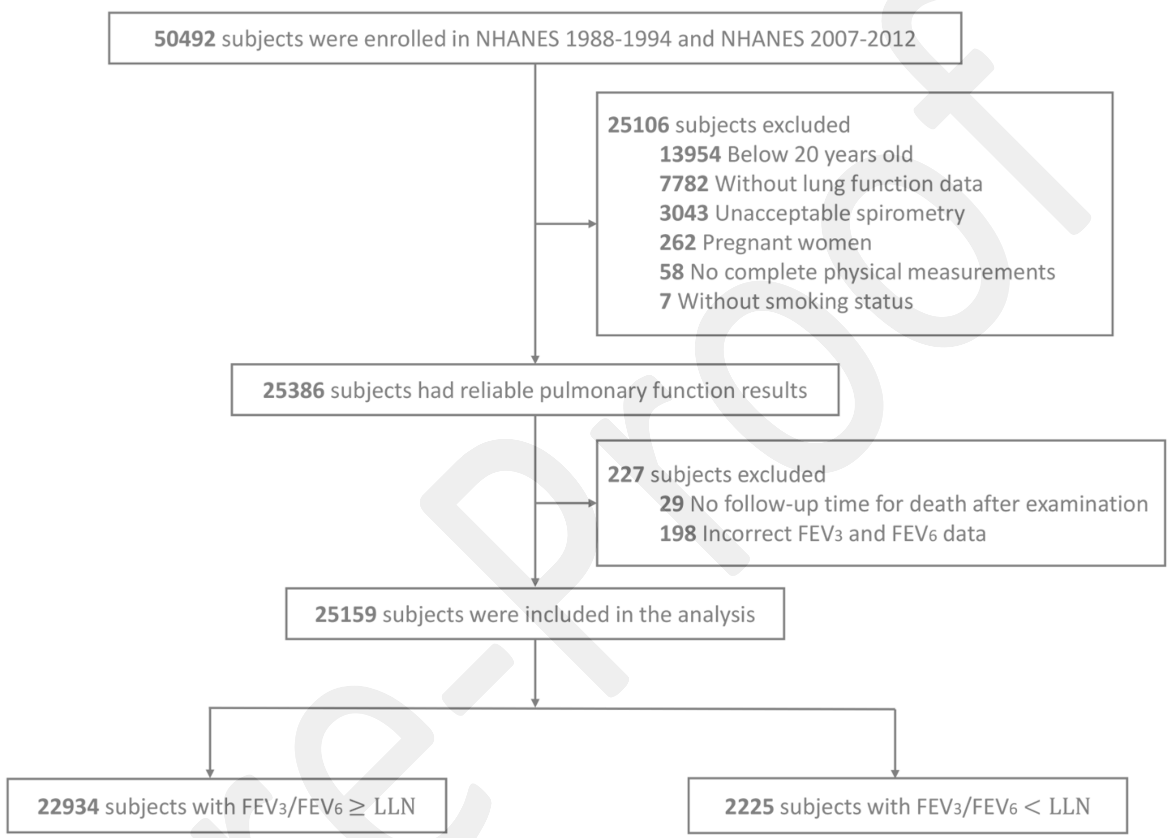
Abbreviations: FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Figure Legends

Figure 1. Flowchart of the study

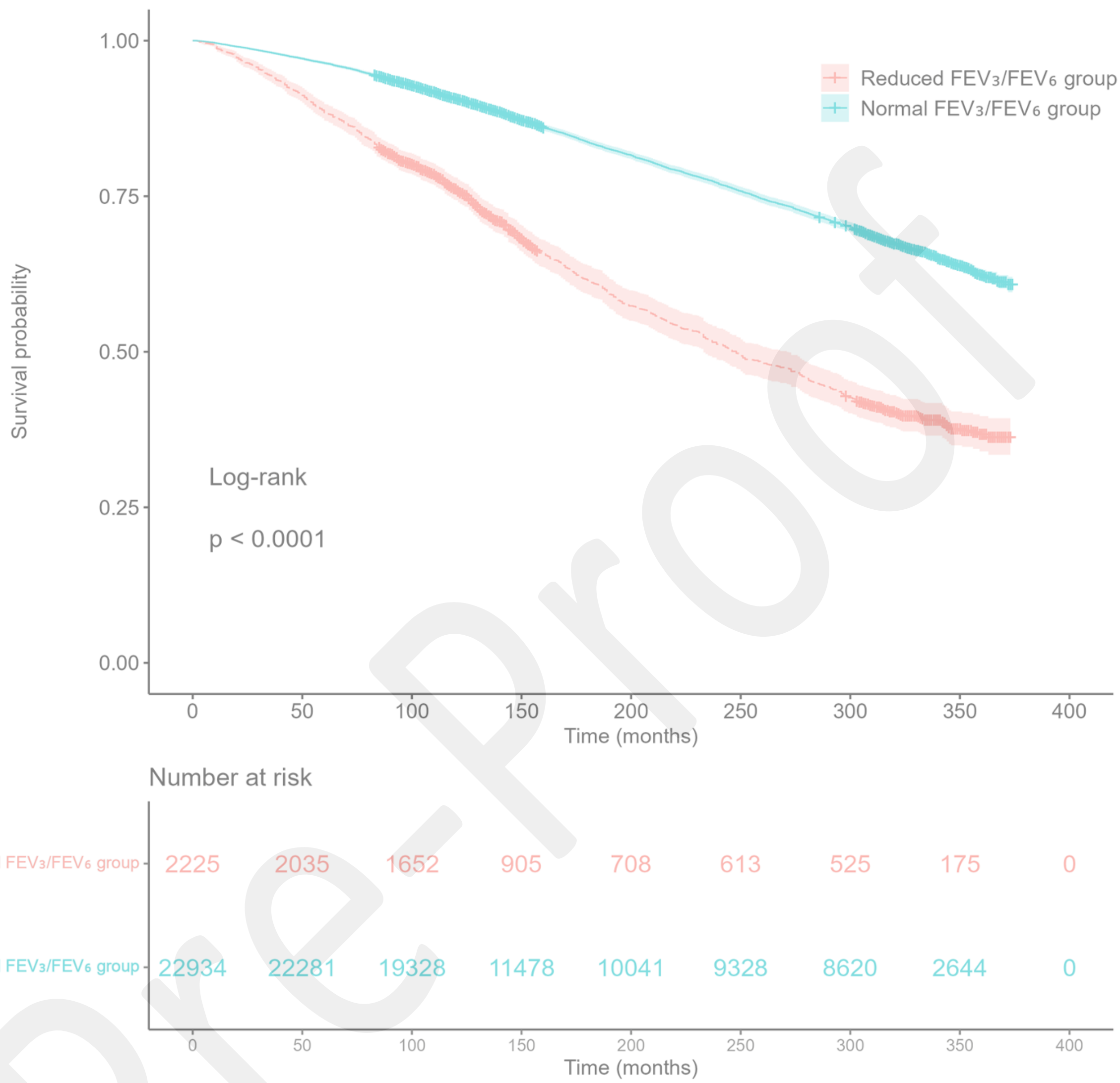
Abbreviations: NHANES = National Health and Nutrition Examination Survey; FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal.



Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Figure 2. Kaplan-Meier Survival Curves for all-cause mortality

Abbreviations: FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s.

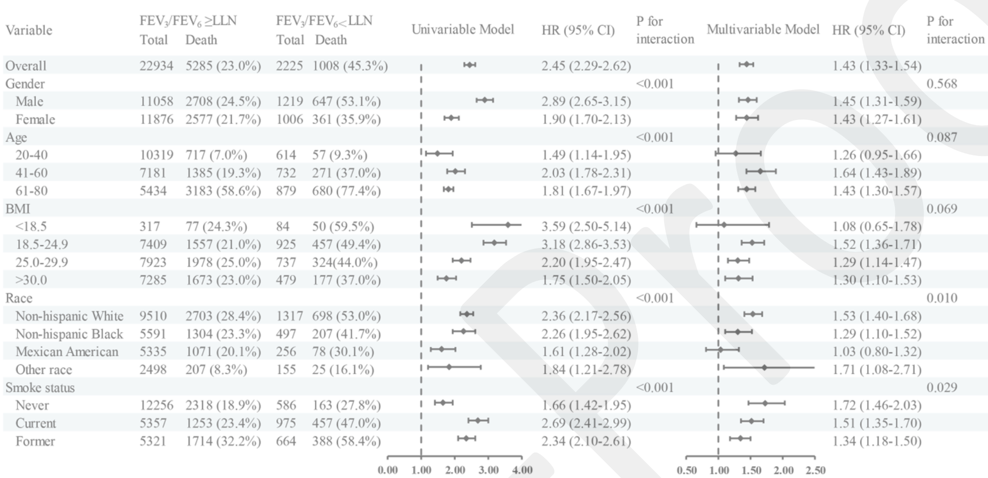


Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Figure 3. Associations between FEV_3/FEV_6<LLN and risk of mortality

Multivariable model adjusted for age, sex, smoking status, body surface area, body mass index, race, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

Abbreviations: FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal; BMI = body mass index; HR= hazard ratio; CI = confidence interval.



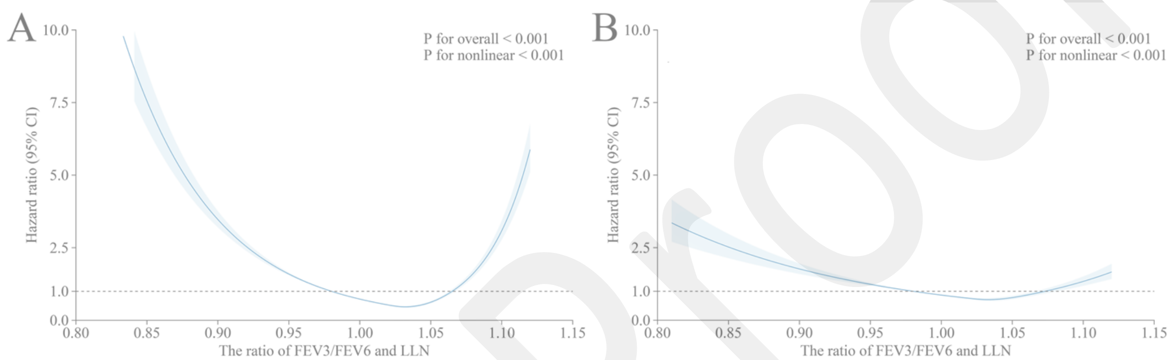
Variable	FEV_3/FEV_6 ≥LLN Total	FEV_3/FEV_6 ≥LLN Death	FEV_3/FEV_6<LLN Total	FEV_3/FEV_6<LLN Death	Univariable Model HR (95% CI)	P for interaction	Multivariable Model HR (95% CI)	P for interaction
Overall	22934	5285 (23.0%)	2225	1008 (45.3%)	2.45 (2.29-2.62)		1.43 (1.33-1.54)	
Gender						<0.001		0.568
Male	11058	2708 (24.5%)	1219	647 (53.1%)	2.89 (2.65-3.15)		1.45 (1.31-1.59)	
Female	11876	2577 (21.7%)	1006	361 (35.9%)	1.90 (1.70-2.13)		1.43 (1.27-1.61)	
Age						<0.001		0.087
20-40	10319	717 (7.0%)	614	57 (9.3%)	1.49 (1.14-1.95)		1.26 (0.95-1.66)	
41-60	7181	1385 (19.3%)	732	271 (37.0%)	2.03 (1.78-2.31)		1.64 (1.43-1.89)	
61-80	5434	3183 (58.6%)	879	680 (77.4%)	1.81 (1.67-1.97)		1.43 (1.30-1.57)	
BMI						<0.001		0.069
<18.5	317	77 (24.3%)	84	50 (59.5%)	3.59 (2.50-5.14)		1.08 (0.65-1.78)	
18.5-24.9	7409	1557 (21.0%)	925	457 (49.4%)	3.18 (2.86-3.53)		1.52 (1.36-1.71)	
25.0-29.9	7923	1978 (25.0%)	737	324(44.0%)	2.20 (1.95-2.47)		1.29 (1.14-1.47)	
>30.0	7285	1673 (23.0%)	479	177 (37.0%)	1.75 (1.50-2.05)		1.30 (1.10-1.53)	
Race						<0.001		0.010
Non-hispanic White	9510	2703 (28.4%)	1317	698 (53.0%)	2.36 (2.17-2.56)		1.53 (1.40-1.68)	
Non-hispanic Black	5591	1304 (23.3%)	497	207 (41.7%)	2.26 (1.95-2.62)		1.29 (1.10-1.52)	
Mexican American	5335	1071 (20.1%)	256	78 (30.1%)	1.61 (1.28-2.02)		1.03 (0.80-1.32)	
Other race	2498	207 (8.3%)	155	25 (16.1%)	1.84 (1.21-2.78)		1.71 (1.08-2.71)	
Smoke status						<0.001		0.029
Never	12256	2318 (18.9%)	586	163 (27.8%)	1.66 (1.42-1.95)		1.72 (1.46-2.03)	
Current	5357	1253 (23.4%)	975	457 (47.0%)	2.69 (2.41-2.99)		1.51 (1.35-1.70)	
Former	5321	1714 (32.2%)	664	388 (58.4%)	2.34 (2.10-2.61)		1.34 (1.18-1.50)	

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Figure 4. Nonlinear relationship between FEV_3/FEV_6 and all-cause mortality

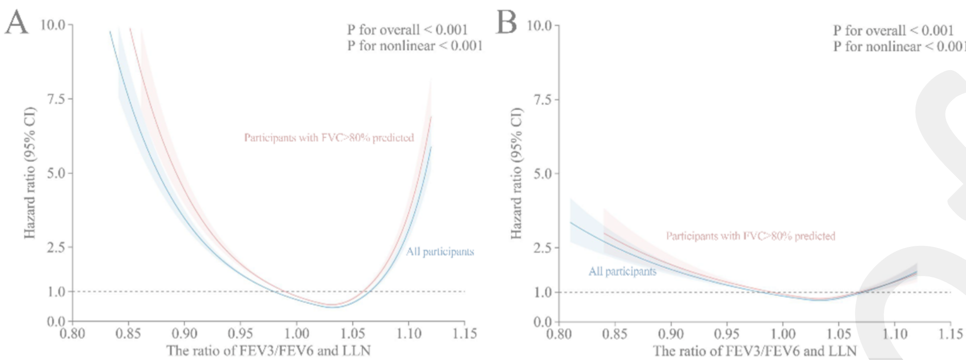
The nonlinear relationship between FEV_3/FEV_6 and all-cause mortality was investigated before (A) and after (B) adjustment for age, sex, race, body surface area, body mass index, smoking status, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

Abbreviations: FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s; LLN = lower limit of normal.



Online Supplement

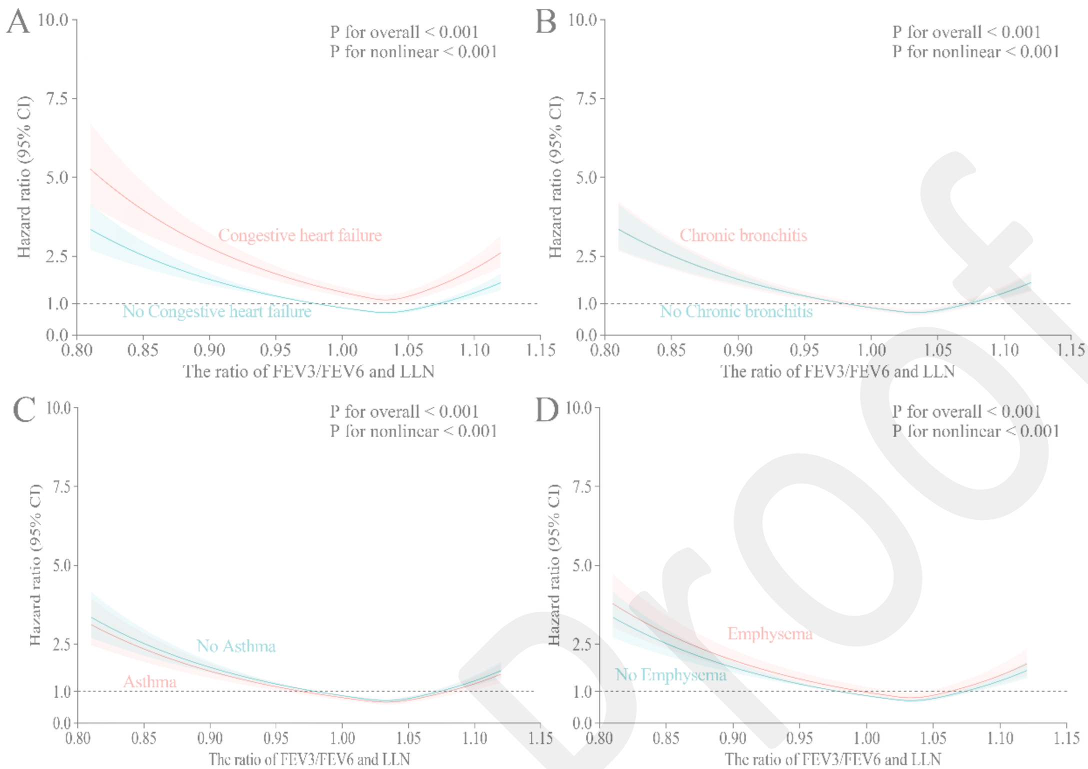
Figure S1. Sensitivity analysis between FEV_3/FEV_6 and all-cause mortality after excluding participants with FVC < 80% of predicted value



The sensitivity analysis between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality was investigated before (A) and after (B) adjustment for age, sex, race, body surface area, body mass index, smoking status, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

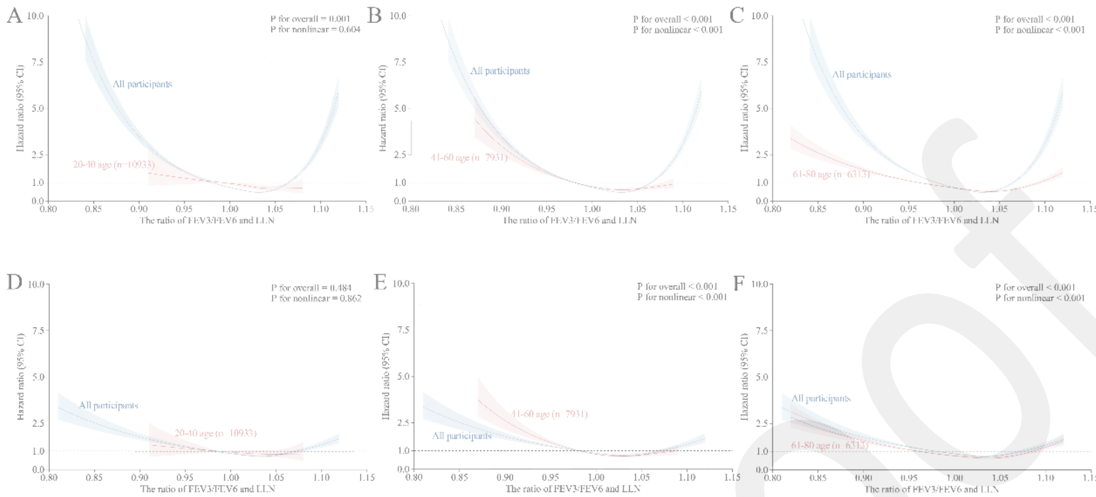
Figure S2. Sensitivity analysis between FEV_3/FEV_6 and all-cause mortality after stratifying by comorbidities.



The sensitivity analysis between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality was investigated after adjustment for age, sex, race, body surface area, body mass index, smoking status, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

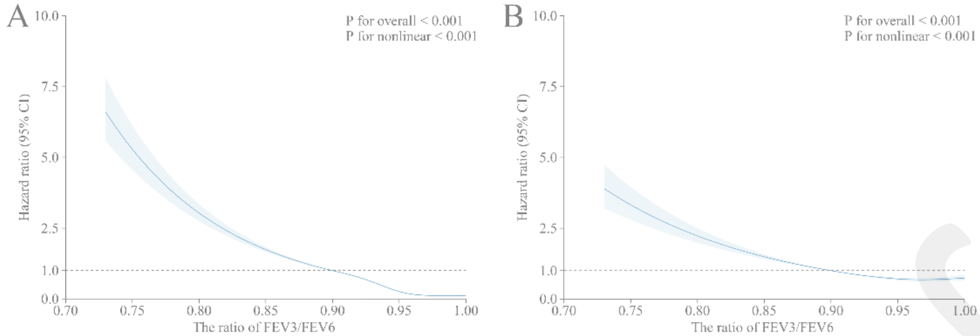
Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649

Figure S3. Sensitivity analysis between FEV_3/FEV_6 and all-cause mortality after stratifying by age.



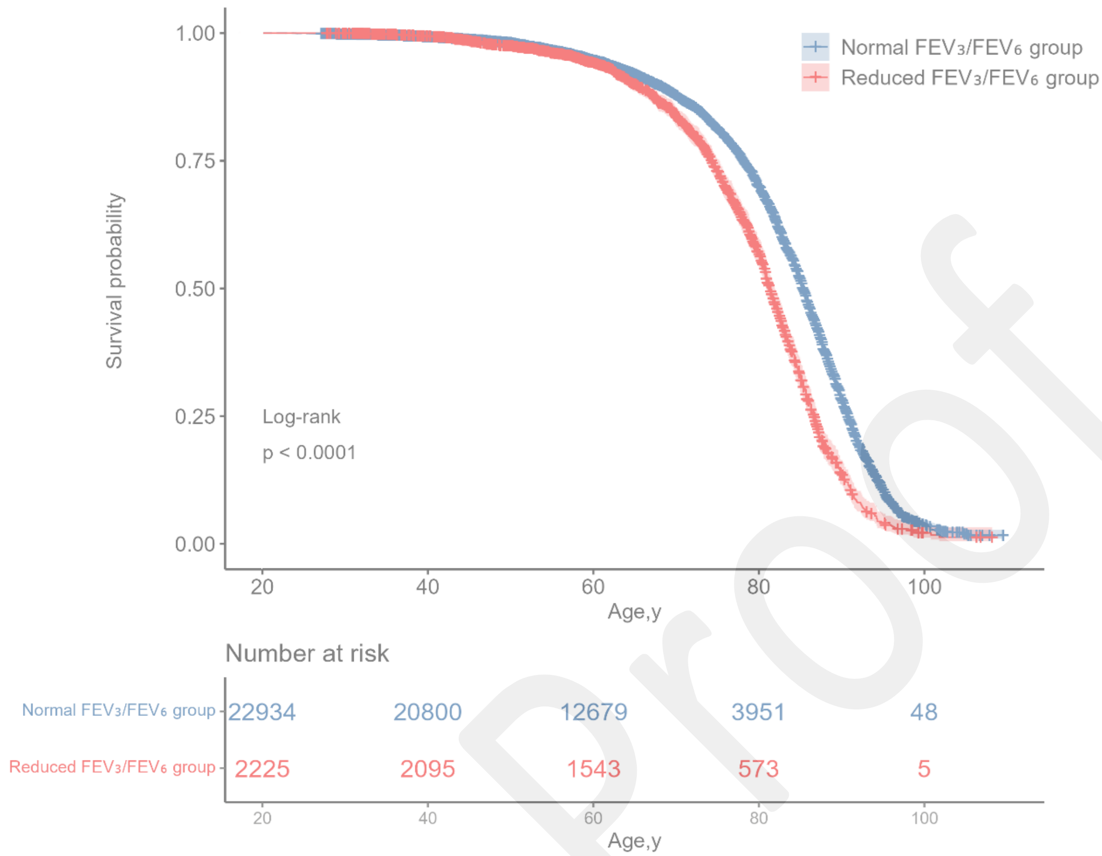
The sensitivity analysis between the ratio of FEV_3/FEV_6 to LLN and all-cause mortality was investigated in before (A, B, C) and after (D, E, F) adjustment for sex, race, body surface area, body mass index, smoking status, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

Figure S4. The relationship between FEV_3/FEV_6 as a standalone variable and all-cause mortality.



The sensitivity analysis between FEV_3/FEV_6 and all-cause mortality was investigated in before (A) and after (B) adjustment for sex, race, body surface area, body mass index, smoking status, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

Figure S6. Kaplan-Meier Survival Curves for all-cause mortality using age as the time-axis.



Abbreviations: FEV_3 = forced expiratory volume in 3 s; FEV_6 = forced expiratory volume in 6 s.

Table S1. Sensitivity analysis for association of FEV_3/FEV_6 and all-cause mortality using age as the time-axis.

Models	FEV_3/FEV_6 ≥LLN		FEV_3/FEV_6 <LLN		FEV_3/FEV_6 <LLN vs. FEV_3/FEV_6	
	Total	Death	Total	Death	hazard ratio (95%	P value
Crude model	22934	5285 (23.0%)	2225	1008 (45.3%)	1.53 (1.43-1.64)	<0.001
Model 1*	22934	5285 (23.0%)	2225	1008 (23.0%)	1.59 (1.48-1.70)	<0.001
Model 2†	20933	4732 (22.6%)	2047	918 (44.8%)	1.35 (1.25-1.45)	<0.001
Model 3‡	20760	4689 (22.6%)	2012	905 (45.0%)	1.30 (1.21-1.41)	<0.001
Model 4§	20760	4689 (22.6%)	2012	905 (45.0%)	1.08 (0.99-1.17)	0.077

*Model 1 was adjusted for age, sex, race, body mass index, and body surface area.

†Moder 2 was further adjusted for smoke status, poverty income ratio, and education level.

‡Model 3 was further adjusted for comorbidity (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension) on the basis of model 2.

§Model 4 was adjusted for pre-bronchodilator FEV_1 % of predicted in addition to the variables in model 3.

Published online March 31, 2026 https://doi.org/10.15326/jcopdf.2025.0649