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Association between FEV_1/FVC levels and all-cause mortality in the general population

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Abstract

Background The ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC) is an essential tool for the diagnosis of chronic obstructive pulmonary disease (COPD). However, the relationship between levels of FEV_1/FVC and mortality in the general population remains unclear, particularly its non-linear relationship. Therefore, we aimed to explore the association between the FEV_1/FVC and all-cause mortality in the general population.

Methods The data of participants included in the National Health and Nutrition Examination Survey (1988–1994 and 2007–2012 cycles) were analyzed. Participants aged ≥20 years, who were not pregnant, who underwent quality-controlled lung function tests, and with follow-up data on mortality status were enrolled. The study outcome was all-cause mortality. The participants were grouped by FEV_1/FVC ratio in 0.10 increments. Cox proportional-hazards models were used to estimate the association between the FEV_1/FVC ratio and all-cause mortality before and after confounder adjustment. Non-linear associations were explored using restricted cubic spline curves.

Results Overall, 25,501 participants were included. During the median follow up of 308 months, 6431 (25.2%) deaths were recorded. Among all participants, the mean age is 46.3 years, and 48.7% of which were male. In unadjusted model, individuals with an FEV_1/FVC ratio < 0.90 had an increased risk of all-cause mortality compared to those with an FEV_1/FVC ratio ≥ 0.90. After adjusting for age, sex, body mass index, race, and smoking status, participants in the $0.60 \le FEV_1/FVC < 0.90$ group had a lower all-cause mortality risk than those in the $FEV_1/FVC \ge 0.90$ group, while the mortality risk of individuals with an FEV_1/FVC ratio < 0.50 was higher. Restricted cubic splines revealed a U-shaped association between the FEV_1/FVC ratio and all-cause mortality. Below and above the inflection point, an inverse trend was observed.

Conclusion Our study first revealed a U-shaped association between the level of FEV_1/FVC and all-cause mortality in general population.

Clinical trial number Not applicable.

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Keywords Forced expiratory volume in 1 s, Forced vital capacity, General population, All-cause mortality, Non-linear relationship

Background

The ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) is a crucial measure to assess airway obstruction and lung disease [1]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends a post-bronchodilator FEV_1/FVC ratio < 0.70 to confirm persistent airflow limitation and COPD [2]. Most studies use this FEV_1/FVC ratio cut-off to determine COPD, and it has been concluded that COPD is significantly associated with increased mortality [3].

The association between the FEV_1/FVC ratio and all-cause mortality has been recognized previously, but only among male subjects [4]. More recent studies have focused on the accuracy of FEV_1/FVC ratio < 0.70 for COPD assessment, as well as exploring other useful clinical values for the FEV_1/FVC ratio. Bhatt et al.'s study supported the use of an FEV_1/FVC ratio threshold < 0.70 as an effective marker for predicting COPD-related hospitalization and mortality [5]. Researchers have also emphasized the importance of grading COPD severity based on significant clinical values. A new severity classification scheme, namely the STAR classification, which incorporates the FEV_1/FVC ratio, has been shown to provide better differentiation of patient symptoms, disease burden, and prognosis than the existing classification based on percentage predicted FEV_1 [6]. The FEV_1/FVC ratio has also demonstrated similar predictive power to percentage predicted FEV_1 for predicting acute exacerbation of COPD (AECOPD) [7].

However, most studies are based on specific populations, especially COPD patients, with limited exploration of the general population. The evidence linking the FEV_1/FVC ratio with all-cause mortality risk remains insufficient, and there has been little investigation into their potential non-linear relationship. Thus, the present study aims to investigate the association between the FEV_1/FVC ratio and all-cause mortality within a large representative sample of the US population. We also use restricted cubic spline models to evaluate whether a non-linear relationship exists between the FEV_1/FVC ratio and all-cause mortality.

Study design and methods

Study population

All data were obtained from the National Health and Nutrition Examination Survey (NHANES), a series of nationally representative cohort surveys designed to monitor the public health and nutritional status of the US population. The Centers for Disease Control and Prevention oversees the NHANES to provide key health data for the United States. The protocols used in the NHANES were approved by the Research Ethics Review Board of the National Center for Health Statistics. Written informed consent was obtained from all participants involved in the survey. The datasets generated and analyzed in this study are available from the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm) [8].

The study population included participants from two NHANES cycles (1988–1994 and 2007–2012), comprising a total of 50,492 participants. Lung function data were only available for these two cycles; therefore, participants from these specific timeframes were ultimately included in the analysis. The key inclusion criteria were (1) age ≥ 20 years and (2) completion of qualifying pre-bronchodilator spirometry assessments. The main exclusion criteria were (1) unavailable spirometry data; (2) pregnancy; (3) incomplete physical measurements; (4) missing information on smoking status; and (5) missing data on the follow-up time to death after the examination.

Pulmonary function testing

We reviewed all spirometry data from the NHANES study and found that most participants had available pre-bronchodilator data, whereas post-bronchodilator data were only available for a small subset of participants. Thus, we decided to use the pre-bronchodilator spirometry data in our analysis. Pre-bronchodilator spirometry was conducted using Ohio 822/827 dry-rolling volume seal spirometers. For the participants from the 1988–1994 survey cycle, both reproducible FEV_1 and FVC measurements with ≥ 2 acceptable trials were included, while efforts that were at least grade B in quality according to the American Thoracic Society standards for acceptability and reproducibility were included from the 2007–2012 NHANES cycle [9, 10]. The participants were divided into the following eight groups by 0.10 increments in the FEV_1/FVC ratio: $FEV_1/FVC < 0.30$, $0.30 \le FEV_1/FVC < 0.40$, $0.40 \le FEV_1/FVC < 0.50$, $0.50 \le FEV_1/FVC < 0.60$, $0.60 \le FEV_1/FVC < 0.70$, $0.70 \le FEV_1/FVC < 0.80$, $0.80 \le FEV_1/FVC < 0.90$, and $0.90 \le FEV_1/FVC \le 1.00$ (reference group).

Mortality ascertainment

The study outcome was all-cause mortality. To obtain the mortality status in the follow-up population, we consulted the NHANES public-use mortality file as of December 31, 2019, which matched records with the National Center for Health Statistics with the National

Death Index through a probability-matching algorithm [11].

Assessment of covariates

Demographic and health-related information was collected from NHANES household interviews, including age, sex, body mass index (BMI), race, smoking status, comorbidities, and chronic respiratory symptoms. BMI was calculated as weight in kilograms divided by height in meters squared and divided into four categories: underweight (< 18.5 kg/m^2), normal (≥ 18.5 to < 25.0 kg/m^2), overweight (≥ 25.0 to < 30.0 kg/m^2), and obese (≥ 30.0 kg/m^2). Race was categorized as White Non-Hispanic, Black Non-Hispanic, Mexican-American, or other. Smoking status was recorded as never smoker, former smoker, or current smoker. Participants who claimed to have smoked fewer than 100 cigarettes in their lives were categorized as "never smokers." Former smokers were individuals who had smoked more than 100 cigarettes in their lifetime but who had quit, while current smokers were those currently smoking. Comorbidities included congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes mellitus, and hypertension. Chronic respiratory symptoms included chronic cough, chronic phlegm, wheezing, and dyspnea. During the home interview, participants were asked if they "usually cough on most days for 3 consecutive months or more during the year," "bring up phlegm on most days for 3 consecutive months or more during the year," or "had wheezing or whistling in their chest in the past 12 months."

Statistical analysis

Continuous variables are reported as the mean ± standard deviation, while categorical variables are expressed as count (percentage). The log-rank test and Kaplan–Meier survival analyses were conducted to evaluate differences in event-free survival among the eight groups. The logistic regression model was conducted to estimate the association of FEV_1/FVC ratio and the presence of comorbidities. To evaluate the independent predictive value of the FEV_1/FVC ratio, three Cox proportional-hazards regression models were developed: Model 1 (unadjusted); Model 2 was adjusted for age, sex, BMI, smoking status, and race; Model 3 was adjusted for age, sex, BMI, smoking status, race, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension). The restricted cubic spline (RCS) curve ("ggrcs" package) with five knots was used to illustrate the non-linear association between the FEV_1/FVC ratio and all-cause mortality risk. Subgroup analyses were also performed, with the participants stratified by sex, smoking status, BMI, race, age (20–50 vs. >50 years), comorbidities, and chronic respiratory symptoms. Cox proportional-hazards regression and RCS models were repeated in the subgroup analyses. All statistical analyses were performed using IBM SPSS 25.0 and R version 4.3.1. Two-sided *P* values of < 0.05 were considered statistically significant.

Results

Baseline characteristics

Among the 50,492 participants included in the 1988–1994 and 2007–2012 cycles of the NHANES, we excluded 13,954 individuals aged < 20 years, 7,545 without spirometry data, 3,135 with unacceptable spirometry results, 262 pregnant women, 59 without complete physical measurements, and 7 without data on smoking status. Of the remaining 25,530 participants with reliable spirometry results, 29 were excluded due to missing follow-up time to death. Therefore, a total of 25,501 participants were eligible for inclusion in the present study (Fig. 1).

The baseline characteristics of the study participants are presented in Table 1. The mean age was 46.3 ± 17.3 years, and 48.7% were male. The mean BMI was 28.0 ± 6.3 kg/m^2. In terms of race/ethnicity, 43.1% of the participants were non-Hispanic White, 24.1% were non-Hispanic Black, 22.1% were Mexican–American, and 10.7% were identified as being of another race or ethnicity. In terms of smoking status, 51.2% had never smoked at baseline, 25.0% were current smokers, and 23.7% were former smokers. The average FEV_1/FVC ratio was 0.78 ± 0.09. The participants were stratified into eight groups by the FEV_1/FVC ratio in 0.10 increments, from 0.30 to 1.00. The histogram in Fig. 2 indicated that the FEV_1/FVC ratio was mostly concentrated in the range of $0.70 \le FEV_1/FVC < 0.80$ ($n = 9{,}781$) and $0.80 \le FEV_1/FVC < 0.90$ ($n = 10{,}787$).

Categorical FEV1/FVC ratio and all-cause mortality

Figure 3 presents the all-cause mortality risk curves for the eight groups. During the median follow-up period of 308 months, 6,431 deaths (25.2%) were recorded. In terms of the number of deaths in each FEV_1/FVC ratio group, all participants with an FEV_1/FVC ratio < 0.30 died, as well as 55 participants (82.1%) with a ratio of $0.30 \le FEV_1/FVC < 0.40$, 154 (74.0%) with a ratio of $0.40 \le FEV_1/FVC < 0.50$, 415 (65.3%) with a ratio of $0.50 \le FEV_1/FVC < 0.60$, 1,298 (48.0%) with a ratio of $0.60 \le FEV_1/FVC < 0.70$, 2,718 (27.8%) with a ratio of $0.70 \le FEV_1/FVC < 0.80$, and 1,602 (14.9%) with a ratio of $0.80 \le FEV_1/FVC < 0.90$. The proportion of deaths decreased across the eight groups, with the smallest proportion observed in the $0.90 \le FEV_1/FVC \le 1.00$ group (13.5%).

The associations between the FEV_1/FVC ratio categories and all-cause mortality are summarized in Table 2. Each group of participants was compared with the reference group ($0.90 \le FEV_1/FVC \le 1.00$). 25,501 participants

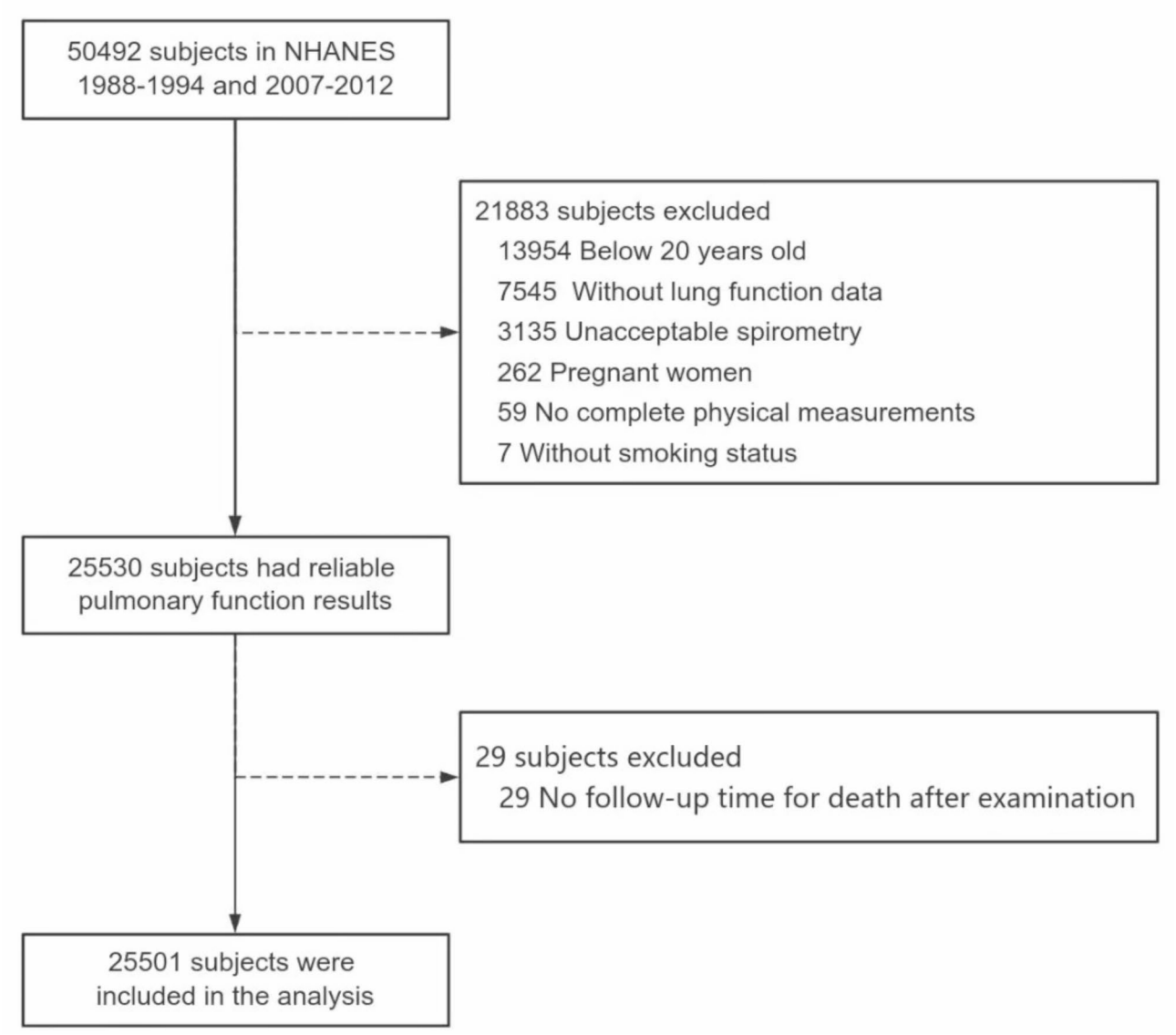

Fig. 1 Study flow chart. Abbreviations: NHANES = National Health and Nutrition Examination Survey

were included in Mode 1 and Model 2, 25,255 participants were included in Model 3. The unadjusted model (Model 1) showed an inverse relationship between the FEV_1/FVC ratio in the eight groups and their mortality risk. The all-cause mortality risk was highest in the group with the lowest FEV_1/FVC ratio and decreased as the FEV_1/FVC ratio increased. The mortality risk was significantly elevated in all groups. After adjusting for age, sex, BMI, race, and smoking status (Model 2), the mortality risk was significantly higher in the groups with an FEV_1/FVC ratio < 0.30 (hazard ratio [HR] 5.03, 95% confidence interval [CI] 2.85–8.87, $P < 0.001$), $0.30 \le FEV_1/FVC < 0.40$ (HR 1.44, 95% CI 1.06–1.96, $P = 0.020$), and $0.40 \le FEV_1/FVC < 0.50$ (HR 1.35, 95% CI 1.08–1.69, $P = 0.007$). The mortality risk decreased in participants with an FEV_1/FVC ratio of between 0.60 and 0.70 (HR 0.79, 95% CI 0.68–0.93, $P = 0.005$), and reached its lowest point in the $0.70 \le FEV_1/FVC < 0.80$ group (HR 0.69, 95% CI 0.59–0.80, $P < 0.001$). However, the negative association was not maintained in participants with an FEV_1/FVC ratio ≥ 0.80. The mortality risk inversely increased in the $0.80 \le FEV_1/FVC < 0.90$ group (HR 0.76, 95% CI 0.65–0.88, $P < 0.001$). The trend indicated that a lower FEV_1/FVC ratio was associated with a higher mortality risk, particularly in those with severe obstruction (FEV_1/FVC < 0.50), while a higher ratio conferred a protective effect, particularly in individuals with an FEV_1/FVC ratio of between 0.70 and 0.80, but the protective effect diminished when the FEV_1/FVC ratio exceeded 0.80. In Model 3, we added comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension) into adjustment to evaluate

Table 1 Demographics and clinical features of NHANES participants at baseline

Characteristic	Pre-bronchodilator FEV_1/FVC		Total (*N* = 25501)
	≥ 0.70 (*N* = 21871)	< 0.70 (*N* = 3630)	
Age — year	43.8 ± 16.4	61.1 ± 14.7	46.3 ± 17.3
Male sex— no. (%)	10,196 (46.6)	2217 (61.1)	12,413 (48.7)
Body mass index — kg/m^2	28.2 ± 6.4	26.8 ± 5.6	28.0 ± 6.3
Race— no. (%)			
White Non-Hispanic	8717 (39.9)	2282 (62.9)	10,999 (43.1)
Black Non-Hispanic	5440 (24.9)	708 (19.5)	6148 (24.1)
Mexican-American	5221 (23.9)	410 (11.3)	5631 (22.1)
Other	2493 (11.4)	230 (6.3)	2723 (10.7)
Smoking status— no. (%)			
Never smoker	12,001 (54.9)	1060 (29.2)	13,601 (51.2)
Current smoker	5157 (23.6)	1231 (33.9)	6388 (25.0)
Former smoker	4713 (21.5)	1339 (36.9)	6052 (23.7)
Comorbidity— no. (%)			
Congestive heart failure	438 (2.0)	182 (5.0)	620 (2.4)
Stroke	393 (1.8)	155 (4.3)	548 (2.2)
Asthma	1900 (8.7)	630 (17.4)	2530 (9.9)
Chronic bronchitis	908 (4.2)	401 (11.1)	1309 (5.1)
Emphysema	124 (0.6)	250 (6.9)	374 (1.5)
Cancer	1251 (5.7)	566 (15.6)	1817 (7.1)
Diabetes	1783 (8.2)	405 (11.2)	2188 (8.6)
Hypertension	5730 (26.3)	1439 (39.8)	7169 (28.2)
Chronic respiratory symptoms— no. (%)			
Chronic cough	1270 (5.8)	539 (14.8)	1809 (7.1)
Chronic phlegm	1266 (5.8)	552 (15.2)	1818 (7.1)
Wheezing	2682 (12.3)	907 (25.0)	3589 (14.1)
Shortness of breath	2598 (11.9)	831 (22.9)	3429 (13.4)
Pre-bronchodilator lung function			
FEV_1, L	3.15 ± 0.87	2.32 ± 0.82	3.03 ± 0.91
FEV_1 percent predicted, %	100.2 ± 14.2	80.9 ± 19.5	97.4 ± 16.5
FVC, L	3.90 ± 1.06	3.68 ± 1.16	3.87 ± 1.08
FEV_1/FVC	0.81 ± 0.06	0.63 ± 0.08	0.78 ± 0.09

Data are mean ± standard deviation or n (%). Abbreviations: NHANES = National Health and Nutrition Examination Survey; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity

the impact of comorbidities on all-cause mortality. The result was similar to Model 2.

The survival advantage of the $0.70 \le FEV_1/FVC < 0.80$ group compared with the $0.90 \le FEV_1/FVC \le 1.00$ group was consistent across various subgroups stratified by age (20–50 vs. >50 years), smoking status, sex, BMI, race, comorbidities, and chronic respiratory symptoms (Table S1).

Association between FEV_1/FVC and comorbidities

Table S2 presents the association between FEV_1/FVC ratio and the presence of comorbidities. The unadjusted logistic regression analysis shown strong associations between low FEV_1/FVC ratios and higher risk of congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension. After adjusting for confounders, low FEV_1/FVC ratio remained significantly associated with higher risk of asthma, chronic bronchitis, and emphysema. However, there was no significant association between low FEV_1/FVC and congestive heart failure, stroke, cancer, diabetes, and hypertension.

The non-linear relationship

The associations between the FEV_1/FVC ratio categories and all-cause mortality risk have been described above. Here, we reveal that a non-linear relationship existed when the FEV_1/FVC ratio was considered as a continuous variable ($P_{non-linear} < 0.010$). The L-shaped association between the FEV_1/FVC ratio and all-cause mortality was shown in the unadjusted RCS analysis (Fig. 4). In contrast, the adjusted smoothed plots displayed a U-shaped association between the FEV_1/FVC ratio and all-cause mortality. Below and above the inflection point, an

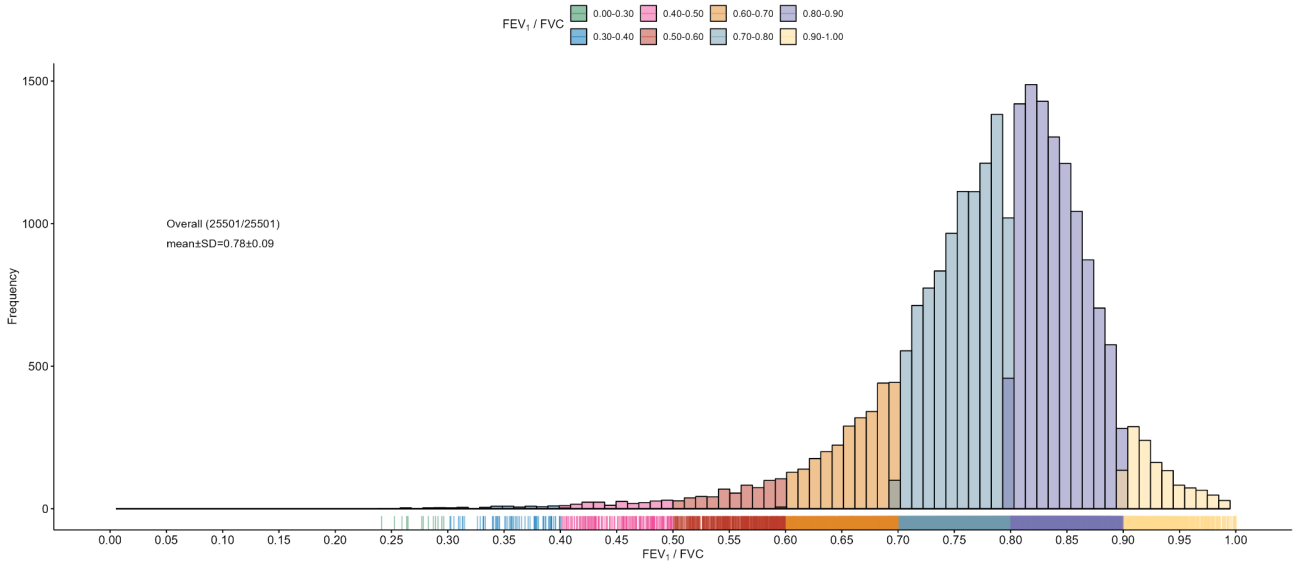

Fig. 2 Distribution of FEV_1/FVC in NHANES Participants. Abbreviations: FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; SD=standard deviation

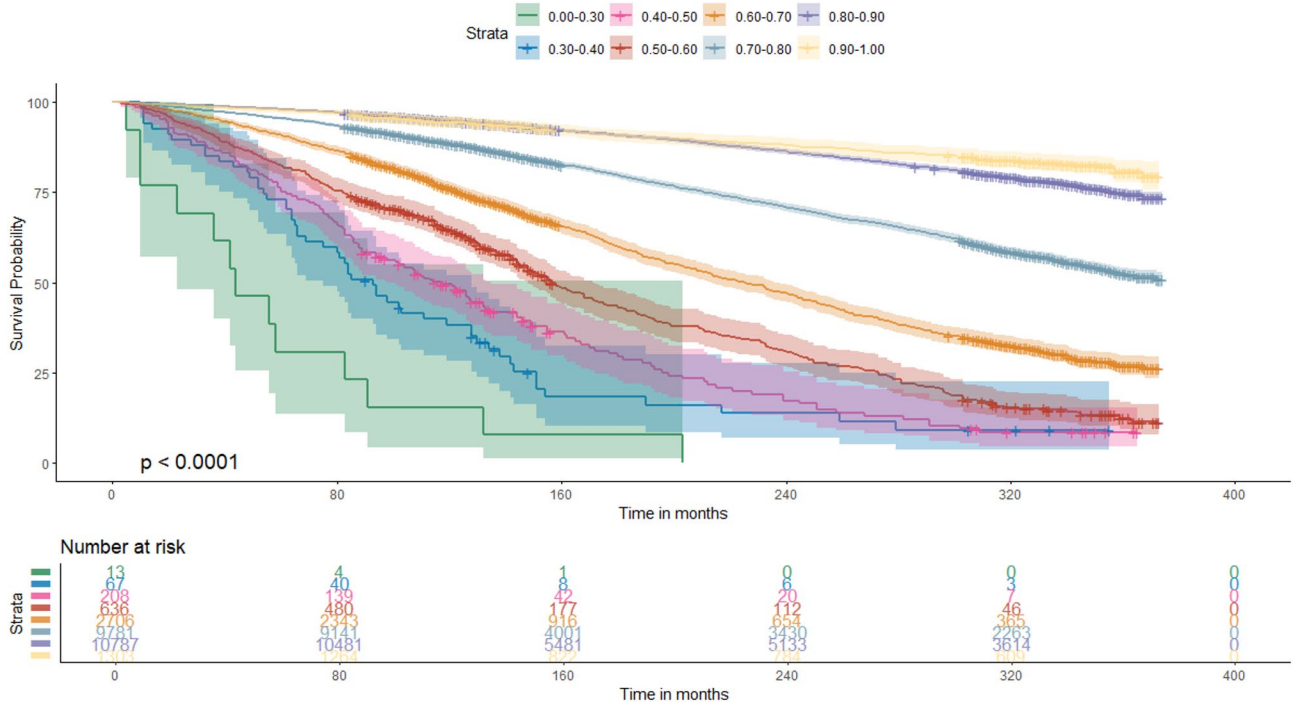

Fig. 3 Kaplan-Meiercurve for all-cause mortality among the eight groups ofFEV1/FVC. Abbreviations: FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity

inverse trend in mortality risk was found. Overall, the subgroup analyses aligned with the trends observed in the general population, demonstrating consistent L-shaped and U-shaped patterns. Notably, participants aged > 50 years showed no significant difference in their mortality risk curves before and after adjusting for confounding variables, indicating the stability of the association between the FEV_1/FVC ratio and all-cause mortality in this age group.

Discussion

In the present study, which was based on data from the NHANES, all-cause mortality risk was lowest in the $0.70 \leq FEV_1/FVC < 0.80$ group and inversely increased. We observed a U-shaped relationship between the FEV_1/

Table 2 Association between categorical FEV_1/FVC and mortality

FEV_1/FVC	*N*		Model 1 (*N* = 25501)		Model 2 (*N* = 25501)		Model 3 (*N* = 25255)	
	Total	Death	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
$0.90 \le FEV_1/FVC \le 1.00$	1303	176 (13.5%)	Reference	—	Reference	—		
$FEV_1/FVC < 0.30$	13	13 (100.0%)	48.56 (27.62–85.38)	< 0.001	5.03 (2.85–8.87)	< 0.001	3.53 (1.98–6.29)	< 0.001
$0.30 \le FEV_1/FVC < 0.40$	67	55 (82.1%)	19.21 (14.18–26.02)	< 0.001	1.44 (1.06–1.96)	0.020	1.22 (0.89–1.68)	0.216
$0.40 \le FEV_1/FVC < 0.50$	208	154 (74.0%)	15.26 (12.28–18.96)	< 0.001	1.35 (1.08–1.69)	0.007	1.25 (0.99–1.57)	0.060
$0.50 \le FEV_1/FVC < 0.60$	636	415 (65.3%)	10.23 (8.57–12.21)	< 0.001	0.99 (0.83–1.19)	> 0.926	1.00 (0.83–1.20)	1.000
$0.60 \le FEV_1/FVC < 0.70$	2706	1298 (48.0%)	6.23 (5.32–7.29)	< 0.001	0.79 (0.68–0.93)	0.005	0.80 (0.68–0.94)	0.007
$0.70 \le FEV_1/FVC < 0.80$	9781	2718 (27.8%)	2.91 (2.50–3.39)	< 0.001	0.69 (0.59–0.80)	< 0.001	0.70 (0.60–0.81)	< 0.001
$0.80 \le FEV_1/FVC < 0.90$	10,787	1602 (14.9%)	1.29 (1.10–1.51)	0.001	0.76 (0.65–0.88)	< 0.001	0.76 (0.65–0.88)	< 0.001

Model 1: Unadjusted. Model 2: Adjusted for age, sex, BMI, race, and smoking status. Model 3: Adjusted for age, sex, BMI, race, smoking status, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension). Abbreviations: HR = hazard ratio; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity

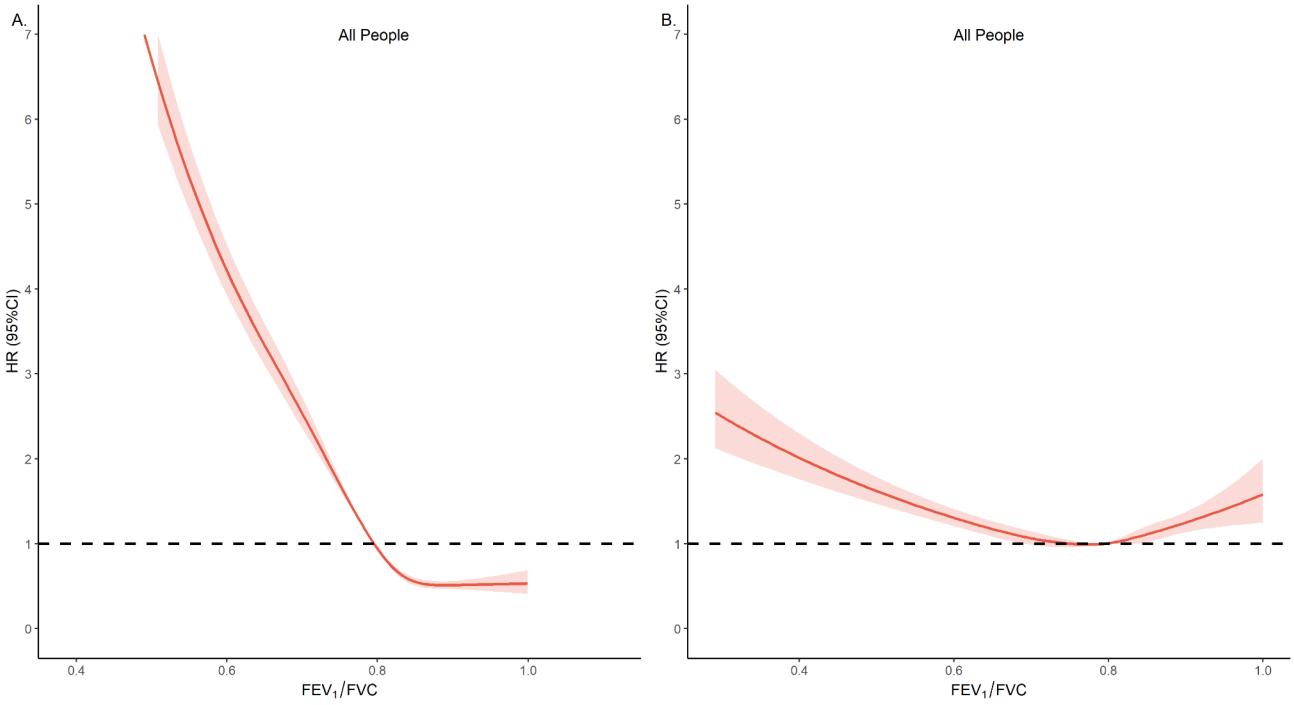

Fig. 4 Non-linear association between FEV1/FVC and all-cause mortality. The solid curved line represents the estimates for the association of FEV1/FVC and all-cause mortality. Shaded areas represent 95% confidence intervals. (**A**) Unadjusted RCS curves; (**B**) Adjusted RCS curves: adjusted for age, sex, Body mass index, race, smoking status, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension). Abbreviations: FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; RCS=the restricted cubic spline

FVC ratio and all-cause mortality risk in the general US population. The subgroup analyses were consistent with this trend.

To our knowledge, this is the first study to systematically evaluate the relationship between the FEV_1/FVC ratio and all-cause mortality, particularly in terms of its non-linear association. The association was quite complex, demonstrating significant differences before and after adjusting for confounding variables. Before adjustment, a lower FEV_1/FVC ratio was associated with a higher all-cause mortality risk, especially in individuals with an FEV_1/FVC ratio < 0.50, indicating the requirement for closer monitoring in high-risk populations. After confounder adjustment, both extremely high and low FEV_1/FVC ratios were associated with increased mortality, warranting further investigation into the underlying pathophysiological mechanisms. These findings suggest that the FEV_1/FVC ratio can be used not only to diagnose COPD but also to assess mortality risk.

The relationship between spirometry indices and respiratory health outcomes has long been a focus of research on respiratory diseases. Most previous studies have evaluated the association between COPD (FEV_1/FVC ratio < 0.70) and mortality. For instance, a study using data from the NHANES 2007-2012 cycle showed that COPD is significantly associated with an

increased all-cause mortality risk [12]. Recent research has explored the clinical value of the FEV_1/FVC ratio beyond its diagnostic thresholds. For instance, a prospective cohort study demonstrated that a reduced FEV_1/FVC ratio is independently associated with an increased risk of future AECOPD, highlighting its potential as a biomarker for AECOPD risk stratification [7]. Other studies have indicated that both the STAR and GOLD grading systems have similar capabilities for predicting all-cause mortality, suggesting that low FEV_1/FVC ratio, like low percentage predicted FEV_1, is a critical predictor of mortality [13]. On the basis of the established links between COPD and mortality, as well as the potential clinical value of the FEV_1/FVC ratio, our research not only compared individuals with COPD with those with normal lung function, but it also investigated whether an FEV_1/FVC ratio beyond the 0.70 threshold is associated with all-cause mortality. We stratified patients into groups by the FEV_1/FVC ratio at intervals of 0.10 to comprehensively explore its relationship with all-cause mortality. Bhatt et al.'s study similarly divided the FEV_1/FVC ratio into multiple categories, showing a negative correlation between the incidence density ratio of COPD-related hospitalizations/mortality and the FEV_1/FVC ratio. However, no clear inflection point was identified, and participants with an FEV_1/FVC ratio of at least 0.77 had the lowest risk of COPD-related events [5]. We observed similar conclusions in our unadjusted Cox proportional-hazards regression models. Although all-cause mortality was measured as an outcome in our research, the FEV_1/FVC ratio still showed a negative correlation with all-cause mortality, with the mortality risk decreasing as the FEV_1/FVC ratio increased. After adjusting for confounding variables, we observed a turning point in which the mortality risk reached the lowest in participants with an FEV_1/FVC ratio of between 0.70 and 0.80. Despite further increases in the FEV_1/FVC ratio beyond this range, no additional reductions in mortality risk were observed.

The results of the RCS analysis, which considered the FEV_1/FVC ratio as a continuous variable, further elucidated the relationship between the FEV_1/FVC ratio and all-cause mortality, revealing a U-shaped association. This pattern emerged because while a lower FEV_1/FVC ratio is typically linked to obstructive lung diseases, such as COPD, leading to poor outcomes, a higher ratio may indicate restrictive lung diseases, such as interstitial lung disease or thoracic abnormalities. People with such diseases have a lower total lung capacity and face a higher mortality risk than healthy individuals, explaining why those with an excessively high FEV_1/FVC ratio also have increased mortality [14]. It is noteworthy that the RCS curves showed differing trends after compared with before adjustment for confounding factors. In the unadjusted model, the relationship between the FEV_1/FVC ratio and all-cause mortality was L-shaped, whereas after adjustment, the association was U-shaped. This change may have resulted from adjusting for the confounding variable of age. When age alone was adjusted, the curve shifted from an L-shaped curve to a U-shaped curve, while adjustment for other variables did not produce this effect. Thus, it is suggested that age might be a crucial factor influencing this association, though the specific mechanisms require further exploration.

This study has several notable strengths. It focuses on a large sample of the general population, allowing for broader applicability of the findings on the association between the FEV_1/FVC ratio and all-cause mortality. Moreover, the use of both adjusted and unadjusted Cox proportional-hazards regression models and RCS curves strengthened the evidence for a non-linear U-shaped relationship between the FEV_1/FVC ratio and all-cause mortality. These approaches allow for a clearer understanding of how lung function correlates with mortality risk across different FEV_1/FVC ratios. Additionally, the subgroup analyses further enhanced the credibility of the study's conclusions, providing reassurance that the general trends observed in the study population are consistent across different strata, bolstering the overall robustness and reliability of the findings.

The study also has several limitations. First, despite our efforts to control for confounding factors through multivariable adjustments and subgroup analyses, the influence of unmeasured confounders and unaccounted relevant comorbidities on the accuracy of the findings cannot be excluded. Second, owing to the limited availability of post-bronchodilator spirometry data, we ultimately used pre-bronchodilator spirometry results for the analysis. Although previous research has indicated that post-bronchodilator spirometry slightly outperforms pre-bronchodilator measures in predicting mortality, the difference is minimal [15]. Therefore, it is unlikely that the use of post-bronchodilator data significantly impacted our findings. Thirdly, comorbidities and chronic respiratory symptoms were assessed based on participants' self-reports, which may have led to underreporting and consequently affected the accurate evaluation of these conditions. Finally, our analysis only evaluated the prognostic value of the baseline FEV_1/FVC ratio; therefore, it remains unclear whether changes in the FEV_1/FVC ratio during follow-up could influence mortality risk. This warrants further investigation to better understand the long-term implications of changes in the FEV_1/FVC ratio on mortality.

Conclusion

This study identified a U-shaped association between the FEV_1/FVC ratio and all-cause mortality risk in the general US population. The FEV_1/FVC ratio could be

applied to evaluate mortality risk in the general population, rather than being used solely as a diagnostic tool for COPD.

Abbreviations

AECOPD	Acute exacerbation of COPD
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
NHANES	The National Health And Nutrition Examination Survey
RCS	The restricted cubic spline

Supplementary Information

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Supplementary Material 1

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Author contributions
L.T, F.W, Y.Z 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. L.T, F.W were guarantors. L.T, F.W, S.Z designed the study. J.O participated in data organization and data collection. L.T, S.Z, J.L, R.P participated in data analysis. S.L, Q.Z, Y.C, X.G, J.C, Q.W, Z.W, Z.D contributed to interpretation of the findings. L.T drafted the manuscript. All authors contributed to article modification and the last version of the manuscript. All authors read and approved the final manuscript before submission.

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Data availability
The datasets generated and analyzed during the current study are available in the NHANES repository, https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
In accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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