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ORIGINAL RESEARCH

Risk of All-Cause Mortality in Mild Chronic Obstructive Pulmonary Disease: Evidence From the NHANES III and 2007–2012

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Background: It is unclear whether patients with Global Initiative for Chronic Obstructive Lung Disease stage 1 (mild) chronic obstructive pulmonary disease (COPD) have a higher risk of all-cause mortality than participants with normal spirometry results.

Methods: We used the data from the National Health and Nutrition Examination Survey (NHANES) III and 2007–2012, which included participants aged 20–79 years, to investigate whether patients with mild COPD (whole population and subgroups) have a higher risk of all-cause mortality than participants with normal spirometry. Mild COPD was defined as prebronchodilator forced expiratory volume in 1 second /forced vital capacity <0.70 and FEV_1 ≥80% of the predicted value. All-cause mortality risk is the total risk of death from all causes over a given period of time. We performed subgroup analyses by sex, age, smoking status, race, body mass index, and level of education. We also performed sensitivity analyses using the lower limit of normal to define COPD.

Results: 1,760 patients (64.5% male; median aged 59 years) with mild COPD and 19,969 participants with normal spirometry (46.9% male; median aged 43 years) were followed up (median 308 months). Patients with mild COPD had a higher all-cause mortality risk than participants with normal spirometry (adjusted: Hazard Ratios 1.13, 95% Confidence Intervals 1.04–1.23; P = 0.005). The results remained robust in the sensitivity analyses. The subgroup analyses results for male sex, age ≥50 years, and current smokers were consistent with the main analysis.

Conclusion: Patients with mild COPD had a higher all-cause mortality risk than those with normal spirometry, especially males, those aged ≥50 years, and current smokers. These results suggest the need for appropriate management of different subgroups with mild COPD.

Keywords: mild COPD, all-cause mortality, chronic obstructive pulmonary disease, COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease characterized by chronic respiratory symptoms due to persistent and often progressive airflow obstruction resulting from airway and/or alveolar abnormalities (emphysema).[1] It is estimated that more than 5.4 million people will die annually from COPD and related diseases by 2060, and COPD is one of the top three causes of death globally, placing a huge burden on healthcare services and society.[2,3] A better understanding of the natural history of COPD, including the risk of progression associated with

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spirometry test results, could inform treatment and preventive management policies and improve prognosis by reducing the burden of disease through subsequent follow-up and management.

Mild COPD is defined as COPD with mild airflow obstruction according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria, including postbronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.70 and FEV_1 ≥80% of the predicted value.[1,4] The reported prevalence of mild COPD ranges from 2.5% (European Community Respiratory Health Survey of adults aged 20–44 years in high-income countries) to 8.1% (BOLD study of adults aged ≥40 years).[5–7] Symptoms in patients with mild COPD are usually mild and may be overlooked by patients and physicians as being a consequence of smoking and aging. This can mean that patients do not seek medical advice until the disease has worsened.[4] Patients with mild COPD often receive limited or no treatment. However, studies have shown that patients with mild COPD experience accelerated FEV_1 decline and frequent exacerbations, and they may have a lower quality of life than individuals with normal spirometry.[8–11] Moreover, exercise tolerance, diffusion capacity of the lungs for carbon monoxide, and gas exchange can be impaired in patients with mild COPD.[7] Patients with mild COPD are at high risk of disease progression, contributing to the significant disease burden.[8] However, there is controversy among studies as to whether the risk of all-cause mortality is higher in patients with mild COPD and in different subgroups of patients with mild COPD (eg, males, females, different age groups, smokers, non-smokers) than in individuals with normal spirometry.[12–14]

With this in mind, the aim of this study is to explore the relationship between mild COPD and all-cause mortality in the overall population and in subgroups with mild COPD. Identifying patients with mild COPD who are most in need of treatment is useful to achieve early prevention and management and reduce the disease burden.

Methods

Study Participants and Design

The National Health and Nutrition Examination Survey (NHANES) is a survey with a multi-stage, complex, probability sampling design. It is conducted by the Centers for Disease Control and Prevention and was designed to assess the health and nutritional status of the non-institutionalized US population. The survey consists of interviews, physical examinations, and laboratory tests.

In the present study, a total of 50,492 participants were included from the NHANES III (1988–1994) and three subsequent NHANES cycles (2007–2008, 2009–2010, and 2011–2012) from which spirometry data were available. The participants provided written informed consent to participate in the NHANES according to the protocol approved by the National Center for Health Statistics Research Ethics Review Board.[15–18] The mortality status and follow-up time of all participants were extracted from the National Death Index by 31 December 2019.

The participant inclusion criteria were as follows: (1) aged 20–79 years; (2) available qualifying pulmonary function data (participants with a reproducible FEV_1 measurement with ≥2 acceptable trials in the NHANES III,[19] and efforts with at least grade B quality according to American Thoracic Society standards for acceptability and reproducibility in NHANES 2007–2012);[20] and (3) available qualifying follow-up data on all-cause mortality. The participant exclusion criteria were as follows: (1) aged <20 years or ≥80 years; (2) unavailable lung function data; (3) unacceptable spirometry; (4) pregnant women; (5) incomplete physical measurements; (6) unavailable information on smoking status; (7) preserved ratio with impaired spirometry (PRISm; defined as a prebronchodilator FEV_1/FVC ≥0.70 with FEV_1 <80% of the predicted value); and (8) no follow-up time for death.

Definitions of Normal Spirometry, Mild COPD, and GOLD II–IV COPD

Prebronchodilator rather than postbronchodilator spirometry values were considered due to the lack of bronchodilator testing for most subjects in the NHANES. COPD was defined as prebronchodilator FEV_1/FVC <0.70, which is different from the GOLD definition.[1] Normal spirometry was defined as prebronchodilator FEV_1/FVC ≥0.70 and FEV_1 ≥80% of the predicted value. Mild COPD was defined as prebronchodilator FEV_1/FVC <0.70 and FEV_1 ≥80% of the predicted value. GOLD stage II–IV COPD was defined as prebronchodilator FEV_1/FVC <0.70 and FEV_1 <80% of the predicted value. Percent-predicted FEV_1 and FVC were calculated according to the NHANES III value prediction formula.[21]

Covariate Definitions

The following covariate data were collected: (1) demographic characteristics, including age, sex, race, level of education, marital status, and poverty-to-income ratio (PIR); (2) physical examination results, including height, weight, and body mass index (BMI); (3) disease history, including hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, cancer, chronic bronchitis, and emphysema; and (4) respiratory symptoms, including chronic cough, chronic phlegm, and wheezing. The PIR was estimated as the ratio of family income to the poverty threshold, and the participants were divided into low-income (PIR < 1.30), middle-income (1.30 ≤ PIR < 3.50), and high-income (PIR ≥ 3.50) groups. BMI was calculated by dividing the weight (in kg) by the height (in meters squared [m^2]) and classified as <18.5 kg/m^2 (underweight), ≥18.5–25.0 kg/m^2 (normal), ≥25.0–29.9 kg/m^2 (overweight), or ≥30.0 kg/m^2 (obese). The level of education was categorized as <9th grade, 9th–12th grade, and >12th grade. Smoking status was grouped into never smokers, former smokers, and current smokers. When asked the question, "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"). Marital status was grouped as married or living with a partner or unmarried, including widowed, divorced, separated, and never married. Disease history items, including hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, cancer, chronic bronchitis, and emphysema, were ascertained by self-reported physician diagnosis. With regard to cancer history, other cancers and skin cancers were included in the NHANES III, while a history of any type of cancer was included in the 2007–2012 NHANES. The participants were categorized as having respiratory symptoms if they answered "Yes" to the following questions: 1) for cough ≥3 months in a year, "Do you cough on most days for ≥3 consecutive months during the year?"; 2) for phlegm ≥3 months in the past year, "Do you bring up phlegm on most days for 3 consecutive months or more during the year?"; and 3) for wheezing in the past year, "In the past 12 months, have you had wheezing or whistling in your chest?"

Outcomes

The primary outcome was all-cause mortality in patients with mild COPD compared with those with normal spirometry. The secondary outcome was all-cause mortality in subgroups of patients with mild COPD compared with participants with normal spirometry. Death information records were linked to the NHANES data using the Respondent Sequence Number (the unique sequence number for each participant). All participants with adequately identified data were eligible for linkage to mortality data. Linking to the National Death Index was performed by the Research Data Center of the National Center for Health Statistics.[22]

Statistical Analyses

Normally distributed continuous variables are presented as the mean ± standard deviation, while non-normally distributed continuous variables are expressed as the median (interquartile range). Categorical variables are presented as frequency and percentage. Continuous variables were compared between groups using *t*-tests or non-parametric tests, while categorical variables were compared using the chi-square test or Fisher's exact test. We performed the Kaplan–Meier survival analysis to explore the differences in event-free survival. Multivariable Cox regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the relationship between mild COPD and all-cause mortality risk. Two multivariable models were constructed. Model 1 was adjusted for sex, age, BMI, and race. Model 2 was adjusted for sex, age, BMI, race, smoking status, hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, and cancer. These covariates were chosen because we considered them to be clinically relevant confounders in the relationship between mild COPD and all-cause mortality risk. Subgroup analyses were also performed to assess all-cause mortality from mild COPD in different subgroups by sex (male and female), age (<50 and ≥50 years), race (non-Hispanic White, non-Hispanic Black, Mexican-American, and other races), smoking status (never smoker, current smoker, and former smoker), BMI (underweight, normal, overweight, and obese), and level of education (<9th grade, 9th–12th grade, >12th grade). To test the robustness of the model, we performed two sensitivity analyses. We used the lower limit of normal (LLN) instead of a fixed ratio to define spirometric obstruction.[23] In sensitivity analysis 1,

normal spirometry was defined as a prebronchodilator $FEV_1/FVC \geq LLN$ and $FEV_1 > 80\%$ of the predicted value, while a prebronchodilator $FEV_1/FVC < LLN$ and $FEV_1 \geq 80\%$ of the predicted value was defined as mild COPD. In sensitivity analysis 2, normal spirometry was defined as a prebronchodilator $FEV_1/FVC \geq LLN$ and $FEV_1 \geq LLN$, while mild COPD was defined as a prebronchodilator $FEV_1/FVC < LLN$ and $FEV_1 \geq LLN$. A two-sided p value of <0.05 was considered statistically significant. All analyses were performed using SPSS 25.0 and R software (version 4.2.2).

Exemption From Ethical Statements

The data for this study were approved by the National Health Statistics Research Ethics Review Board and all participants provided written informed consent to participate in NHANES. This study was exempted from approval according to national legal guidelines (item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China).

Results

Baseline Characteristics of the Participants

Initially, 50,492 participants were enrolled. After applying the rigorous selection criteria, 17,013 participants aged <20 years or ≥80 years, 5,616 without lung function data, 2,816 with unacceptable spirometry results, 262 who were pregnant, 58 without complete body measurements, 7 without available information on smoking status, 1,453 with PRISm, and 28 without information on the follow-up to death were excluded. Ultimately, 23,239 participants were eligible for inclusion. The study flowchart is shown in Figure 1.

Table 1 shows the characteristics of the participants. Overall, 1,760 participants had mild COPD (64.5% male; median aged 59 years) and 19,969 had normal spirometry (46.9% male; median aged 43 years). Compared with the normal spirometry group, the mild COPD group had a higher median age (62 [49–70] years vs 40 [30-54] years) and a greater proportion of males (64.5%). In addition, the mild COPD group had a higher proportion of current (31.0%) and former

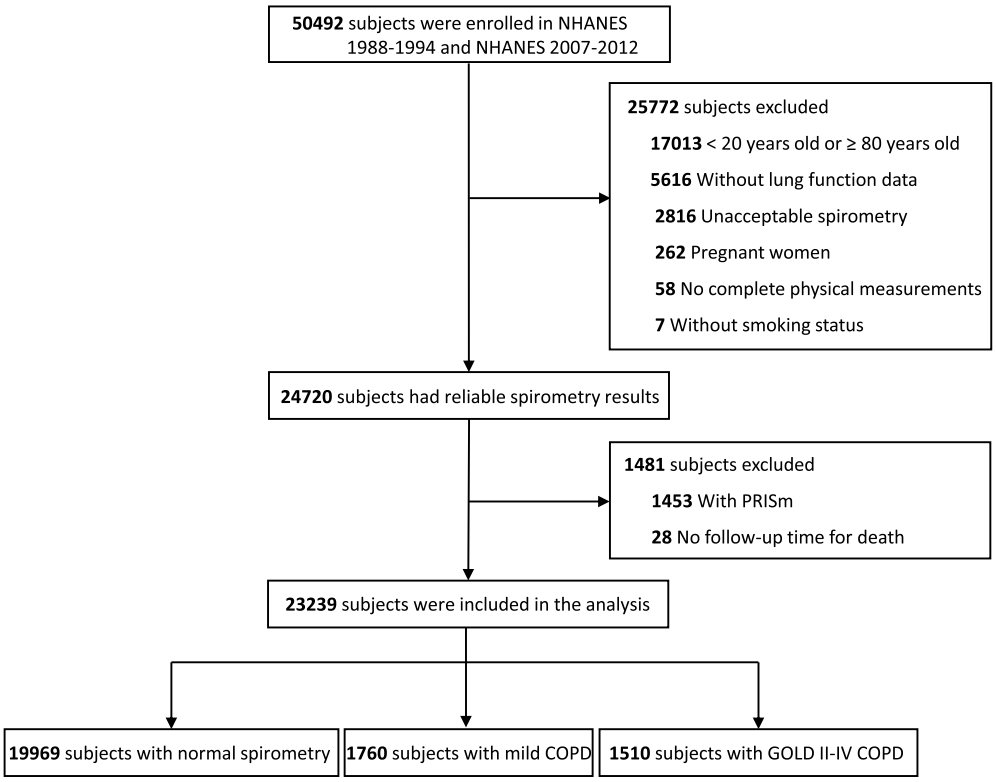

Figure 1 Study flowchart.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; PRISm, preserved ratio with impaired spirometry; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 1 Baseline Clinical Characteristics of the Participants With Different Spirometry Classifications

Characteristic	Normal Spirometry (N=19969)	Mild COPD (N=1760)	P value*	GOLD II–IV COPD (N=1510)	P value†
Age, years	40 (30–54)	62 (49–70)	<0.001	62 (51–70)	0.387
Male sex, n (%)	9368 (46.9)	1135 (64.5)	<0.001	866 (57.4)	<0.001
Body mass index, kg/m^2	27.0 (23.7–31.2)	25.9 (23.3–28.9)	<0.001	26.7 (23.0–30.8)	<0.001
Race, n (%)			<0.001		<0.001
Non-Hispanic white	7695 (38.5)	1031 (58.6)		937 (62.1)	
Non-Hispanic black	4944 (24.8)	332 (18.9)		350 (23.2)	
Mexican-American	4928 (24.7)	243 (13.8)		151 (10.0)	
Other	2402 (12.0)	154 (8.8)		72 (4.8)	
Smoking status, n (%)			<0.001		<0.001
Never smoker	11025 (55.2)	562 (31.9)		335 (22.2)	
Current smoker	4701 (23.5)	545 (31.0)		663 (43.9)	
Former smoker	4243 (21.2)	653 (37.1)		512 (33.9)	
Education Level, n (%)			<0.001		<0.001
Less than 9th grade	2833 (14.2)	320 (18.3)		313 (20.8)	
9th–12th grade	8535 (42.9)	751 (42.8)		722 (48.0)	
Above 12th grade	8535 (42.9)	682 (38.9)		470 (31.2)	
Poverty income ratio, n (%)			<0.001		<0.001
Low-income (PIR < 1.3)	5584 (28.0)	408 (23.2)		454 (30.1)	
Middle-income (1.30≤PIR<3.50)	7471 (37.4)	654 (37.2)		582 (38.5)	
High-income (PIR ≥3.50)	5256 (26.3)	544 (30.9)		355 (23.5)	
Respiratory symptoms, n (%)	3384 (17.0)	450 (25.6)	<0.001	700 (46.4)	<0.001
Chronic cough	1094 (5.5)	176 (10.0)	<0.001	309 (20.5)	<0.001
Chronic phlegm	1094 (5.5)	184 (10.5)	<0.001	285 (18.9)	<0.001
Wheezing	2335 (11.7)	298 (17.0)	<0.001	550 (36.4)	<0.001
FEV_1, L	3.18 (2.64–3.81)	2.77 (2.26–3.30)	<0.001	1.84 (1.43–2.28)	<0.001
FVC, L	3.91 (3.26–4.69)	4.19 (3.41–4.99)	<0.001	3.13 (2.50–3.86)	<0.001
FEV_1/FVC, %	81.1 (77.1–85.0)	67.0 (64.3–68.8)	<0.001	61.0 (54.2–66.0)	<0.001
Comorbidities, n (%)					
Hypertension	4936 (24.8)	620 (35.3)	<0.001	666 (44.3)	<0.001
Diabetes	1466 (7.3)	151 (8.6)	0.164	217 (14.4)	<0.001
Cancer	1004 (5.0)	232 (13.2)	<0.001	227 (15.0)	0.128
Asthma	1667 (8.4)	229 (13.0)	<0.001	368 (24.4)	<0.001
Chronic bronchitis	774 (3.9)	120 (6.8)	<0.001	242 (16.1)	<0.001
Emphysema	90 (0.5)	43 (2.4)	<0.001	175 (11.6)	<0.001

Notes: *Comparison between participants with normal spirometry and patients with mild COPD. †Comparison between patients with mild COPD and patients with GOLD II–IV COPD.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PIR, poverty-to-income ratio; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

smokers (37.1%), and a lower proportion of never smokers (31.9%). The mild COPD group had a higher proportion of patients with respiratory symptoms than the normal spirometry group, including sputum (10.5% vs 5.5%), cough (10.0% vs 5.5%), and wheezing (17.0% vs 11.7%). The proportion of patients with comorbidities in the mild COPD group was also higher than in the normal spirometry group, including hypertension (35.3% vs 24.8%), cancer (13.2% vs 5.0%), asthma (13.0% vs 8.4%), chronic bronchitis (6.8% vs 3.9%), and emphysema (2.4% vs 0.5%).

Association Between Mild COPD and All-Cause Mortality

During the median 308-month follow-up period, 5,116 of the 23,239 participants with follow-up (22.0%) died, including 3,535 with normal spirometry (17.7%), 738 with mild COPD (41.9%), and 843 with GOLD stage II–IV COPD (55.8%). Patients with mild COPD had higher unadjusted mortality rates than participants with normal spirometry (Figure 2).

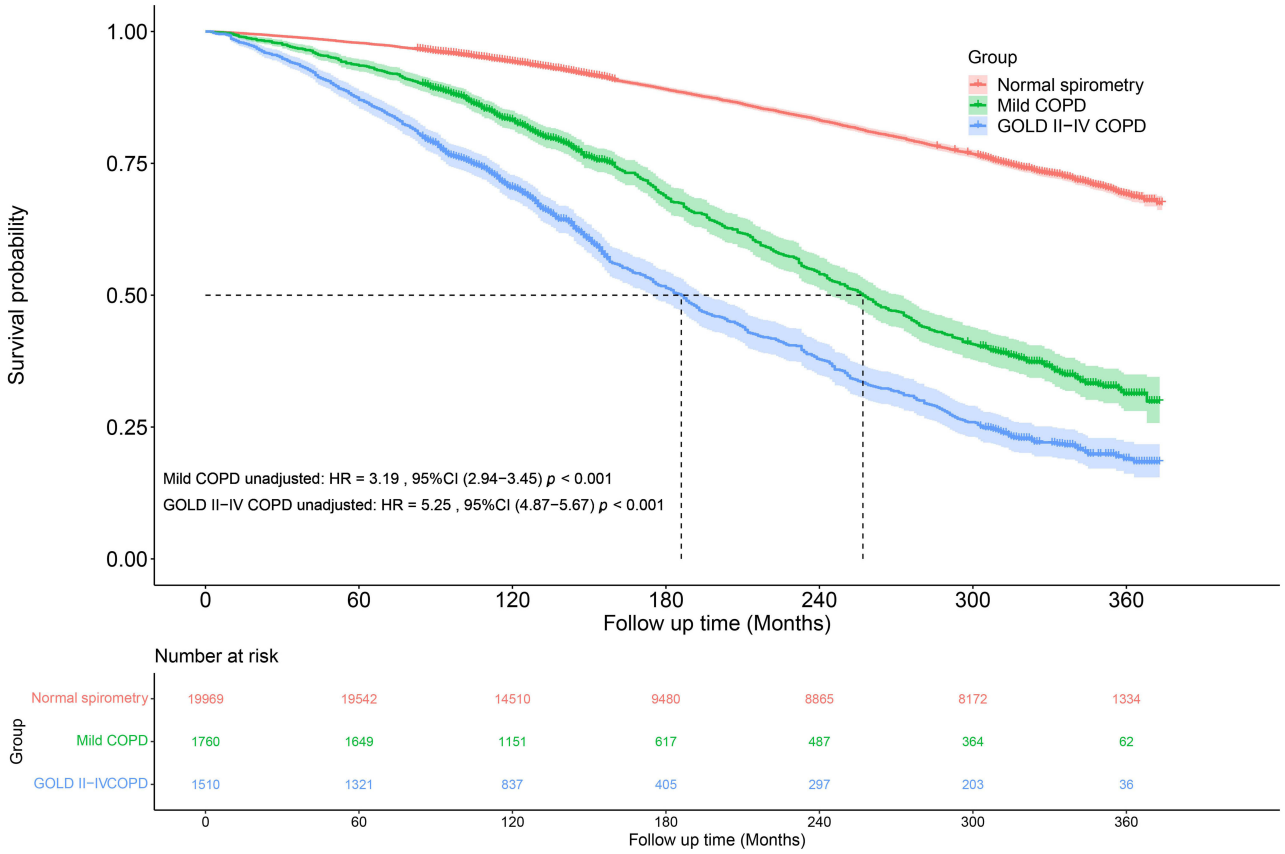

Figure 2 All-cause mortality risk of participants with different spirometry classifications.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; CI, confidence interval.

Table 2 shows the HRs and 95% CIs for all-cause mortality by spirometry category. Patients with mild COPD had a higher risk of all-cause mortality than participants with normal spirometry in the unadjusted model (crude model: HR 3.19, 95% CI 2.94–3.45; P < 0.001). These associations remained significant after adjusting for sex, age, BMI, race (Model 1: HR 1.18, 95% CI 1.08–1.28; P < 0.001), as well as after adjusting for smoking status, hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, and cancer in addition to the factors adjusted in Model 1 (Model 2: HR 1.13, 95% CI 1.04–1.23; P = 0.005).

Sensitivity Analysis

Table 2 shows the results of the sensitivity analysis of the relationship between mild COPD and all-cause mortality. When the LLN criteria were used to define the spirometry categories, the primary outcome of all-cause mortality risk was consistent with the fixed-threshold criteria. Both in sensitivity analysis 1 (adjusted: HR 1.14, 95% CI 1.05–1.24; P = 0.002) and sensitivity analysis 2 (adjusted: HR 1.12, 95% CI 1.02–1.24; P = 0.020), we observed a higher all-cause mortality risk in patients with mild COPD than in those with normal spirometry.

Subgroup Analysis

In the univariable model, patients with mild COPD in all subgroups had a higher risk of all-cause mortality than individuals with normal spirometry. In the multivariable models adjusted for sex, age, BMI, race, smoking status, hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, and cancer, the results of the subgroup analyses for males (HR 1.16, 95% CI 1.04–1.29; P = 0.008), those aged ≥50 years (HR 1.14, 95% CI 1.04–1.24; P = 0.005), current smokers (HR 1.24, 95% CI 1.06–1.46; P = 0.007), those classified as normal weight (HR 1.19, 95% CI 1.03–1.36; P = 0.015), those classified as overweight (HR 1.15, 95% CI 1.01–1.31; P = 0.037), and those with a level of education of

Table 2 Mortality Estimates From the Cox Regression Analysis Stratified by Spirometry Category

Classification	No. of Participants	No. of Deaths (%)	Crude Model*		Model 1†		Model 2‡	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Main analysis								
Normal spirometry	19969	3535 (17.7)	Reference		Reference		Reference	
Mild COPD	1760	738 (41.9)	3.19 (2.94–3.45)	<0.001	1.18 (1.08–1.28)	<0.001	1.13 (1.04–1.23)	0.005
GOLD II–IV COPD	1510	843 (55.8)	5.25 (4.87–5.67)	<0.001	2.08 (1.92–2.25)	<0.001	1.71 (1.58–1.86)	<0.001
Sensitivity analysis 1§								
Normal spirometry	19988	3546 (17.7)	Reference		Reference		Reference	
Mild COPD	1772	754 (42.6)	3.24 (3.00–3.51)	<0.001	1.20 (1.10–1.30)	<0.001	1.14 (1.05–1.24)	0.002
GOLD II–IV COPD	1498	827 (55.2)	5.18 (4.80–5.59)	<0.001	2.06 (1.90–2.23)	<0.001	1.68 (1.55–1.83)	<0.001
Sensitivity analysis 2¶								
Normal spirometry	20921	4243 (20.3)	Reference		Reference		Reference	
Mild COPD	1641	479 (29.2)	1.59 (1.45–1.75)	<0.001	1.23 (1.11–1.35)	<0.001	1.12 (1.02–1.24)	0.020
GOLD II–IV COPD	1067	533 (50.0)	3.61 (3.30–3.95)	<0.001	2.18 (1.99–2.39)	<0.001	1.76 (1.59–1.93)	<0.001

Notes: *Crude model: No covariates were adjusted. †Model 1: Adjusted covariates for Model 1 included sex, age, body mass index, race. ‡Model 2: Adjusted covariates for Model 2 included sex, age, body mass index, race, smoking status, hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, and cancer. §Normal spirometry was defined as an FEV_1/FVC ratio ≥LLN and FEV_1 >80% of the predicted value. Mild COPD was defined as an FEV_1/FVC ratio <LLN and FEV_1 of ≥80% of the predicted value. GOLD II–IV COPD was defined as an FEV_1/FVC ratio <LLN and FEV_1 <80% of the predicted value. ¶Normal spirometry was defined as an FEV_1/FVC ratio ≥LLN and FEV_1 ≥LLN. Mild COPD was defined as an FEV_1/FVC ratio <LLN and FEV_1 ≥LLN. GOLD II–IV COPD was defined as an FEV_1/FVC ratio <LLN and FEV_1 <LLN.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; CI, confidence interval; LLN, lower limit of normal.

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9th–12th grade (HR 1.15, 95% CI 1.01–1.30; P = 0.029) were consistent with the results of the main study. The all-cause mortality risk was not higher in those with mild COPD compared with those with normal spirometry in the following subgroups: females, those aged <50 years, never smokers, former smokers, those classified as underweight/obese, and those with a level of education <9th grade or >12th grade. Moreover, the all-cause mortality risk was not greater when patients with mild COPD were analyzed by race (Table 3).

Table 3 Subgroup Analysis of the Risk of All-Cause Mortality for Different Spirometry Classifications

Subgroup	No. of Participants	No. of Deaths (%)	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Sex						
Male	11369	2789 (24.5)				
Normal spirometry	9368	1799 (19.2)	Reference		Reference	
Mild COPD	1135	488 (43.0)	3.07 (2.78–3.39)	<0.001	1.16 (1.04–1.29)	0.008
GOLD II–IV COPD	866	502 (58.0)	5.22 (4.72–5.77)	<0.001	1.67 (1.49–1.86)	<0.001
Female	11870	2327 (19.6)				
Normal spirometry	10601	1736 (16.4)	Reference		Reference	
Mild COPD	625	250 (40.0)	3.10 (2.72–3.54)	<0.001	1.07 (0.93–1.22)	0.376
GOLD II–IV COPD	644	341(53.0)	5.08 (4.52–5.71)	<0.001	1.82 (1.60–2.07)	<0.001
Age						
<50 years old	14312	1229 (8.6)				
Normal spirometry	13533	1110 (8.2)	Reference		Reference	
Mild COPD	447	51 (11.4)	1.52 (1.15–2.01)	0.003	1.08 (0.81–1.43)	0.612
GOLD II–IV COPD	332	68 (20.5)	3.16 (2.47–4.04)	<0.001	1.93 (1.48–2.50)	<0.001
≥50 years old	8927	3887 (43.5)				
Normal spirometry	6436	2425 (37.7)	Reference		Reference	
Mild COPD	1313	687 (52.3)	1.58 (1.45–1.71)	<0.001	1.14 (1.04–1.24)	0.005
GOLD II–IV COPD	1178	775 (65.8)	2.53 (2.33–2.74)	<0.001	1.76 (1.61–1.92)	<0.001
Smoking status						
Never smoker	11922	1892 (15.9)				
Normal spirometry	11025	1552 (14.1)	Reference		Reference	
Mild COPD	562	198 (35.2)	3.30 (2.84–3.82)	<0.001	1.09 (0.93–1.27)	0.284
GOLD II–IV COPD	335	142 (42.4)	4.20 (3.54–4.99)	<0.001	1.75 (1.46–2.10)	<0.001
Current smoker	5909	1535 (26.0)				
Normal spirometry	4701	916 (19.5)	Reference		Reference	
Mild COPD	545	223 (40.9)	2.95 (2.55–3.42)	<0.001	1.24 (1.06–1.46)	0.007
GOLD II–IV COPD	663	396 (59.7)	5.55 (4.92–6.26)	<0.001	1.91 (1.66–2.19)	<0.001
Former smoker	5408	1689 (31.2)				
Normal spirometry	4243	1067 (25.2)	Reference		Reference	
Mild COPD	653	317 (48.6)	2.55 (2.25–2.90)	<0.001	1.08 (0.95–1.23)	0.251
GOLD II–IV COPD	512	305 (59.6)	4.17 (3.67–4.74)	<0.001	1.69 (1.47–1.94)	<0.001

(*Continued*)

Table 3 (Continued).

Subgroup	No. of Participants	No. of Deaths (%)	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Race						
Non-Hispanic white	9663	2571 (26.6)				
Normal spirometry	7695	1565 (20.3)	Reference		Reference	
Mild COPD	1031	461 (44.7)	2.81 (2.53–3.12)	<0.001	1.10 (0.98–1.22)	0.102
GOLD II–IV COPD	937	545 (58.2)	4.85 (4.39–5.35)	<0.001	1.97 (1.76–2.20)	<0.001
Non-Hispanic black	5626	1315 (23.4)				
Normal spirometry	4944	980 (19.8)	Reference		Reference	
Mild COPD	332	150 (45.2)	3.24 (2.73–3.85)	<0.001	1.16 (0.97–1.39)	0.113
GOLD II–IV COPD	350	185 (52.9)	4.52 (3.85–5.29)	<0.001	1.35 (1.13–1.61)	0.001
Mexican-American	5322	1023 (19.2)				
Normal spirometry	4928	830 (16.8)	Reference		Reference	
Mild COPD	243	104 (42.8)	3.41 (2.78–4.18)	<0.001	1.17 (0.94–1.45)	0.170
GOLD II–IV COPD	151	89 (58.9)	5.17 (4.16–6.44)	<0.001	1.51 (1.20–1.90)	0.001
Other	2628	207 (7.9)				
Normal spirometry	2402	160 (6.7)	Reference		Reference	
Mild COPD	154	23 (14.9)	2.58 (1.67–4.00)	<0.001	1.22 (0.77–1.93)	0.396
GOLD II–IV COPD	72	24 (33.3)	5.72 (3.72–8.79)	<0.001	1.71 (1.03–2.83)	0.038
BMI						
<18.5 kg/m^2 (underweight)	347	91 (26.2)				
Normal spirometry	261	36 (13.8)	Reference		Reference	
Mild COPD	26	12 (46.2)	4.35 (2.26–8.39)	<0.001	1.37 (0.61–3.07)	0.451
GOLD II–IV COPD	60	43 (71.7)	10.68 (6.76–16.88)	<0.001	1.64 (0.90–3.01)	0.108
≥18.5–25 kg/m^2 (normal)	7869	1622 (20.6)				
Normal spirometry	6647	1006 (15.1)	Reference		Reference	
Mild COPD	711	301 (42.3)	4.05 (3.56–4.61)	<0.001	1.19 (1.03–1.36)	0.015
GOLD II–IV COPD	511	315 (61.6)	7.38 (6.50–8.39)	<0.001	1.93 (1.67–2.24)	<0.001
≥25–30 kg/m^2 (overweight)	8013	1865 (23.3)				
Normal spirometry	6834	1296 (19.0)	Reference		Reference	
Mild COPD	690	308 (44.6)	3.23 (2.85–3.66)	<0.001	1.15 (1.01–1.31)	0.037
GOLD II–IV COPD	489	261 (53.4)	4.69 (4.10–5.37)	<0.001	1.54 (1.33–1.78)	<0.001
≥30 kg/m^2 (obese)	7010	1538 (21.9)				
Normal spirometry	6227	1197 (19.2)	Reference		Reference	
Mild COPD	333	117 (35.1)	2.26 (1.87–2.73)	<0.001	0.93 (0.76–1.13)	0.475
GOLD II–IV COPD	450	224 (49.8)	3.74 (3.24–4.31)	<0.001	1.61 (1.38–1.88)	<0.001
Education level						
Less than 9th grade	3466	1349 (38.9)				
Normal spirometry	2833	927 (32.7)	Reference		Reference	
Mild COPD	320	201 (62.8)	2.74 (2.35–3.20)	<0.001	1.13 (0.96–1.34)	0.133
GOLD II–IV COPD	313	221 (70.6)	3.63 (3.13–4.20)	<0.001	1.26 (1.07–1.49)	0.006

(*Continued*)

https://doi.org/10.2147/COPD.S497634

Table 3 (Continued).

Subgroup	No. of Participants	No. of Deaths (%)	Univariate Models		Multivariate Model*	
			HR (95% CI)	P value	HR (95% CI)	P value
9th–12th grade	10008	2434 (24.3)				
Normal spirometry	8535	1679 (19.7)	Reference		Reference	
Mild COPD	751	336 (44.7)	3.24 (2.88–3.64)	<0.001	1.15 (1.01–1.30)	0.029
GOLD II–IV COPD	722	419 (58.0)	5.10 (4.58–5.69)	<0.001	1.82 (1.62–2.05)	<0.001
Above 12th grade	9685	1308 (13.5)				
Normal spirometry	8533	914 (10.7)	Reference		Reference	
Mild COPD	682	196 (28.7)	3.33 (2.85–3.89)	<0.001	1.06 (0.90–1.25)	0.483
GOLD II–IV COPD	470	198 (42.1)	6.48 (5.55–7.56)	<0.001	2.01 (1.69–2.38)	<0.001

Notes: *Adjusted covariates included sex, age, BMI, race, smoking status, hypertension, diabetes mellitus, congestive heart failure, stroke, asthma, and cancer.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PIR, poverty-to-income ratio; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Discussion

We confirmed the higher risk of all-cause mortality in patients with mild COPD compared with those with normal spirometry in the overall population, as well as in specific subgroups, including males, patients aged ≥50 years, and current smokers.

Patients with mild COPD seldom visit the clinic and are rarely diagnosed due to the paucity of chronic respiratory symptoms, and the occurrence of acute exacerbations is uncommon. However, previous studies have found that a certain percentage of patients have chronic respiratory symptoms and a small percentage of patients have acute exacerbations, both of which are associated with rapid lung function decline.[9,24] Moreover, it has been shown that patients with mild COPD have a poor prognosis, which is consistent with the results of our previous meta-analysis.[25] Although patients with mild COPD have few symptoms and few acute exacerbations, they have a rapid decline in lung function and a high risk of all-cause mortality in the long-term. Therefore, patients with mild COPD should be managed with the necessary interventions and follow-up to reduce the likelihood of a poor prognosis.

The present study showed that in the subgroup of current smokers, patients with mild COPD had a higher risk of all-cause mortality than those with normal spirometry, whereas no such relationship was found in the subgroups of never smokers and former smokers. It is well known that smoking is a major risk factor for the development of COPD, as well as its progression and death from COPD, and it is the only behavioral risk that can be controlled.[24] Smoking is known to cause chronic bronchial and systemic inflammation, which may exacerbate impaired lung function, promote target organ damage, and increase mortality risk.[26,27] It has been reported that exposure to cigarette smoke leads to extracellular matrix destruction, inadequate blood supply, and death of lung epithelial cells.[28,29] In a previous study, the mean rate of decline in FEV_1 was substantially higher in continuous smokers than in never smokers.[30] Smoking cessation is essential for the prevention and control of COPD. This is because quitting smoking not only reduces the risk of developing COPD, but it also reduces lung function decline over time in patients diagnosed with COPD.[31] There is an increasing body of evidence suggesting that smoking cessation reduces COPD symptoms, COPD exacerbations, hospitalizations, and mortality.[31] Previous studies have shown that adults with COPD are more likely to report current smoking, which may be related to nicotine dependence, making it more difficult to quit.[24] Another study showed that smoking cessation slows the accelerated decline in lung function and improves survival compared with continued smoking.[32] Evidence-based smoking cessation treatments are available, including Food and Drug Administration-approved smoking cessation medications and behavioral interventions. These treatments increase the likelihood of successful cessation, especially when used in combination.[31] Smoking cessation treatment in patients with mild COPD may reduce the accelerated

decline in lung function or increased mortality that characterizes this disease.[33] The Lung Health Study has also convincingly demonstrated the long-term benefits of sustained and, to a lesser extent, intermittent smoking cessation on FEV_1 in patients with mild COPD.[32]

In the present study, we found that mild COPD was associated with a higher risk of all-cause mortality in the male subgroup of patients with mild COPD, but the same relationship was not observed in the female subgroup. Previous studies have also indicated that male patients with COPD have poorer survival than female patients, which may be due to phenotypic differences in COPD between males and females. In particular, chronic bronchitis is more common in females, while emphysema is more common in males, with the latter demonstrating a more rapid decline in lung function and a higher mortality rate.[24,34]

We also observed a higher risk of all-cause mortality in the mild COPD group than in the normal spirometry group in the subgroup aged ≥50 years, while the all-cause mortality risk was not higher in the subgroup aged <50 years. This result may be related to the duration of follow-up, as these patients had a short follow-up period, and although no significant difference in all-cause mortality risk was observed for the subgroup aged <50 years, the presence of all-cause mortality risk in this population should not be discounted. It is known that lung function generally peaks at around the age of 20–25 years and begins to decline around the age of 40–50 years. Moreover, it is becoming increasingly clear that respiratory diseases, especially COPD, originate early in life. They affect the lungs early on in growth and development, and they develop over the course of many years, which in turn affects the lung condition.[1,35,36] COPD manifests more in middle-aged and older populations with significant morbidity and mortality, and it is possible that structural and functional lung abnormalities of varying degrees are present in these populations at a young age, but they may not be severe enough to be of concern.[37] Even though we observed no increase in the risk of all-cause mortality in the subgroup aged <50 years compared with the population with normal spirometry, it again cannot be excluded that mild COPD is associated with a higher risk of all-cause mortality in this population.

Strengths and Limitations

Our study has several strengths. First, the data used for this study were based on a population-based survey. Therefore, the sampling characteristics of the participants were rigorous and standardized, which makes the results of this study representative. Second, this study included a large study population, a wide range of covariate adjustments were made, and the mortality follow-up period was relatively long. Finally, we performed two sensitivity analyses using thresholds based on the LLN of FEV_1/FVC. Previous studies have suggested that using a fixed FEV_1/FVC <0.70 to define airflow obstruction may lead to overdiagnosis of COPD in older adults and underdiagnosis in approximately 1% of younger adults compared with using a threshold based on the LLN of FEV_1/FVC in mild COPD.[38–41] The results of the sensitivity analysis based on the LLN in this study were consistent with the results of the main analysis, illustrating the robustness of the results.

The present study also has some limitations that should be considered. First, most of the participants in the NHANES did not have available pulmonary function data after inhalation of bronchodilators, so our study was primarily based on analyzing only the data before inhalation of bronchodilators. Previous studies have found that lung function predicts mortality better after bronchodilator inhalation than before bronchodilator inhalation, but the difference between the two was small.[42] Second, the NHANES measured spirometry only once at baseline. Thus, we were unable to comment on differences in the rate of lung function decline between patients with mild COPD and those with normal spirometry. Finally, despite adjusting for possible confounders, we could not control for all potential variables; therefore, we could not completely rule out the effects of residual confounders.

Conclusions

In conclusion, this study found that patients with mild COPD had a higher all-cause mortality risk than those with normal spirometry, especially males, patients aged ≥50 years, and current smokers. However, this relationship was not observed in females, patients aged <50 years, never smokers, and former smokers. Appropriate management, follow-up, and treatment should be provided to these specific subgroups. Further investigations are needed in the future to evaluate the rate of lung function decline in patients with mild COPD compared with individuals with normal spirometry.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests in this work.

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