

Original Research

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

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Abstract

Background: The forced expiratory volume in 3 seconds (FEV₃) to forced expiratory volume in 6 seconds (FEV₆) ratio is a novel spirometry measure that identifies early airflow abnormalities, but its long-term prognosis value in the general population remains unclear. We aimed to evaluate the long-term all-cause mortality risk among participants with a reduced FEV₃/FEV₆.

Methods: Data were obtained from the National Health and Nutrition Examination Survey cycles 1988–1994 and 2007–2012. Reduced FEV₃/FEV₆ was defined as an FEV₃/FEV₆ less than the lower limit of normal. Multivariable logistic regression was used to assess the relationship of reduced FEV₃/FEV₆ with comorbidities and chronic respiratory symptoms. The relationship between reduced FEV₃/FEV₆ and all-cause mortality was evaluated using Cox regression models. The nonlinear relationship between FEV₃/FEV₆ and all-cause mortality was assessed using restricted cubic splines. Subgroup 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% (2225/25,159) had reduced FEV₃/FEV₆. Participants with reduced FEV₃/FEV₆ exhibited increased risks of congestive heart failure, asthma, chronic bronchitis, emphysema, respiratory symptoms, and all-cause mortality risk (adjusted hazard ratio=1.23, 95% confidence interval: 1.13–1.34, *P*<0.001). The findings remained consistent across subgroups. A nonlinear U-shaped association was observed between FEV₃/FEV₆ and all-cause mortality, with the turning point at 1.04.

Conclusions: Participants with reduced FEV₃/FEV₆ had worse respiratory health outcomes, suggesting that FEV₃/FEV₆ can be used as a prognostic spirometry indicator.

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Abbreviations:

BMI=body mass index; **BSA**=body surface area; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **FEV₁**=forced expiratory volume in 1 second; **FEV₁ %pred**=FEV₁ percentage predicted; **FEV₃**=forced expiratory volume in 3 seconds; **FEV₆**=forced expiratory volume in 6 seconds; **FVC**=forced vital capacity; **HR**=hazard ratio; **LLN**=lower limit of normal; **NCHS**=National Centers for Health Statistics; **NHANES**=National

Health and Nutrition Examination Survey; **OR**=odds ratio; **PIR**=poverty-to-income ratio; **RCS**=restricted cubic spline; **SAD**=small airway dysfunction; **SPIROMICS**=SubPopulation and Intermediate Outcome Measures In COPD Study

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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 (FEV₁) 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 in 3 seconds (FEV₃) to forced expiratory volume in 6 seconds (FEV₆) ratio (FEV₃/FEV₆) 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% using an FEV₃/FEV₆ ratio less than the lower limit of normal (LLN) as the diagnostic indicator.⁶ FEV₃/FEV₆<LLN in individuals with a normal FEV₁ to 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 FEV₃/FEV₆ reflects mild pulmonary structural, functional, and clinical abnormalities.⁷ The SubPopulation and InteRmediate Outcome Measures In COPD Study (SPIROMICS) study of current and former smokers without chronic obstructive pulmonary disease (COPD) found that an FEV₃/FEV₆<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 FEV₃/FEV₆<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 FEV₃/FEV₆ in the general population remains limited, particularly its potential nonlinear relationship with all-cause mortality and long-term prognosis require further investigations.

In this study, we aimed to explore the clinical characteristics and long-term prognosis of participants with an FEV₃/FEV₆<LLN based on the general population analyzed in the National Health and Nutrition Examination Survey (NHANES). We also aimed to explore whether participants with reduced FEV₃/FEV₆ had an elevated risk of all-cause death, both overall and after subgroup stratification. This study also sought to explore the potential nonlinear relationship between FEV₃/FEV₆ and all-cause mortality.

Methods**Study Population**

We conducted 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 United States. 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 2 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 FEV₃/FEV₆ 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 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 FEV₁ 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, an FEV₃/FEV₆<LLN was defined as

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reduced FEV₃/FEV₆. The LLN for prebronchodilator FEV₃/FEV₆ 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 FEV₃/FEV₆ for the other races included in the dataset.⁵

Mortality Ascertainment

The study outcome 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 4 categories: underweight (<18.5kg/m²), normal (≥18.5kg/m² to <25kg/m²), overweight (≥25.0kg/m² to <30.0kg/m²), and obese (≥30.0kg/m²). The following formula¹² was used to calculate body surface area (BSA): $BSA (m^2) = (\text{body weight [kg]}^{0.425} \times \text{height [cm]}^{0.725} \times 0.007184)$. 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 ratio (PIR) 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 3 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 FEV₃/FEV₆. Five Cox regression models were constructed to evaluate the association between all-cause mortality and reduced FEV₃/FEV₆. 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 FEV₁ percentage predicted (FEV₁ %pred).

Based on the crude Cox regression model and Model 3, we performed subgroup analyses to assess the association between reduced FEV₃/FEV₆ and all-cause mortality in different subgroups stratified by sex, age, BMI, race, and smoking status. We included FEV₃/FEV₆ and subgroup variables as interaction terms in the model analyses to test for potential interaction effects. To investigate whether there was a nonlinear relationship between the ratio of FEV₃/FEV₆ to LLN and all-cause mortality, we used restricted cubic spline (RCS) analysis with 5 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 an FVC<80% of the predicted value were excluded; (2) age was used as a categorical variable (20–40, 41–60, 61–80); (3) comorbidity including congestive heart failure, asthma, chronic bronchitis, and emphysema were used as a categorical variable; (4) the relationship between FEV₃/FEV₆ as a stand-alone variable and all-cause mortality was examined; and (5) age was used as the time axis in survival analyses.¹⁵ Statistical significance was set at *P*<0.05 (2-tailed). All analyses used R, version 4.3.2, and SPSS, version 27.0.

Results

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=7782), with unacceptable spirometry (n=3043), 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 (n=29) or incorrect FEV₃ or FEV₆ data (n=198). Finally, 25,159 participants were enrolled, among whom 8.8% (2225/25,159) exhibited reduced FEV₃/FEV₆ (Figure 1).

The baseline characteristics of the normal FEV₃/FEV₆ and reduced FEV₃/FEV₆ groups are presented in Table 1. The mean age of the participants in the reduced FEV₃/FEV₆ group was 53.2±17.4 years, and 54.8% were male. Compared with the normal FEV₃/FEV₆ group, the majority of participants with reduced FEV₃/FEV₆ were non-Hispanic White (59.2%), current smokers (43.8%), and had a lower level of education and a lower PIR. The reduced FEV₃/FEV₆ group also had significantly lower prebronchodilator FEV₁, FVC, FEV₁ %pred, and FVC percentage predicted values.

Risk of Chronic Respiratory Symptoms and Comorbidities

Table 2 shows the association between reduced FEV₃/FEV₆ and chronic respiratory symptoms and comorbidities. The reduced FEV₃/FEV₆ 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 reduced FEV₃/FEV₆ 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), 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 FEV₃/FEV₆ group.

Association of Reduced Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 Seconds With All-Cause Mortality

During the median follow-up period of 308 months, 6393 participants (25.4%) died, of which 45.3% (1008/2225) had reduced FEV₃/FEV₆ and 23.0% (5285/22,934) had normal FEV₃/FEV₆. The all-cause mortality risk curves in the normal and reduced FEV₃/FEV₆ groups are shown in

Figure 2. The analyses demonstrated that participants in the reduced FEV₃/FEV₆ group exhibited significantly higher all-cause mortality than those in the normal FEV₃/FEV₆ group (log-rank *P*<0.001).

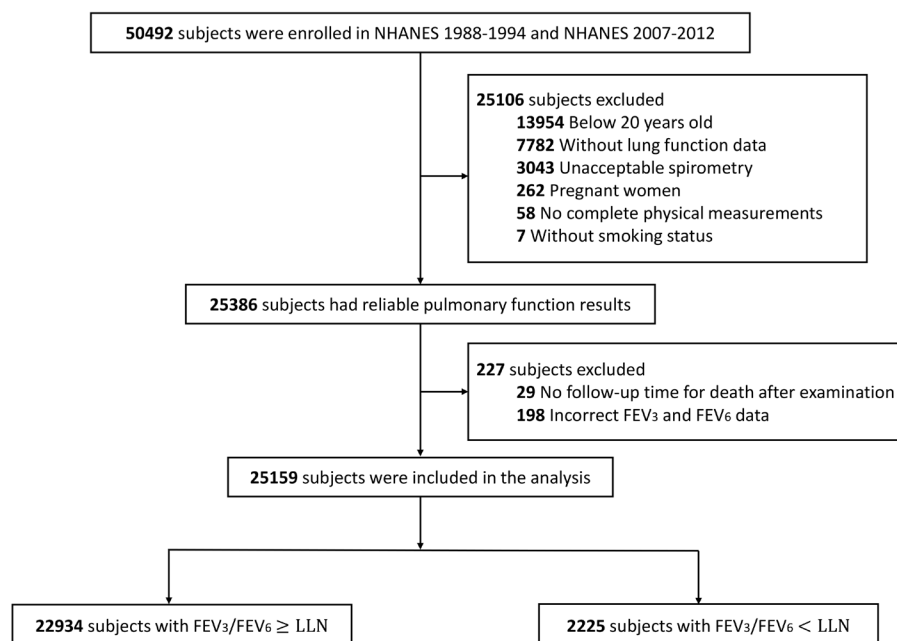
Table 3 shows the 5 Cox regression models. Compared with the normal FEV₃/FEV₆ group, the reduced FEV₃/FEV₆ group exhibited a significantly increased risk of all-cause mortality in the crude model (hazard ratio [HR] 2.45, 95% CI 2.29–2.62, *P*<0.001). The reduced FEV₃/FEV₆ group still exhibited an increased 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 FEV₃/FEV₆ 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 FEV₁ %pred 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 3, subgroup analyses were performed to evaluate the association between FEV₃/FEV₆ and all-cause mortality according to sex, age, BMI, race, and smoking status. In the univariable model, reduced FEV₃/FEV₆ was associated with higher all-cause mortality in all subgroups, revealing significant interactions between FEV₃/FEV₆ 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 FEV₃/FEV₆ and race and smoking status only.

Nonlinear Relationship Between the Ratio of Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 seconds to Lower Limit of Normal and Mortality

Figure 4 illustrates the RCS analysis curves prior to and following adjustment for the aforementioned covariates, revealing a consistent U-shaped association between the ratio of FEV₃/FEV₆ to LLN and all-cause mortality with an inflection point at 1.04 (all *P*_{nonlinearity} <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 FEV₃/FEV₆ ratio was negatively associated with all-cause mortality, while an abnormally elevated ratio on the right was positively associated.

Figure 1. Flowchart of the Study

NHANES=National Health and Nutrition Examination Survey; FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds; LLN=lower limit of normal

Sensitivity Analyses

Figure S1 and Figure S2 in the online supplement reveal that the U-shaped nonlinear relationship between the ratio of FEV₃/FEV₆ to LLN and all-cause mortality remained stable in sensitivity analyses, which excluded participants with FVC<80% predicted value or treated comorbidity as a categorical variable. Stratified analysis in Figure S3 in the online supplement 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 FEV₃/FEV₆ ratio and all-cause mortality shown in Figure S4 in the online supplement. When age was used as the survival analysis time scale, the all-cause mortality risk curves in Figure S5 in the online supplement revealed a striking divergence after age 60, with a steep increase in risk specifically for the reduced FEV₃/FEV₆ group. The pattern aligns with the Cox regression models in Table S1 in the online supplement, which remained consistent with the primary analysis.

Discussion

This study revealed that participants with reduced FEV₃/FEV₆ had an increased risk of comorbidities, chronic respiratory symptoms, and all-cause mortality compared with participants with normal FEV₃/FEV₆. The above results were consistent across the subgroup analyses. Furthermore, a nonlinear U-shaped relationship between FEV₃/FEV₆ 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 FEV₃/FEV₆ and all-cause mortality. Concurrently, it is the first study to explore the nonlinear relationship between FEV₃/FEV₆ and all-cause mortality risk. These findings suggest that FEV₃/FEV₆ can serve not only as a marker to evaluate the risk of developing chronic multimorbidity, but also as an independent prognostic marker of lung function in clinical practice.

Reduced FEV₃/FEV₆ serves as an early indicator of SAD.⁵ The small airways are defined¹⁶ as those with a luminal diameter of <2mm. 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 (COPD Genetic Epidemiology study cohort) demonstrated associations between FEV₃/FEV₆ <LLN and respiratory deterioration and dyspnea.^{5,7} Additionally, Knox-Brown 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 FEV₃/FEV₆ 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 FEV₃/FEV₆ ratio to define small airway obstruction, showing that participants

Table 1. Baseline Characteristics in Participants Stratified According to Prebronchodilator Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 Seconds Ratio

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)	
9th–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)	
Prebronchodilator 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 (%).

FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds; LLN=lower limit of normal; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity**Table 2. The Risk of Chronic Respiratory Symptoms and Comorbidity in Participants With a Reduced Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 Seconds Ratio**

Variable	FEV ₃ /FEV ₆ <LLN	FEV ₃ /FEV ₆ ≥LLN	Unadjusted		Adjusted ^a	
			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

^aModels were adjusted for sex, age, race, body mass index, and smoking status.

n / N

FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds; LLN=lower limit of normal; OR=odds ratio; CI=confidence interval

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Table 3. Risk of Death in Participants With a Reduced Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 Seconds Ratio

Models	FEV ₃ /FEV ₆ ≥LLN		FEV ₃ /FEV ₆ <LLN		FEV ₃ /FEV ₆ <LLN vs. FEV ₃ /FEV ₆ ≥LLN	
	Total	Death	Total	Death	Hazard Ratio (95% confidence interval)	P Value
Crude Model	22934	5285 (23.0%)	2225	1008 (45.3%)	2.45 (2.29–2.62)	<0.001
Model 1^a	22934	5285 (23.0%)	2225	1008 (23.0%)	1.68 (1.57–1.80)	<0.001
Model 2^b	20933	4732 (22.6%)	2047	918 (44.8%)	1.45 (1.35–1.57)	<0.001
Model 3^c	20760	4689 (22.6%)	2012	905 (45.0%)	1.43 (1.33–1.55)	<0.001
Model 4^d	20760	4689 (22.6%)	2012	905 (45.0%)	1.23 (1.13–1.34)	<0.001

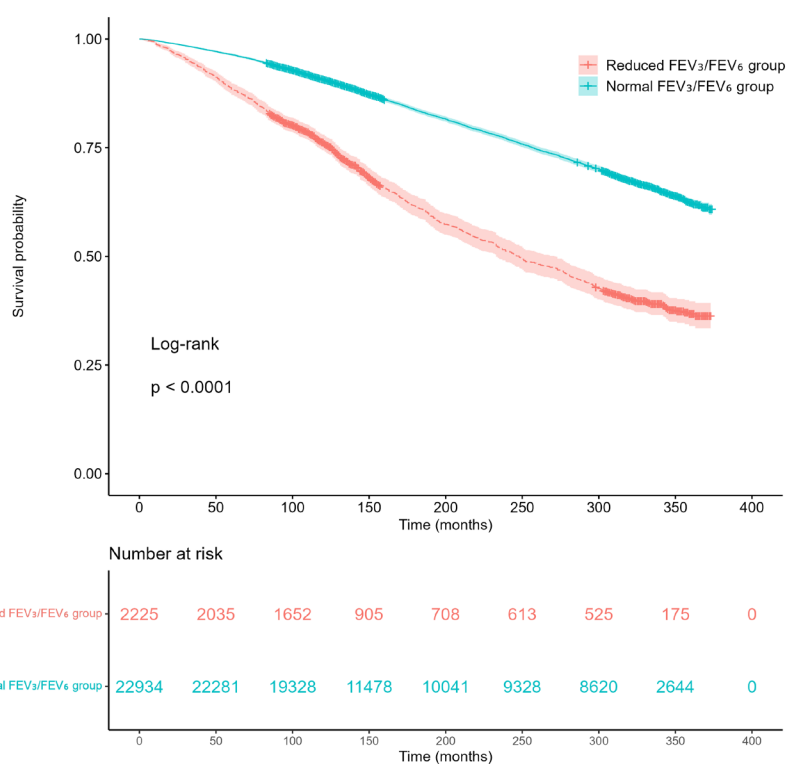
^aModel 1 was adjusted for age, sex, race, body mass index, and body surface area.

^bModel 2 was further adjusted for smoke status, poverty income ratio, and education level.

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

^dModel 4 was adjusted for prebronchodilator FEV₁ %pred in addition to the variables in model 3.

FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds; LLN=lower limit of normal; FEV₁ %pred=forced expiratory volume in 1 second percentage predicted

Figure 2. Kaplan-Meier Survival Curves for All-Cause Mortality

FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds

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 FEV₃/FEV₆ had an increased risk of chronic bronchitis, asthma, emphysema, and congestive heart failure. The Assessment of Small Airways Involvement in Asthma 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 participants with isolated small airway obstruction are more likely to be diagnosed with cardiovascular disease, even without coexisting airflow obstruction, possibly mediated through small airway obstruction upregulated inflammatory processes.¹⁶ However, no significant association was observed between participants with reduced FEV₃/FEV₆ and cancer, which may be related to the insufficiency of the cancer data included.

This study revealed a nonlinear U-shaped relationship

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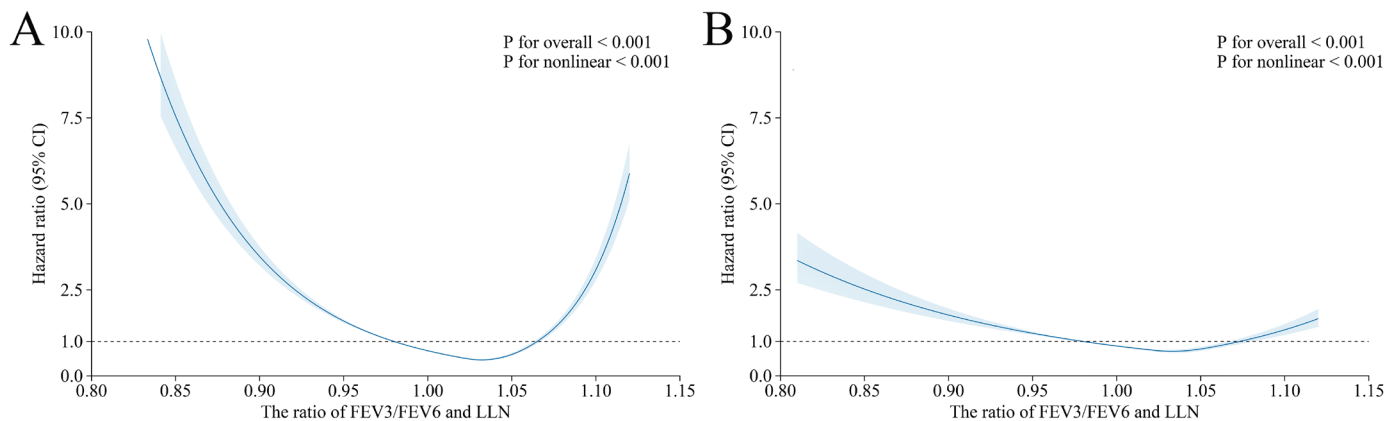
Figure 3. Associations Between a Forced Expiratory Volume in 3 Seconds to Forced Expiratory Volume in 6 Seconds Ratio < Lower Limit of Normal and Risk of Mortality

Variable	FEV ₃ /FEV ₆ ≥ LLN		FEV ₃ /FEV ₆ < LLN		Univariable Model	HR (95% CI)	P for interaction	Multivariable Model	HR (95% CI)	P for interaction
	Total	Death	Total	Death						
Overall	22934	5285 (23.0%)	2225	1008 (45.3%)		2.45 (2.29-2.62)			1.43 (1.33-1.55)	
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)	

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).

FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds; LLN=lower limit of normal; CI=confidence interval; HR=hazard ratio; BMI=body mass index

Figure 4. Nonlinear Relationship Between a Forced Expiratory Volume in 3 seconds to Forced Expiratory Volume in 6 Seconds Ratio and All-Cause Mortality



The nonlinear relationship between FEV₃/FEV₆ 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).

FEV₃=forced expiratory volume in 3 seconds; FEV₆=forced expiratory volume in 6 seconds; LLN=lower limit of normal; CI=confidence interval

between the ratio of FEV₃/FEV₆ to LLN and all-cause mortality risk. Reduced FEV₃/FEV₆ may increase all-cause mortality through a combination of mechanisms, including small airway remodeling, mucus plugging, immune cell infiltration, and systemic inflammation.^{2,25} In patients with comorbid chronic airway disease, reduced FEV₃/FEV₆ 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 FEV₃/FEV₆ and increased

all-cause mortality. Notably, an excessive FEV₃/FEV₆ 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 FEV₁/

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 FEV₃/FEV₆ 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.

The association between reduced FEV₃/FEV₆ 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 FEV₃/FEV₆ and increased mortality showed a consistent effect direction across all subgroups, underscoring the robustness of the finding. Previous cohort studies have been conducted only in the population of smokers, ignoring the role of reduced FEV₃/FEV₆ in never-smokers.^{5,7,30} Our study found that reduced FEV₃/FEV₆ 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 FEV₃/FEV₆ 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 FEV₃/FEV₆ and all-cause mortality. Second, our study used 5 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 FEV₃/FEV₆ 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 FEV₃/FEV₆ 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, 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 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 FEV₃/FEV₆ and all-cause mortality. Finally, the data comprised 2 components of spirometry that used different quality control criteria and operational standards, which has the potential to influence the accuracy of FEV₃/FEV₆ measurements.

Conclusion

In summary, this analysis of data from the NHANES showed that participants with reduced FEV₃/FEV₆ had a higher risk of chronic respiratory symptoms, comorbidities, and all-cause mortality. Moreover, we observed a nonlinear U-shaped relationship between FEV₃/FEV₆ and all-cause mortality risk. These results suggest that FEV₃/FEV₆ could be a sensitive prognostic spirometry indicator in the general population.

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Author contributions: SL and FW 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. SL, JL, and FW were responsible for the concept and design. SL, JL, JO, RP, SZ, LT, QZ, YC, XG, JC, QW, ZW, ZD, YZ, and FW were responsible for the acquisition, analysis, or interpretation of data. SL, JL, and FW were in charge of the statistical analysis. SL, JL, and FW drafted the manuscript. SL and FW were the study guarantors. All authors contributed to the critical revision of the manuscript and approved of the final version.

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Declaration of Interest

The authors declare that they have no conflicts of interest.

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