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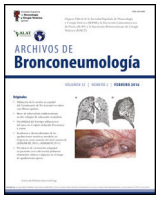

Original Article

Association of Forced Expiratory Volume in 0.5 s With All-Cause Mortality Risk in Adults

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ABSTRACT

Introduction: Previous studies have proposed forced expiratory volume in 0.5 s ($FEV_{0.5}$) to determine health outcomes in infants and young children, but few studies exist in adults. This study aims to investigate the associations between $FEV_{0.5}$ and all-cause mortality in adults.
Methods: Participants were enrolled from the National Health and Nutrition Examination Survey (NHANES) (1988–1994 [NHANES III] and 2007–2012 cycles). Participants aged ≥ 20 years, not pregnant with qualifying prebronchodilator $FEV_{0.5}$ data, acceptable spirometry, complete body measurements, and follow-up data for mortality were included. The association between $FEV_{0.5}$ and all-cause mortality risk was evaluated by multivariable Cox regression. Restricted cubic spline analysis was used to evaluate the non-linear relationship between $FEV_{0.5}$ and all-cause mortality. Subgroup analyses were conducted with stratification by sex, age, body mass index, smoking status, and race.
Results: Overall, 25,357 individuals were included, with a median follow-up of 308 months. The mean ± standard deviation age was 46.1 ± 7.2 years, and the mean prebronchodilator $FEV_{0.5}$ was 2412 ± 699 mL. A reduction in $FEV_{0.5}$ was associated with an increased all-cause mortality risk. A non-linear relationship was observed between $FEV_{0.5}$ and all-cause mortality risk. The results were maintained in subgroups analyses.
Conclusion: $FEV_{0.5}$ was inversely associated with all-cause mortality risk in adults, indicating its potential for monitoring respiratory health.

Introduction

Pulmonary function testing is non-invasive and is a useful method to evaluate respiratory diseases. Pulmonary function test results include forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), which are important for diagnosing respiratory diseases, as well as for identifying the subtype, severity, and nature of the respiratory disease. Evidence suggests that individuals with below-average FEV_1 but still within the normal range have a higher risk of mortality than those with a higher FEV_1. Therefore, relying on the assumption that an individual's FEV_1 falls within the normal range to predict health outcomes may inadvertently exclude some at-risk individuals. The same conclusion was reached in previous studies on FVC.[1–3] The existing literature does not adequately address the question of how observed changes in FVC in a single patient can inform clinical decision making.[4] Therefore, it is imperative to identify supplementary indicators to achieve a more precise assessment of respiratory health outcomes.

The published literature predominantly describes the respiratory health of preschool children due to the physiological

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constraint that infants and preschoolers typically exhale within a duration of 1 s. Consequently, forced expiratory volume in 0.5 s ($FEV_{0.5}$) has emerged as a potentially precise indicator within this demographic. Several studies have demonstrated a noteworthy correlation between $FEV_{0.5}$ and respiratory health in preschool children, thus affirming its utility as a pivotal marker for lung function assessment.[5,6] The insights obtained from these investigations offer valuable perspectives on the spectrum of lung diseases in infants and young children, the efficacy of therapeutic interventions, and the dynamics of disease progression. Nonetheless, the understanding of the associations between $FEV_{0.5}$ and respiratory health outcomes in adults requires improvement. Understanding the associations between $FEV_{0.5}$ and respiratory health outcomes in adults has important implications for monitoring respiratory health prognosis in this population.

In this study, we aim to elucidate the associations between $FEV_{0.5}$ and all-cause mortality, comorbidities, and chronic respiratory symptoms. The analysis is based on a substantial sample of representative US civilians.

Methods

Study Design and Population

We utilized data from the National Health and Nutrition Examination Survey (NHANES), a collaborative effort spearheaded by the Centers for Disease Control and Prevention and the National Centers for Health Statistics (NCHS) in the US. Ethical approval for the NHANES protocol was duly obtained from the Research Ethics Review Board of the NCHS, and all participants provided written informed consent. Our dataset, which was sourced from the NHANES website (www.cdc.gov/nchs/nhanes/), spans the 1988–1994 (NHANES III) and 2007–2012 cycles due to the availability of $FEV_{0.5}$ data and the fact that these cycles encompassed a comprehensive array of demographic, examination, and questionnaire data.

This study included all baseline data from the participants who had complete data on $FEV_{0.5}$. The main inclusion criteria were (1) age $\geq$ 20 years; (2) non-pregnant; (3) acceptable spirometry; (4) qualifying $FEV_{0.5}$ data; (5) complete demographic data and information on smoking status; and (6) complete follow-up data for all-cause mortality.

Lung Function Assessment

The majority of the participants in the NHANES III and NHANES 2007–2012 completed prebronchodilator pulmonary function measurements, while only a small number completed postbronchodilator pulmonary function measurements. Therefore, this study was based on an analysis of the prebronchodilator spirometry data. All pulmonary function measurements were obtained using the Ohio 822/827 Dry Rolled Volume Sealed Spirometer. In the NHANES study, spirometry was performed in accordance with previously recommended guidelines of the American Thoracic Society (ATS).

Stringent quality control measures were applied, necessitating the exclusion of participants who failed to meet the pulmonary function testing criteria. In the NHANES III (1988–1994), individuals with reproducible FEV_1 and FVC measurements with $\geq$2 acceptable trials were included.[7] In the NHANES 2007–2012, individuals with FEV_1 and FVC that were considered to be of grade A (exceeding the ATS data collection standards) or grade B (meeting the ATS data collection standards) in terms of quality were included.[8–10] Lower limit of normal (LLN) for FEV_1 and FVC is calculated using the GLI online calculator with a race-neutral approach.[11,12]

All participants were systematically stratified into four quartiles based on their prebronchodilator $FEV_{0.5}$ values, designated as group I (0 mL to <1937 mL), group II ($\geq$1937 mL to <2388 mL), group III ($\geq$2388 mL to <2884 mL), and group IV ($\geq$2884 mL).

Outcome

The primary outcome was the all-cause mortality. The secondary outcomes were the risks of comorbidities and chronic respiratory symptoms. The all-cause mortality data were obtained from the comprehensive death certificate records of the National Death Index (NDI) of the NCHS. Information regarding comorbidities and chronic respiratory symptoms was gathered from the questionnaire data on the same date as the pulmonary function tests. This involved inquiring with the patients as to whether they had ever been informed that they had comorbidities by a medical professional, including a doctor or another healthcare provider. Data on chronic respiratory symptoms were gathered via patient self-reporting, wherein the participants were questioned about whether they had experienced cough, cold, sputum production, runny nose, or any other respiratory illness.[13–15]

Covariate Definitions

Information on various demographic and health-related factors was gathered on the same date as the pulmonary function tests, including age, sex, race, smoking status, educational level and poverty income ratio from the NHANES household interviews. 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 ($\geq$18.5 kg/m^2 to <25 kg/m^2), overweight ($\geq$25.0 kg/m^2 to <30.0 kg/m^2), and obese ($\geq$30.0 kg/m^2). Body surface area (BSA) was calculated using the following formula: BSA (m^2) = (body weight [kg])$^{0.425}$ $\times$ (height [cm])$^{0.725}$ $\times$ 0.007184.[16] Race was categorized as Mexican–American, non-Hispanic White, non-Hispanic Black, or other race. Educational level was categorized as Less than 9th grade, 9–12th grade or above 12th grade. Poverty income ratio (PIR) was categorized as low-income (PIR < 1.3), middle-income (3.50 > PIR $\geq$ 1.30) or high-income (PIR $\geq$ 3.50). The criteria for classifying smoking status are as follows: “Have you smoked at least 100 cigarettes in your entire life?”, participants who answered “No” were classified as “never smokers.” Those who answered “Yes” were identified as smokers, and based on their answer to the question, “Do you smoke cigarettes now?”, they were classified as “current smokers” (“Yes”) or “former smokers” (“No”).

Statistical Analysis

Continuous variables were compared between the groups by analysis of variance, while categorical variables were compared using Pearson’s Chi-square test. The multivariable logistic regression model was used to estimate the association of $FEV_{0.5}$ with the presence of comorbidities and the presence of chronic respiratory symptoms. Trends in these associations were calculated using quartiles as quasi-continuous variables in the multivariable logistic regression model.

Kaplan–Meier survival analyses were performed to identify differences in all-cause mortality between the groups. The multivariable Cox regression models were used to estimate the association between $FEV_{0.5}$ and all-cause mortality risk. The proportional-hazards assumption was checked graphically using the Schoenfeld residual test. To further understand the association between $FEV_{0.5}$ and all-cause mortality, we performed Cox proportional-hazards regression analyses with restricted cubic spline (RCS) analysis utilizing five knots. The trend in the associ-

Table 1
Baseline Characteristic of Participants Included in This Study.

Characteristic	Total Participants (n = 25,357)	Group I (n = 6352)	Group II (n = 6339)	Group III (n = 6328)	Group IV (n = 6338)	P Value
Age, yr	46.1 (17.2)	61.0 (14.6)	46.7 (15.9)*	41.0 (14.8)*,†	35.9 (12.1)*,†,‡	<0.001
Male Sex, n (%)	12,353 (48.7)	1352 (10.9)	1909 (15.5)*	3301 (26.7)*,†	5791 (46.9)*,†,‡	<0.001
Body mass index, kg/m²	28.0 (6.3)	28.7 (6.9)	28.1 (6.5)*	27.7 (6.2)*,†	27.4 (5.4)*,†	<0.001
Race, n (%)						<0.001
Non-Hispanic white	10,894 (43.0)	2899 (26.6)	2550 (23.4)*	2617 (24.0)*	2828 (26.0)†,‡	
Non-Hispanic black	6130 (24.2)	1830 (29.9)	1708 (27.9)	1441 (23.5)*,†	1151 (18.8)*,†,‡	
Mexican-American	5613 (22.1)	952 (17.0)	1348 (24.0)*	1572 (28.0)*,†	1741 (31.0)*,†,‡	
Other	2720 (10.7)	671 (24.7)	733 (26.9)	698 (25.7)	618 (22.7)†	
Smoke status, n (%)						<0.001
Never smoker	12,991 (51.2)	3184 (24.5)	3450 (26.6)*	3226 (24.8)†	3131 (24.1)†	
Current smoker	6362 (25.1)	1449 (22.8)	1470 (23.1)	1641 (25.8)*,†	1802 (28.3)*,†,‡	
Former smoker	6004 (23.7)	1719 (28.6)	1419 (23.6)*	1461 (24.3)*	1405 (23.4)*	
Education level, n (%)						<0.001
Less than 9th grade	3989 (15.8)	1535 (38.5)	952 (23.9)*	829 (20.8)*,†	673 (16.9)*,†,‡	
9–12th grade	10,961 (43.4)	2857 (26.1)	2808 (25.6)	2666 (24.3)*	2630 (24.0)*,†	
Above 12th grade	10,315 (40.8)	1938 (18.8)	2558 (24.8)*	2809 (27.2)*,†	3010 (29.2)*,†,‡	
Poverty income ratio, n (%)						<0.001
Low-income (PIR < 1.3)	7134 (30.7)	2006 (28.1)	1780 (25.0)*	1715 (24.0)*	1633 (22.9)*,†	
Middle-income (3.50 > PIR ≥ 1.30)	9506 (40.9)	2385 (25.1)	2365 (24.9)	2390 (25.1)	2366 (24.9)	
High-income (PIR ≥ 3.50)	6590 (28.4)	1290 (19.6)	1673 (25.4)*	1748 (26.5)*	1879 (28.5)*,†	
Pre-bronchodilator spirometry						
$FEV_{0.5}$, mL	2412 (699)	1539 (321)	2169 (128)*	2619 (142)*,†	3324 (346)*,†,‡	<0.001
FEV_1, mL	3041 (909)	1931 (394)	2721 (231)*	3301 (261)*,†	4213 (497)*,†,‡	<0.001
FVC, mL	3875 (1075)	2705 (605)	3505 (503)*	4142 (558)*,†	5153 (691)*,†,‡	<0.001
$FEV_{0.5}$/FVC, %	62.5 (8.9)	58.0 (11.3)	62.9 (7.9)*	64.1 (7.5)*,†	65.1 (6.5)*,†,‡	<0.001
FEV_1/FVC, %	78.4 (8.8)	72.4 (10.9)	78.5 (7.3)*	80.5 (6.9)*,†	82.1 (5.7)*,†,‡	<0.001

Definition of abbreviations: PIR = poverty income ratio; $FEV_{0.5}$ = forced expiratory volume in 0.5 s; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.
Data are shown as mean (SD) unless otherwise specified.
* Significantly different from Group I (P < 0.05).
† Significantly different from Group II (P < 0.05).
‡ Significantly different from Group III (P < 0.05).

ation between $FEV_{0.5}$ and all-cause mortality risk was calculated using quartiles as quasi-continuous variables in the multivariable Cox regression model.

Subgroup analyses were also performed to evaluate the impact of $FEV_{0.5}$ on all-cause mortality across various subgroups stratified by age (20–40, 41–60, and 61–80 years), sex, race (Mexican–American, non-Hispanic White, non-Hispanic Black, other race), BMI (underweight, normal, overweight, obese), and smoking status (never smoker, former smoker, current smoker). To verify whether $FEV_{0.5}$ adds prognostic value beyond FEV_1 and FVC, we repeated the analysis in the subgroups with $FEV_1 \geq$ LLN, FVC ≥ LLN, and both FEV_1 and FVC ≥ LLN. In cases of missing data, we used a deletion measure and abstained from using data interpolation. P < 0.05 was considered statistically significant for all tests. R Studio, version 4.3.3, and SPSS, version 29.0, were used to conduct the statistical analyses.

Results

Baseline Characteristics of the Study Participants

Of the 50,492 participants from the NHANES III (n = 20,050) and NHANES 2007–2012 (n = 30,442), 25,357 were included in the present analysis after applying the eligibility criteria. Reasons for exclusion are shown in Fig. S1. The baseline characteristics of the participants are presented in Table 1. The median follow-up time was 308 months. The mean age was 46.1 ± 7.2 years, and the mean BMI was 28.0 ± 6.3 kg/m². Fig. S2 illustrates the $FEV_{0.5}$ distribution at baseline. The mean $FEV_{0.5}$ was 2412 ± 699 mL, with a median (interquartile range) $FEV_{0.5}$ of 2388 (1937–2884) mL. There were 6352 participants in group I, 6339 in group II, 6328 in group III, and 6338 in group IV. Compared with individuals in groups II, III, and IV, individuals in group I tended to be older and have higher BMI.

Association Between $FEV_{0.5}$ and All-Cause Mortality Risk

Fig. 1 illustrates the results of all-cause mortality in the different groups. Significant differences in all-cause mortality were observed among the four groups (log-rank P < 0.05). During follow-up, group I had 3054 deaths (48.1%), group II had 1474 deaths (23.3%), group III had 1051 deaths (16.6%), and group IV had 716 deaths (11.3%). Table 2 reports the results of the association between $FEV_{0.5}$ and all-cause mortality risk in the different groups. In the univariable regression analysis, compared with individuals in group IV, individuals in groups I, II, and III had a higher risk of all-cause mortality ($HR_{group\ I}$ 6.70, 95% confidence interval [CI] 6.17–7.27; $HR_{group\ II}$ 2.31, 95% CI 2.11–2.53; $HR_{group\ III}$ 1.56, 95% CI 1.42–1.72; all P < 0.05; P_{trend} < 0.05). After adjustment for age, sex, smoking, body mass index, body surface area, race, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, Asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension), the multivariable regression analysis results were consistent. Compared with individuals in group IV, individuals in groups I, II, and III had a higher risk of all-cause mortality ($HR_{group\ I}$ 1.77, 95% CI 1.57–2.00; $HR_{group\ II}$ 1.28, 95% CI 1.15–1.43; $HR_{group\ III}$ 1.15, 95% CI 1.04–1.28; all P < 0.05; P_{trend} < 0.05). $FEV_{0.5}$ was numerically higher than FEV_3 and FEV_3/FVC in its ability (the concordance index of the multivariable Cox regression model) to identify the risk of all-cause mortality, but the difference did not reach statistical significance (Fig. S3).

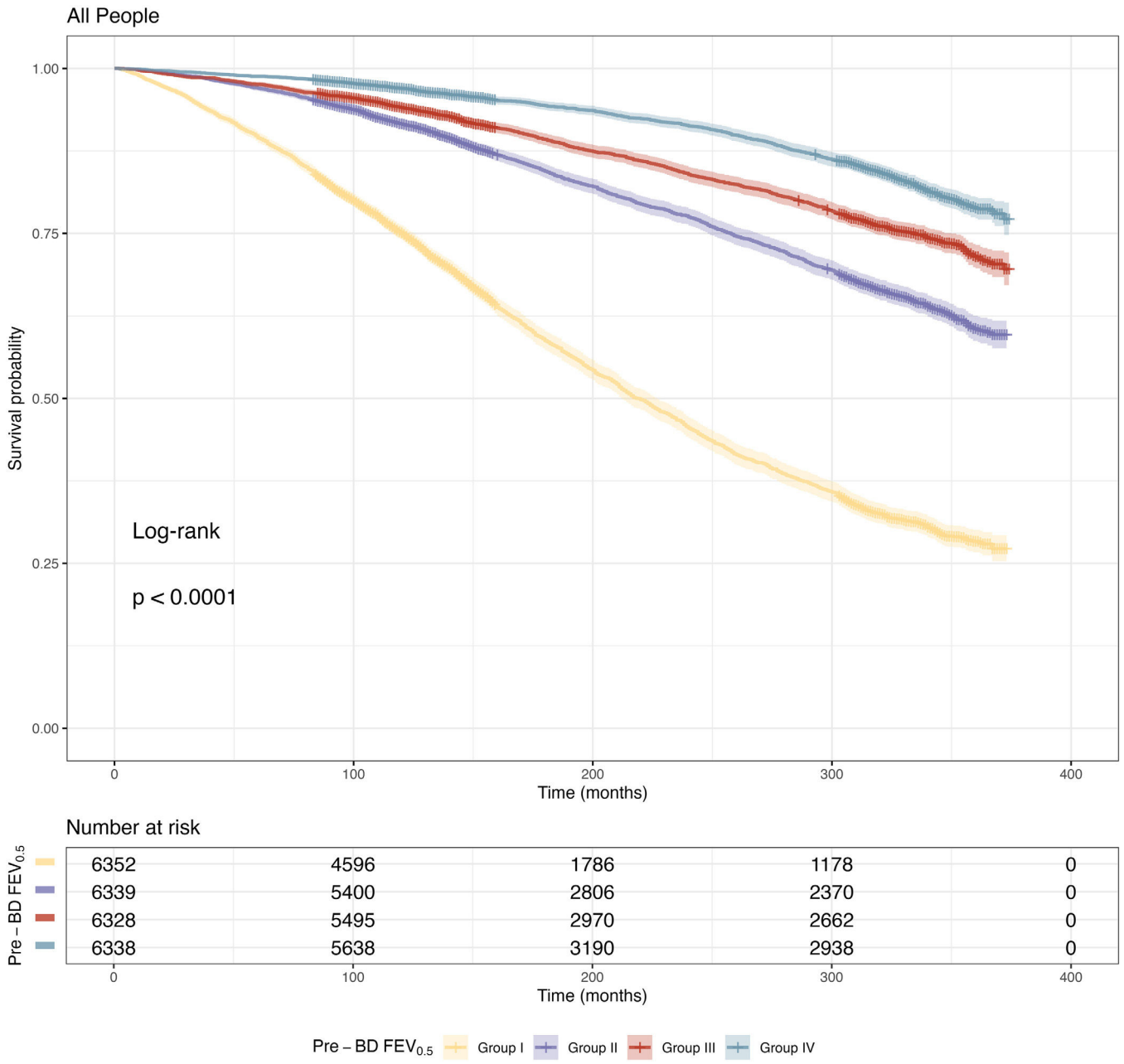

Fig. 1. Mortality risk stratified by prebronchodilator forced expiratory volume in 0.5 s levels at baseline. Definition of abbreviations: BD = bronchodilator; $FEV_{0.5}$ = forced expiratory volume in 0.5 s.

Table 2
Associations Between Pre-Bronchodilator Forced Expiratory Volume in 0.5 s and Risk of All-Cause Mortality.

Group	Unadjusted				Adjusted*			
	N	HR (95% CI)	*P* Value	*P* Trend	*N*	HR (95% CI)	*P* Value	*P* Trend
Group I	25,357	6.70 (6.17–7.27)	<0.001	<0.001	22,957	1.77 (1.57–2.00)	<0.001	<0.001
Group II		2.31 (2.11–2.53)	<0.001			1.28 (1.15–1.43)	<0.001	
Group III		1.56 (1.42–1.72)	<0.001			1.15 (1.04–1.28)	0.008	
Group IV		Reference				Reference		

Definition of abbreviations: HR = hazard ratio; CI = confidence interval; *N* = number of participants included in the analysis.
* Adjust for age, sex, smoking, body mass index, body surface area, race, educational level, poverty income ratio, and comorbidities (congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes, and hypertension).

Table 3
Association Between Comorbidity and Chronic Respiratory Symptoms and Pre-Bronchodilator Forced Expiratory Volume in 0.5 s.

Variable	Group	Unadjusted (N = 25,357)				Adjusted*		
		OR (95% CI)	P Value	P Trend	N	OR (95% CI)	P Value	P Trend
Congestive heart failure	Group I	9.73 (6.95–13.63)	<0.001	<0.001	23,131	3.54 (2.27–5.52)	<0.001	<0.001
	Group II	3.28 (2.28–4.73)	<0.001			1.92 (1.26–2.92)	0.002	
	Group III	2.42 (1.66–3.54)	<0.001			1.75 (1.16–2.65)	0.007	
	Group IV	Reference				Reference		
Stroke	Group I	9.64 (6.72–13.84)	<0.001	<0.001	23,152	1.90 (1.18–3.05)	0.008	0.006
	Group II	3.82 (2.60–5.61)	<0.001			1.63 (1.05–2.52)	0.029	
	Group III	2.17 (1.43–3.28)	<0.001			1.36 (0.88–2.11)	0.166	
	Group IV	Reference				Reference		
Asthma	Group I	2.29 (2.03–2.58)	<0.001	<0.001	23,156	6.53 (5.37–7.93)	<0.001	<0.001
	Group II	1.48 (1.31–1.69)	<0.001			2.74 (2.32–3.24)	<0.001	
	Group III	1.32 (1.16–1.51)	<0.001			1.89 (1.63–2.20)	<0.001	
	Group IV	Reference				Reference		
Chronic bronchitis	Group I	6.10 (4.98–7.47)	<0.001	<0.001	23,150	5.14 (3.84–6.89)	<0.001	<0.001
	Group II	2.68 (2.16–3.34)	<0.001			2.54 (1.95–3.30)	<0.001	
	Group III	2.23 (1.78–2.79)	<0.001			2.08 (1.62–2.66)	<0.001	
	Group IV	Reference				Reference		
Emphysema	Group I	16.42 (9.89–27.24)	<0.001	<0.001	23,154	11.36 (6.17–20.93)	<0.001	<0.001
	Group II	3.46 (1.98–6.04)	<0.001			3.25 (1.77–5.97)	<0.001	
	Group III	2.64 (1.48–4.70)	<0.001			2.45 (1.34–4.47)	0.004	
	Group IV	Reference				Reference		
Cancer	Group I	6.24 (5.22–7.46)	<0.001	<0.001	23,155	1.94 (1.49–2.52)	<0.001	<0.001
	Group II	3.57 (2.96–4.30)	<0.001			2.12 (1.68–2.67)	<0.001	
	Group III	2.18 (1.79–2.66)	<0.001			1.68 (1.35–2.10)	<0.001	
	Group IV	Reference				Reference		
Diabetes	Group I	5.90 (5.06–6.88)	<0.001	<0.001	23,145	2.41 (1.91–3.04)	<0.001	<0.001
	Group II	2.91 (2.47–3.43)	<0.001			1.90 (1.55–2.33)	<0.001	
	Group III	1.76 (1.48–2.10)	<0.001			1.45 (1.19–1.77)	<0.001	
	Group IV	Reference				Reference		
Hypertension	Group I	4.33 (3.99–4.71)	<0.001	<0.001	23,065	1.43 (1.24–1.65)	0.001	<0.001
	Group II	1.92 (1.76–2.10)	<0.001			1.14 (1.01–1.29)	0.032	
	Group III	1.37 (1.25–1.50)	<0.001			1.06 (0.95–1.18)	0.284	
	Group IV	Reference				Reference		
Chronic cough	Group I	2.26 (1.96–2.61)	<0.001	<0.001	19,808	2.65 (2.11–3.32)	<0.001	<0.001
	Group II	1.29 (1.10–1.51)	0.001			1.49 (1.22–1.82)	<0.001	
	Group III	1.23 (1.05–1.44)	0.012			1.34 (1.12–1.61)	0.001	
	Group IV	Reference				Reference		
Chronic phlegm	Group I	1.92 (1.67–2.20)	<0.001	<0.001	19,803	2.42 (1.94–3.03)	<0.001	<0.001
	Group II	1.24 (1.07–1.45)	0.005			1.56 (1.28–1.89)	<0.001	
	Group III	1.11 (0.95–1.30)	0.205			1.26 (1.06–1.51)	0.009	
	Group IV	Reference				Reference		
Wheezing	Group I	2.41 (2.18–2.68)	<0.001	<0.001	23,157	5.43 (4.58–6.43)	<0.001	<0.001
	Group II	1.50 (1.35–1.68)	<0.001			2.58 (2.23–2.97)	<0.001	
	Group III	1.32 (1.18–1.48)	<0.001			1.81 (1.59–2.06)	<0.001	
	Group IV	Reference				Reference		
Shortness of breath	Group I	5.61 (4.94–6.36)	<0.001	<0.001	12,651	4.38 (3.57–5.37)	<0.001	<0.001
	Group II	2.80 (2.46–3.20)	<0.001			2.53 (2.13–3.00)	<0.001	
	Group III	1.87 (1.63–2.14)	<0.001			1.78 (1.52–2.09)	<0.001	
	Group IV	Reference				Reference		

Definition of abbreviations: OR = odds ratio; CI = confidence interval; N = number of participants included in the analysis.
* Adjusted for age, sex, smoking, body mass index, body surface area, race, educational level, and poverty income ratio.

Associations of $FEV_{0.5}$ With Comorbidities and Chronic Respiratory Symptoms

Table 3 illustrates the results of the association between $FEV_{0.5}$ and the presence of comorbidities and chronic respiratory symptoms in each group. In terms of chronic respiratory symptoms, the univariable regression analysis revealed that individuals in groups I, II, and III exhibited an elevated risk of chronic cough, wheezing, and dyspnea than those in group IV. These associations persisted in the multivariable regression analysis, which also identified an increased presence of chronic cough, chronic phlegm, wheezing, and dyspnea in groups I, II, and III after adjustment for age, sex, smoking, body mass index, body surface area, race, educational level, and poverty income ratio.

In terms of comorbidities, the multivariable regression model revealed a heightened risk of congestive heart failure, asthma, chronic bronchitis, emphysema, cancer, and diabetes mellitus among individuals in groups I, II, and III compared with those in group IV. Similarly, for stroke and hypertension, an increased presence was observed exclusively in groups I and II when compared with group IV.

Chracteristic	Pre-BD $FEV_{0.5}$	Number of Total	Number of Mortality	HR(95%CI)	P value
Subgroup					
All people	Group I	5703	2657	1.77 (1.57–2.00)	<0.001
	Group II	5762	1325	1.28 (1.15–1.43)	<0.001
	Group III	5787	954	1.15 (1.04–1.28)	0.008
	Group IV	5805	660	1.00 (1.00–1.00)	Reference
Sex					
Male	Group I	1192	787	1.83 (1.58–2.11)	<0.001
	Group II	1717	803	1.47 (1.30–1.67)	<0.001
	Group III	2982	777	1.21 (1.08–1.35)	0.001
	Group IV	5288	641	1.00 (1.00–1.00)	Reference
Female	Group I	4411	1870	1.68 (1.05–2.68)	0.032
	Group II	4045	522	1.12 (0.71–1.79)	0.621
	Group III	2805	177	1.17 (0.73–1.88)	0.520
	Group IV	517	19	1.00 (1.00–1.00)	Reference
Age (years)					
20–40	Group I	653	58	1.16 (0.80–1.68)	0.432
	Group II	2268	170	1.29 (0.99–1.69)	0.062
	Group III	3208	203	1.10 (0.89–1.36)	0.368
	Group IV	4012	271	1.00 (1.00–1.00)	Reference
41–60	Group I	1694	467	2.11 (1.71–2.60)	<0.001
	Group II	2168	406	1.49 (1.24–1.79)	<0.001
	Group III	1841	340	1.25 (1.06–1.48)	0.008
	Group IV	1518	263	1.00 (1.00–1.00)	Reference
61–80	Group I	3256	2132	1.92 (1.57–2.35)	<0.001
	Group II	1326	749	1.37 (1.13–1.66)	0.002
	Group III	738	411	1.21 (0.99–1.48)	0.060
	Group IV	275	126	1.00 (1.00–1.00)	Reference
BMI (kg/m^2)					
<18.5	Group I	134	76	1.95 (0.38–10.14)	0.427
	Group II	115	21	1.13 (0.23–5.65)	0.878
	Group III	87	9	1.43 (0.39–7.05)	0.657
	Group IV	38	2	1.00 (1.00–1.00)	Reference
18.5–24.9	Group I	1645	883	1.83 (1.47–2.68)	<0.001
	Group II	1913	406	1.30 (1.07–1.58)	0.008
	Group III	2106	292	1.09 (0.90–1.31)	0.390
	Group IV	2019	212	1.00 (1.00–1.00)	Reference
25.0–29.9	Group I	1748	899	1.74 (1.43–2.12)	<0.001
	Group II	1908	493	1.29 (1.09–1.54)	0.004
	Group III	1931	393	1.21 (1.03–1.43)	0.022
	Group IV	2253	263	1.00 (1.00–1.00)	Reference
≥30	Group I	2076	799	1.60 (1.28–2.01)	<0.001
	Group II	1825	405	1.20 (0.98–1.47)	0.074
	Group III	1663	260	1.07 (0.88–1.30)	0.528
	Group IV	1495	183	1.00 (1.00–1.00)	Reference
Smoke status					
Never smoker	Group I	2786	1185	1.80 (1.44–2.24)	<0.001
	Group II	3108	497	1.23 (1.02–1.49)	0.034
	Group III	2954	292	1.12 (0.93–1.35)	0.220
	Group IV	2869	206	1.00 (1.00–1.00)	Reference
Current smoker	Group I	1294	643	1.92 (1.55–2.38)	<0.001
	Group II	1353	350	1.38 (1.14–1.68)	<0.001
	Group III	1497	306	1.26 (1.06–1.51)	0.010
	Group IV	1622	238	1.00 (1.00–1.00)	Reference
Fromer smoker	Group I	1523	829	1.71 (1.40–2.09)	<0.001
	Group II	1301	478	1.27 (1.06–1.53)	0.009
	Group III	1336	356	1.09 (0.92–1.31)	0.319
	Group IV	1314	216	1.00 (1.00–1.00)	Reference
Race					
Non–Hispanic white	Group I	2599	1559	1.83 (1.55–2.16)	<0.001
	Group II	2394	697	1.25 (1.08–1.46)	0.003
	Group III	2474	500	1.15 (1.00–1.33)	0.058
	Group IV	2691	326	1.00 (1.00–1.00)	Reference
Non–Hispanic black	Group I	1630	646	1.71 (1.33–2.20)	<0.001
	Group II	1552	337	1.34 (1.08–1.67)	0.009
	Group III	1318	228	1.12 (0.90–1.39)	0.319
	Group IV	1051	145	1.00 (1.00–1.00)	Reference
Mexican–American	Group I	803	348	1.68 (1.26–2.23)	<0.001
	Group II	1173	250	1.25 (0.99–1.59)	0.064
	Group III	1378	194	1.13 (0.91–1.41)	0.274
	Group IV	1498	166	1.00 (1.00–1.00)	Reference
Other	Group I	571	104	1.27 (0.66–2.46)	0.469
	Group II	643	41	0.87 (0.48–1.56)	0.634
	Group III	617	32	1.01 (0.58–1.77)	0.978
	Group IV	565	23	1.00 (1.00–1.00)	Reference

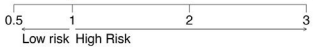

Fig. 2. Multivariable associations between prebronchodilator forced expiratory volume in 0.5 s and risk of all-cause mortality. Definition of abbreviations: BMI = body mass index; BD = bronchodilator; $FEV_{0.5}$ = forced expiratory volume in 0.5 s. Adjust for age, sex, smoking, body mass index, body surface area, race, educational level, poverty income ratio, and comorbidities.

Subgroup Analysis

Fig. 2 illustrates the association between $FEV_{0.5}$ and all-cause mortality risk across the various subgroups stratified by sex, age, BMI, race, and smoking status. The association between $FEV_{0.5}$ and all-cause mortality risk remained almost consistent even after stratifying the participants into subgroups by sex (male, female), age (20–40, 41–60, 61–80 years), race (Mexican–American, non-Hispanic White, non-Hispanic Black), BMI (normal, overweight, obese), and smoking status (never smoker, former smoker, current smoker). Among the male subgroup, individuals in groups I, II, and III exhibited an increased all-cause mortality risk when compared with individuals in group IV. However, among females, only those in group I demonstrated a significantly elevated risk of all-cause mortality when compared with individuals in group IV. In the subgroup stratified by other race and in the underweight subgroup, there was no statistically significant difference in the risk of all-cause mortality between individuals in groups I, II, and III and individuals in group IV. In subgroup with FEV_1 > LLN, FVC > LLN, or both FEV_1 and FVC > LLN, individuals in groups I, II, and III had a higher risk of all-cause mortality after adjustment compared with individuals in group IV (Table S1).

Non-Linear Association Between $FEV_{0.5}$ and All-Cause Mortality Risk

Fig. 3 illustrates the non-linear association between $FEV_{0.5}$ and all-cause mortality risk. The association between $FEV_{0.5}$ and all-cause mortality risk manifested as an L-shaped curve. With the exception of the other race subgroup and the underweight sub-

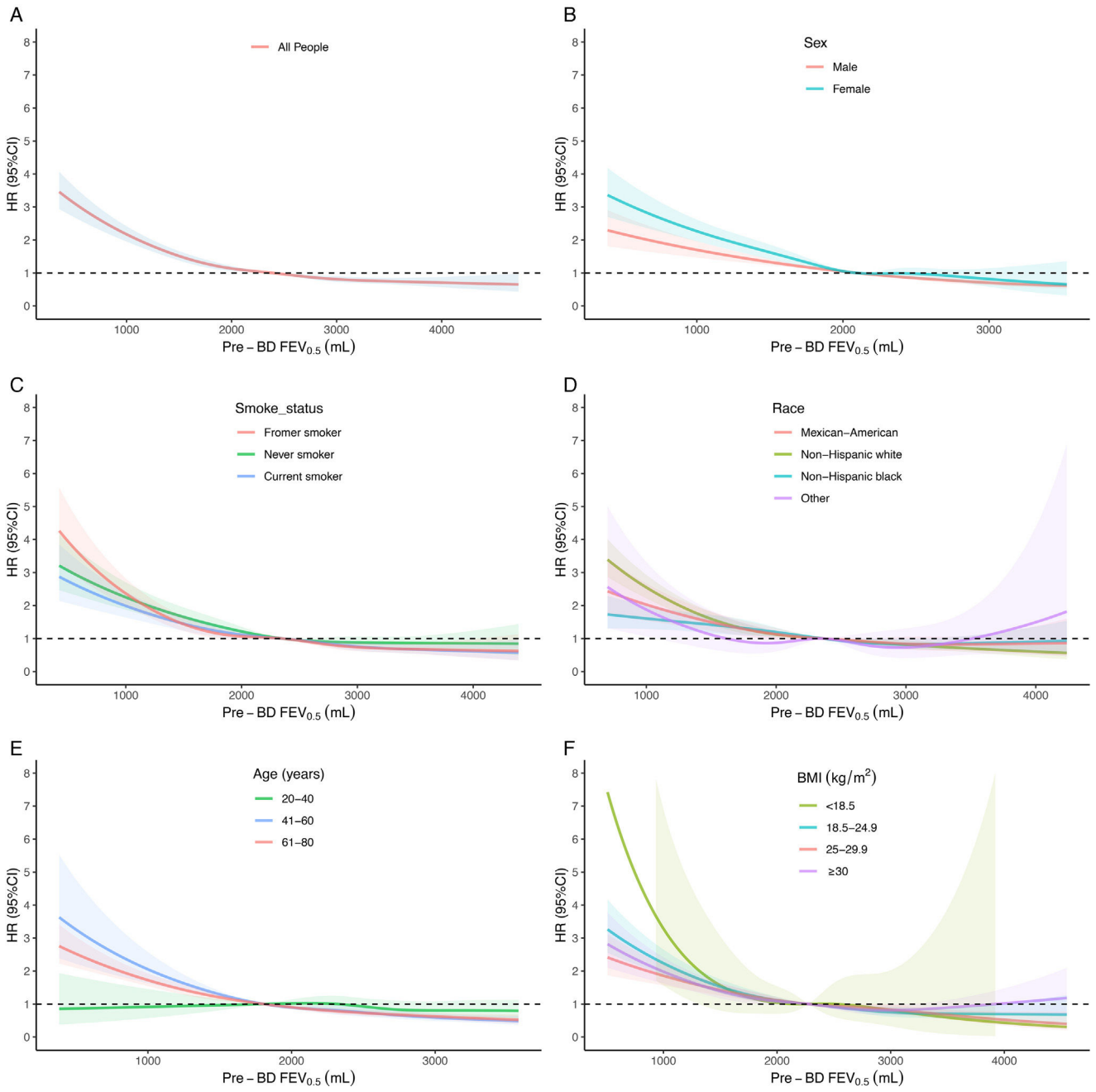

Fig. 3. Nonlinear associations between prebronchodilator forced expiratory volume in 0.5 s and risk of all-cause mortality. Definition of abbreviations: BMI = body mass index; BD = bronchodilator; $FEV_{0.5}$ = forced expiratory volume in 0.5 s. Adjust for age, sex, smoking, body mass index, body surface area, race, educational level, poverty income ratio, and comorbidities. Panel A shows the non-linear relationship between $FEV_{0.5}$ and risk of all-cause mortality in all participants. Panel B shows the non-linear relationship between $FEV_{0.5}$ and the risk of all-cause mortality in the male and female groups. Panel C shows the non-linear relationship between $FEV_{0.5}$ and the risk of all-cause mortality in populations with different smoking status. Panel D shows the non-linear relationship between $FEV_{0.5}$ and risk of all-cause mortality for people of different races. Panel E shows the non-linear relationship between $FEV_{0.5}$ and risk of all-cause mortality in different age groups. Panel F shows the non-linear relationship between $FEV_{0.5}$ and risk of all-cause mortality for people with different BMI.

group, a similar trend was observed in all subgroups stratified by sex, smoking status, age, race, and BMI.

Discussion

In the present study, adults with a lower $FEV_{0.5}$ exhibited an elevated presence of four chronic respiratory symptoms, eight comorbidities, and risk of all-cause mortality. An L-shaped non-linear association was observed between $FEV_{0.5}$ and all-cause mortality risk. The above results were mostly consistent in the subgroup analyses.

The present study builds on past research by extending the association between $FEV_{0.5}$ and respiratory health outcomes to the adult population. The associations between $FEV_{0.5}$ and the presence of non-respiratory diseases and risk of all-cause mortality have also been broadened. This provides a new perspective suggesting that $FEV_{0.5}$ is not only a measure of lung function, but that it may also be a biomarker of overall health.[2] The analysis results in the subgroups of FEV_1 > LLN, FVC > LLN, and both FEV_1 and FVC > LLN suggest that the clinical implementation of $FEV_{0.5}$ measurement may provide additional prognostic value beyond that of FEV_1 and FVC.

FEV_1 is a useful tool for categorizing the severity of obstructive lung diseases, including asthma and chronic obstructive pulmonary disease. Multiple studies have suggested associations between FEV_1 and a variety of diseases, including congestive heart failure, stroke, asthma, chronic bronchitis, emphysema, cancer, diabetes mellitus, hypertension, chronic cough, chronic phlegm, wheezing, and dyspnea.[17–26] Some studies have also indicated an association between FEV_1 and all-cause mortality risk.[27,28] The associations of FEV_1 with these comorbidities and chronic respiratory symptoms remained consistent when $FEV_{0.5}$ was evaluated instead of FEV_1 in the present study.

$FEV_{0.5}$ is defined as the volume of gas expelled from the lungs within half a second of the onset of expiration. $FEV_{0.5}$ provides insight into the patency of the airway during the initial expiration phase. Inflammation or structural alterations to the airway may result in alterations to airflow and a consequent change in $FEV_{0.5}$. Given that $FEV_{0.5}$ encompasses the initial phase of expiration, it may prove more susceptible than FEV_1 to the effects of inflammation or structural alterations. This is due to the fact that FEV_1 measures expiratory volume over the course of 1 s, which may encompass some degree of expiration driven by alveolar elastic retraction forces. Some studies have demonstrated that FEV_1 remains unimpaired during the initial stages of disease, and it has been observed that the decline in FEV_1 becomes evident several years later, which may mean that opportunities for early intervention are missed.[29,30] In contrast, $FEV_{0.5}$ is more specifically oriented toward the initial emptying of the airway. Consequently, the reduction in $FEV_{0.5}$ may be more pronounced than the reduction in FEV_1 during the initial stage of airway disease.

Although our study has made several important discoveries, there are also limitations that should be considered. First, given that the NHANES only performed postbronchodilator spirometry measurements in a limited number of individuals with airflow obstruction, therefore the present analysis was based on the prebronchodilator spirometry measurements, as these were obtained in the majority of the NHANES population. Some studies have demonstrated that postbronchodilator spirometry is a more accurate predictor of mortality than prebronchodilator spirometry, but the difference between the two is relatively minor.[31] The association between postbronchodilator $FEV_{0.5}$ and all-cause mortality risk still warrants further investigation. Therefore, we consider that our findings remain meaningful. Second, our study is based on NHANES 1988–1994 and 2007–12, while the standardization of spirometry was published in 2005.[9] NHANES 1988–1994 lacks data on the sharp initiation of the maneuver such as the back-extrapolated volume or time to PEF. Therefore, the quality of lung function tests in NHANES 1988–94 is determined solely based on the repeatability of FEV_1 and FVC, which may affect the accurate measurement of $FEV_{0.5}$. Third, we did not conduct further analyses on causes of mortality due to the absence of data on causes of mortality in NHANES 1988–94. Further research is needed to explore the association between $FEV_{0.5}$ and respiratory-related mortality. Fourth, since spirometry measurements were only obtained from the participants on a single occasion during the course of the NHANES, we were unable to examine the impact of $FEV_{0.5}$ decline on respiratory health outcomes. Finally, because the study population was restricted to US adults, our results may not be generalizable to individuals in other countries and regions.

Conclusions

In this study, $FEV_{0.5}$ was inversely associated with the increased risk of all-cause mortality, the presence of comorbidities, and chronic respiratory symptoms in adults.

Authors' Contributions

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

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Conflict of Interest

None.

Acknowledgments

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2024.12.006.

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