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ORIGINAL RESEARCH

Association Between Opioid and Benzodiazepine Use and All-Cause Mortality in Individuals with Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study

Hao Jiang[1,*], Xiaomin Zhang[2,*], Jian Zhang[1], Jie Liang[1], Liping Wang[1]

[1]Department of Anesthesiology, Harbin Medical University Cancer Hospital, Harbin, People's Republic of China; [2]Department of Anesthesiology, Beidahuang Industry Group General Hospital, Harbin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Liping Wang; Jie Liang, Department of Anesthesiology, Harbin Medical University Cancer Hospital, No. 150 of Haping Road, Nangang District, Harbin, Heilongjiang, 150081, People's Republic of China, Email applew708@126.com; 830625@hrbmu.edu.cn

Background: Opioids and benzodiazepines are frequently prescribed for managing pain and anxiety in chronic obstructive pulmonary disease (COPD) patients. This study aimed to determine whether opioid use, with or without benzodiazepine use, is associated with increased all-cause mortality in COPD patients.

Methods: This prospective cohort study included adults aged ≥20 years with COPD from the US National Health and Nutrition Examination Survey 2007–2012. The primary outcome was all-cause mortality, which were obtained through linkage to registries. Weighted Cox proportional hazards regression models were used to evaluate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. Additionally, subgroup and sensitivity analyses were used to evaluate the robustness of our findings.

Results: This study enrolled 811 participants, representing 10.84 million COPD individuals in the United States (mean [standard error] age, 58.7 [0.6] years). During a median follow-up of 9.6 years, mortality rates were 57.8 per 1000 person-years in patients using only opioids, 41.3 per 1000 person-years in patients using only benzodiazepines, 45.7 per 1000 person-years in patients using both opioids and benzodiazepines, and 27.0 per 1000 person-years in patients using neither. In the fully adjusted model, COPD patients prescribed both opioids and benzodiazepines (HR: 1.76; 95% CI: 1.11–2.78) and those prescribed opioids only (HR: 1.68; 95% CI: 1.13–2.49) had significantly higher all-cause mortality compared to non-users. After adjusting for propensity scores, the mortality risk for opioid-only users slightly increased (HR: 1.87; 95% CI: 1.25–2.81). Further, subgroup analysis revealed an elevated mortality risk in patients over 60 years receiving coprescriptions or opioids only, but not in younger participants. In contrast, benzodiazepine-only users aged 60 or younger showed increased mortality risk.

Conclusion: Opioid use, with or without benzodiazepine use, was associated with higher mortality in COPD patients over 60, while benzodiazepine-only use was associated with higher mortality aged 60 or younger.

Keywords: opioid, benzodiazepine, chronic obstructive pulmonary disease, mortality, national health and nutrition examination survey, NHANES

Background

Chronic obstructive pulmonary disease (COPD), currently the third leading cause of death in the United States,[1] substantially impacts quality of life for affected individuals and poses a major public health challenge. The primary goal of pharmacological treatment for COPD is to improve quality of life and manage symptoms while decreasing the frequency of exacerbations.[2]

Opioids are not exclusively prescribed for cancer-related pain, they are also utilized for a variety of chronic pain conditions, including osteoarthritis, rheumatoid arthritis, and chronic lower back pain,[3] and opioid-based therapy has been

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conditionally recommended for those experiencing advanced refractory dyspnea in patients with COPD.[2] Current data indicate that approximately 40% of advanced COPD patients are prescribed opioids.[4] Benzodiazepines are prescribed for anxiety, insomnia and chronic breathlessness associated with or caused by COPD.[5] Alarmingly, it has been observed that 65% of COPD patients are diagnosed with anxiety and/or depressive disorders, yet only 31% receive treatment for their mental health conditions.[6] Coprescribing opioids and benzodiazepines can increase the risk of life-threatening overdose because both types of drugs can cause sedation and suppress breathing,[7] and the adverse respiratory effects of these drugs may pose a particular risk of death in patients with COPD.[8,9] It is therefore tempting to speculate that the increased mortality risk in COPD patients may be attributed to opioid use alone or in combination with benzodiazepines; however, investigating this issue remains challenging.

Hitherto, it has not been clear whether opioid use—with or without benzodiazepine use—directly contributes to long-term mortality among individuals with COPD, as opposed to merely serving as an indicator of underlying advanced illness which itself is the actual risk factor for increased mortality.

The purpose of this study was to fill this void by evaluating the association between opioid use, with or without benzodiazepine use, and long-term all-cause mortality among adults with COPD from a comprehensive, nationally representative US dataset linked to the National Death Index (NDI), with approximately 13 years of follow-up (2007–2019).

Methods

Data Sources

The National Health and Nutrition Examination Survey (NHANES) was utilized to access a nationally representative sample of approximately 5000 US participants for every two-year cycle. The study data were collected from the 2007–2008, 2009–2010, and 2011–2012 NHANES cycles, with mortality data extending through 2019. The NHANES protocols were approved by the Institutional Review Boards (IRBs) of the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC). Informed consent was obtained from all participants. Since this study utilized publicly available deidentified data from the NHANES database, informed consent was waived. Consequently, ethical approval and consent were not necessary, and the Ethics Review Committee of Harbin Medical University Cancer Hospital granted an exemption for the study (ethic-number: 2024–0012). Further information on the NHANES methods, procedures, and IRB approval is available on the NHANES website, accessed on May 2, 2023. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Participants

Spirometry data were collected for eligible participants ≥20 years of age. Two primary measures, forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), were selected for analysis. Participants diagnosed with COPD met at least one of the following criteria: (I) postbronchodilator spirometry indicating an FEV_1/FVC ratio less than 70%; (II) a previous emphysema diagnosis by a physician; or (III) current use of medications such as selective phosphodiesterase-4 inhibitors, mast cell stabilizers, leukotriene modifiers, or inhaled corticosteroids combined with a history of smoking or chronic bronchitis and age >40 years.[10] Mortality data were collected following the initial home interview. Of the 30,442 respondents who completed the home interview and physical examination, 1063 were diagnosed with COPD. After excluding 120 individuals due to incomplete data of key variables (54 alcohol consumption, 9 coronary heart disease, 7 congestive heart failure, 54 chronic kidney disease), our final sample consisted of 943 individuals. These participants were linked to the NDI, which records more than 99% of US deaths, including dates and primary causes. We excluded 110 individuals who lacked mortality data and those who died within one year post-recruitment to minimize bias from narcotic and benzodiazepine prescriptions given to terminally ill participants (n=22) (Figure 1).

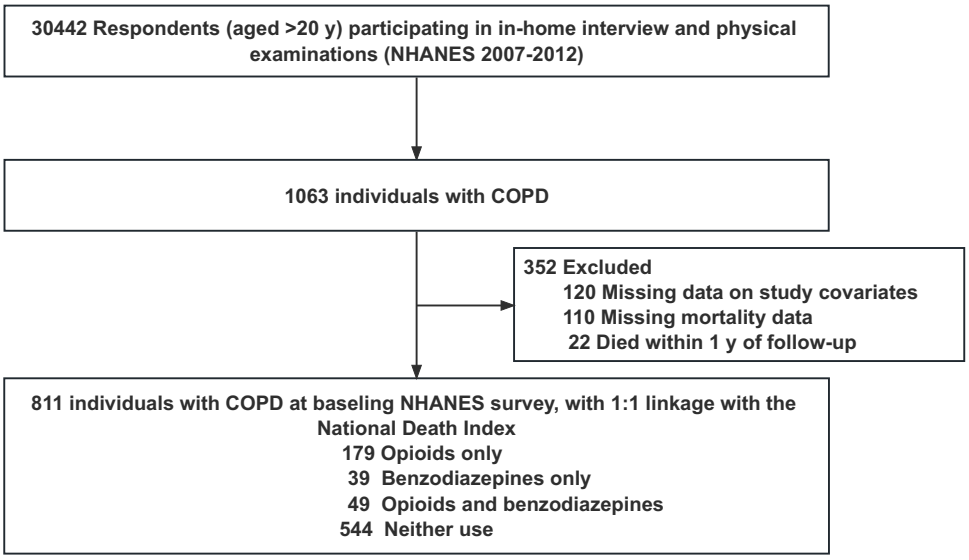

Figure 1 Flowchart of the participant selection. Of the 30,442 respondents who completed the home interview and physical examination between 2007 and 2012, 1,063 were diagnosed with COPD. We excluded those who were missing data on covariates or mortality. We also excluded patients who died within 1 year of follow-up.
Abbreviation: NHANES, National Health and Nutrition Examination Survey.

Collection of Medication Use Data

Annual data on prescription medications were collected from participants at their homes via the NHANES through face-to-face interviews. Participants were asked to present containers with all the medications used within the last 30 days. In cases where the container was unavailable, the medication name was recorded as stated by the participant. The reported medications were then matched to the Multum Lexicon Plus drug database to categorize them into therapeutic medication categories. Among the 1063 respondents diagnosed with COPD who participated in these in-home interviews, all provided complete prescription medication data, with no refusals or missing information. Following methodologies from prior studies,[11,12] we identified 23 types of benzodiazepines, encompassing both short-acting and long-acting agents, as well as selective benzodiazepine receptor modulators (eg, zolpidem). Additionally, more than 60 opioid narcotics, including both generic and brand-name prescription pain medications, were classified under the Multum Lexicon categories: (level 1) 57 central nervous system agents, (level 2) 58 analgesics, (level 3) 60 narcotic analgesics, or 191 narcotic analgesic combinations. The respondents using these opioids were identified as opioid users. However, individuals utilizing opioids to manage opioid dependence or withdrawal, including buprenorphine and methadone, were excluded from the category of prescription opioid users (the complete classification scheme is detailed in Table S1).[13]

Covariates and Confounders

To mitigate confounding factors that could potentially influence mortality rates among individuals with COPD receiving opioids and benzodiazepines, we considered various covariates. The sociodemographic factors included sex, age, body mass index (BMI), and race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Mexican American, or other race inclusive of other Hispanic and multiracial). We also examined the poverty ratio (<=2, >2), educational attainment (subdivided into less than high school, which includes less than 9th grade and 9–11th grade, and more than high school, encompassing high school graduates/GED or equivalent, some college or AA degree, and college graduates or above), and insurance status. Lifestyle factor information, such as information about smoking and alcohol consumption (classified as current, former, or never), was also included. The medical comorbidities considered in our analysis included hypertension, hyperlipidemia, coronary heart disease, congestive heart failure, stroke, diabetes, asthma, cancer, and chronic kidney disease.

Statistical Analysis

This study employed NHANES data, utilizing weights to mirror the complex survey design and guarantee representativeness of the sample at the population level. Specifically, we applied an incorporated mobile examination center (MEC) weight across three cycles to enhance precision and representativeness. Continuous variables are presented as the weighted means ± standard errors (SEs) or median with interquartile ranges (IQR), while categorical variables are expressed as the frequencies (%). The chi-square test was used for categorical variables, and one-way ANOVA was used for continuous variables to compare baseline characteristics between different medication groups. The study groups consisted of individuals COPD who were exposed to opioids, benzodiazepines, or both. The control group comprised individuals with COPD who did not use either medication.

The all-cause mortality rate per 1000 person-years was calculated. To estimate crude mortality hazards, a weighted Cox proportional hazards regression model was used to compare the study groups to control group. We adjusted these mortality hazards for all covariates to obtain refined estimates. To assess the robustness of these findings, stratified analyses were performed by follow-up duration (<50th percentile vs ≥50th percentile of follow-up time) and age group (20–60 vs >60 years).

Sensitivity Analyses

Given that individuals prescribed opioids and benzodiazepines are more likely to have comorbidities, propensity scores were estimated to balance baseline characteristics between the opioid-only group and nonusers of these two drugs group using propensity score matching (PSM), inverse probability treatment weighting (IPTW), standardized mortality ratio weighting (SMRW), PA weighting (PA) and overlap weighting (OW) methods, and conducting a case–control match at a 1:2 ratio, consistent with methods previously described (according to NHANES reporting guidelines, statistical reliability is achieved with sample sizes >420).[14] Our dataset included 179 participants who were exclusively prescribed opioids). We deemed an absolute standardized difference less than 0.1 to indicate minimal covariate imbalance between groups. Then, weighted adjusted mortality hazards were derived for these participants. Furthermore, we repeated the weighted Cox proportional hazards regressions to include participants who died within one year post-recruitment. All analyses were performed using R, version 4.2.1 (R Foundation). A 2-sided *P* value of less than 0.05 indicated statistical significance.

Results

Study Population Characteristics

Our study included 811 participants, representing an estimated 10.84 million COPD patients in the United States (6,563,800 men [60.6%]; mean [SE] age, 58.7 [0.6] years; 9,181,700 White [84.7%]). The baseline characteristics are depicted in Table 1. A total of 2,107,463 participants (19.4%, 95% CI: 15.2%-23.7%) were prescribed opioids only, 542,155 (5.0%, 95% CI: 3.0%-7.0%) received only benzodiazepines, and 507,554 (4.7%, 95% CI: 2.7%-6.6%) were prescribed both. The remaining 7,680,826 individuals (70.9%, 95% CI: 66.2%-75.6%) had no prescription for either of these drug classes.

Patients prescribed only opioids, compared to those not taking either medication, were typically older (mean age: 61.5 vs 58.0 years, SE: 1.1 vs 0.6), predominantly female (49.6% vs 33.9%), had lower incomes (poverty to income ratio >2: 49.8% vs 69.0%), lower education levels (high school graduates: 65.1% vs 80.7%), higher smoking rates (48.5% vs 34.8%), lower alcohol consumption (61.5% vs 29.2%), and increased prevalence of diabetes (29.4% vs 19.5%) and asthma (51.2% vs 29.2%); Patients prescribed only benzodiazepines were more likely to be female (54.1% vs 33.9%), had greater insurance coverage (98.4% vs 86.2%), lower alcohol consumption (58.0% vs 72.6%), and a higher prevalence of hyperlipidemia (94.0% vs 82.2%); Patients with benzodiazepine-opioid coprescriptions were predominantly female (66.0% vs 33.9%), had lower incomes (poverty to income ratio >2: 30.4% vs 69.0%), higher smoking rates (47.6% vs 34.8%), lower alcohol consumption (43.2% vs 72.3%), and an increased prevalence of hyperlipidemia (92.5% vs 82.2%) and congestive heart failure (13.3% vs 4.2%).

Table 1 Baseline Characteristics of Study Participants

Characteristic	*Weighted No. (%)					*P* value		
	All participants	Neither use	Opioids only	BZDs only	Opioid plus BZDs	Opioids vs neither	BZDs vs neither	Opioids plus BZDs vs neither
	(n=10,837,997)	(n = 7,680,826 [70.87%])	(n=2,107,463 [19.45%])	(n = 542,155 [5.00%])	(n = 507,554 [4.68%])			
Age, mean ±SE, y	58.74 ± 0.56	57.96 ± 0.64	61.49 ± 1.07	60.20 ± 2.05	57.41 ± 1.97	0.00	0.29	0.79
Age group, y						0.03	0.79	0.72
20–60	5,512,742.04 (50.86)	4,092,736.77 (53.29)	856,548.80 (40.64)	274,471.63 (50.63)	288,984.85 (56.94)			
≥60	5,325,254.90 (49.14)	3,588,089.12 (46.71)	1,250,914.29 (59. 36)	267,682.63 (49. 37)	218,568.86 (43.06)			
Sex						0.04	0.04	< 0.001
Female	4274197.39 (39.44)	2,600,805.66 (33.86)	1,044,630.38 (49.57)	293,559.65 (54.15)	335,201.70 (66.04)			
Male	6563799.56 (60.56)	5,080,020.24 (66.14)	1,062,832.70 (50.4)	248,594.61 (45.85)	172,352.01 (33.96)			
BMI, mean ±SE, kg/m^2	28.86 ± 0.25	28.70 ± 0.28	29.44 ± 0.66	27.84 ± 1.14	29.90 ± 1.27	0.28	0.46	0.37
BMI group						0.51	0.50	0.07
<30	7,096,473.89 (65.48)	5,106,222.77 (66.48)	1,334,500.21 (63.32)	399,364.00 (73.66)	256,386.91 (50.51)			
≥30	3,741,523.06 (34.52)	2,574,603.12 (33.52)	772,962.88 (36.68)	142,790.25 (26.34)	251,166.80 (49.49)			
Race						0.15	0.07	0.63
White	9181700.4 (84.7)	6,441,273.0 (83.9)	1,816,048.3 (86.2)	518,114.6 (95.6)	406,264.5 (80.0)			
Black	802957.40 (7.41)	551,650.35 (7.18)	189,973.51 (9.01)	4193.09 (0.77)	57,140.45 (11.26)			
Mexican American	125852.56 (1.16)	93,875.06 (1.22)	24,726.58 (1.17)	0.00 (0.00)	7250.92 (1.43)			
Other race	727486.60 (6.71)	594,027.45 (7.73)	76,714.69 (3.64)	19,846.57 (3.66)	36,897.88 (7.27)			
Poverty to income ratio						< 0.001	0.91	0.00
≤2	3,966,055.89 (36.59)	2,382,259.75 (31.02)	1,057,559.90 (50.18)	172,897.62 (31.89)	353,338.62 (69.62)			
>2	6,871,941.06 (63.41)	5,298,566.15 (68.98)	1,049,903.19 (49.82)	369,256.63 (68.11)	154,215.09 (30.38)			
High school graduate	8370614.33 (77.23)	6,199,749.88 (80.72)	1,371,152.68 (65.06)	438,379.81 (80.86)	361,331.96 (71.19)	0.00	0.98	0.22
Insurance	9583597.25 (88.43)	6,618,166.66 (86.16)	1,942,141.11 (92.16)	533,533.79 (98.41)	489,755.68 (96.49)	0.09	0.01	0.01
Smoke						0.02	0.94	0.03
Current	4127089.86 (38.08)	2,670,508.54 (34.77)	1,022,166.75 (48.50)	192,943.49 (35.59)	241,471.07 (47.58)			
Former	4817815.46 (44.45)	3,439,883.72 (44.79)	899,580.53 (42.69)	226,240.34 (41.73)	252,110.86 (49.67)			
Never	1893091.63 (17.47)	1,570,433.63 (20.45)	185,715.80 (8.81)	122,970.42 (22.68)	13,971.77 (2.75)			
Alcohol consumption						0.00	0.03	< 0.0001
Current	7403682.84 (68.31)	5,573,794.51 (72.57)	1,296,241.5 (61.51)	314,473.25 (58.00)	219,173.56 (43.18)			
No	634932.50 (5.86)	543,456.45 (7.08)	72,874.24 (3.46)	12,719.58 (2.35)	5882.23 (1.16)			
Former	2799381.60 (25.83)	1,563,574.93 (20.36)	738,347.33 (35.03)	214,961.43 (39.65)	282,497.91 (55.66)			

(*Continued*)

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Table 1 (Continued).

Characteristic	*Weighted No. (%)					*P* value		
	All participants	Neither use	Opioids only	BZDs only	Opioid plus BZDs	Opioids vs neither	BZDs vs neither	Opioids plus BZDs vs neither
	(n=10,837,997)	(n = 7,680,826 [70.87%])	(n=2,107,463 [19.45%])	(n = 542,155 [5.00%])	(n = 507,554 [4.68%])			
Cancer or malignancy	1875251.95 (17.30)	1,155,512.20 (15.04)	452,250.42 (21.46)	146,645.57 (27.05)	120,843.76 (23.81)	0.11	0.15	0.31
Hyperlipidemia	9045732.38 (83.46)	6,312,426.83 (82.18)	1,754,267.41 (83.24)	509,766.67 (94.03)	469,271.46 (92.46)	0.80	0.01	0.04
Hypertension	5696584.22 (52.56)	3,902,570.73 (50.81)	1,200,757.89 (56.98)	271,199.02 (50.02)	322,056.57 (63.45)	0.26	0.95	0.22
Coronary heart disease	833751.97 (7.69)	457,859.70 (5.96)	242,942.38 (11.53)	75,623.75 (13.95)	57,326.14 (11.29)	0.07	0.11	0.10
Stroke	736655.22 (6.80)	473,750.17 (6.17)	162,731.74 (7.72)	36,606.52 (6.75)	63,566.79 (12.52)	0.44	0.89	0.16
Chronic kidney disease	2235260.73 (20.62)	1,419,592.47 (18.48)	550,600.04 (26.13)	133,921.48 (24.70)	131,146.74 (25.84)	0.12	0.40	0.28
Diabetes	2330440.51 (21.50)	1,494,503.27 (19.46)	618,562.75 (29.35)	99,071.24 (18.27)	118,303.24 (23.31)	0.01	0.87	0.60
Asthma	3774534.75 (34.83)	2,242,826.29 (29.20)	1,077,992.75 (51.15)	237,329.12 (43.78)	216,386.58 (42.63)	< 0.001	0.10	0.12
Congestive heart failure	702182.44 (6.48)	318,939.73 (4.15)	254,903.62 (12.10)	60,790.52 (11.21)	67,548.56 (13.31)	0.01	0.07	0.01

Notes: *An incorporate Mobile Examination Center weight was applied to enhance precision and representativeness of the sample at the population level.
Abbreviations: BZD, Benzodiazepine; SE, Standard error; BMI, Body mass index.

Survival Analysis

In this study, the participants had a median follow-up duration of 9.6 years (range: 1.1–13.3 years). Out of 10,837,997 participants, 4,719,004 (43.5%) were followed up for more than 10 years, for a total of 7269 person-years. We recorded 255 deaths, translating to an overall mortality rate of 35.1 events per 1000 person-years. Specifically, the death rates were 45.7 per 1000 person-years (19 deaths) among those with coprescriptions, 41.3 per 1000 (15 deaths) among benzodiazepine-only users, 57.8 per 1000 (86 deaths) among opioid-only users, and 27.0 per 1000 (135 deaths) in the control group not using either medication (Table S2).

The weighted Kaplan–Meier survival curves, unadjusted for confounding factors, revealed distinct survival probabilities at follow-up initiation. Log rank tests revealed significantly elevated all-cause mortality in the opioid-only ($p < 0.0001$) and opioid-benzodiazepine coprescription groups ($p = 0.031$) compared with the control group. However, such elevations were not detected in the benzodiazepine-only group. Moreover, a statistically significant difference in mortality was not detected between the opioid-only and opioid-benzodiazepine coprescription cohorts (Figure 2).

According to the unadjusted weighted Cox proportional hazards regression models, patients who were prescribed opioids—with or without benzodiazepine use—exhibited an increased mortality risk compared to those not receiving either medication (coprescription: hazard ratio [HR], 2.30 [95% CI, 1.35–3.91]; opioids only: HR, 2.42 [95% CI, 1.69–3.46]) (Table 2). After adjusting for all the covariates listed in Table 1, the increase in mortality risk remained significant in patients who used opioids only (adjusted HR, 1.68 [95% CI, 1.13–2.49]). Additionally, the concurrent use of opioids and benzodiazepines was associated with a significant, albeit smaller, increase in all-cause mortality (adjusted HR 1.76 [95% CI, 1.11–2.78]).

Subgroup and Sensitivity Analyses

Among participants older than 60 years, an elevated mortality risk associated with opioid-benzodiazepine coprescription was observed, with an adjusted HR of 1.89 (95% CI, 1.20–2.97). In contrast, among younger participants, this increase in

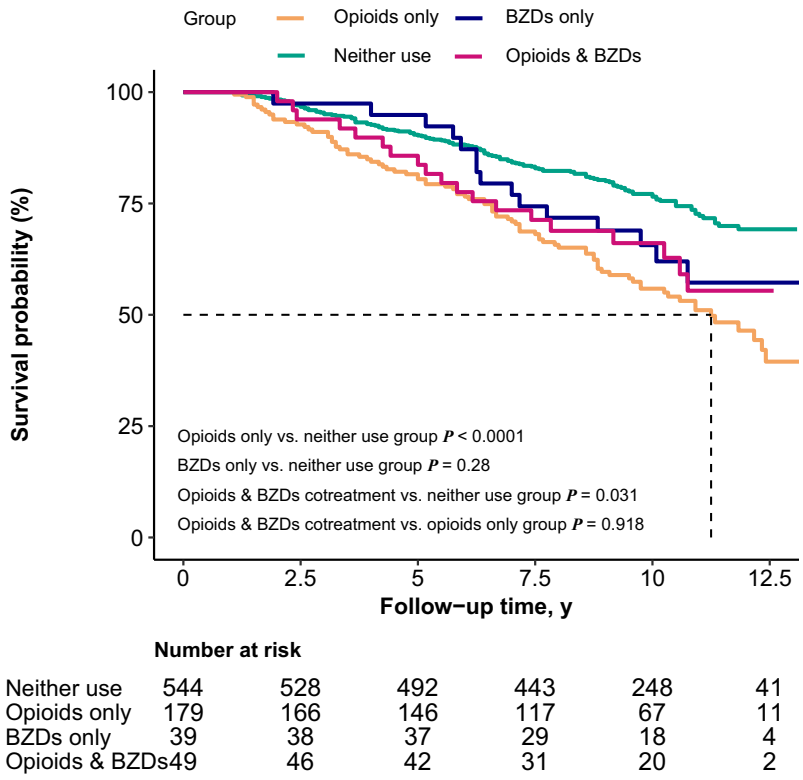

Figure 2 Unadjusted weighted Kaplan–Meier survival curves. Kaplan-Meier survival curves stratified by opioid use only, benzodiazepine (BZD) use only, BZD + opioid cotreatment, and neither BZD nor opioid use. We excluded all participants who died within 1 year of follow-up.

Table 2 Mortality Associated with Opioid or BZD Usage

Characteristic	Crude and #weighted HR (95% CI)	*P* value	*Adjusted and #weighted HR (95% CI)	*P* value
Opioids only vs neither				
All participants	2.42 (1.69, 3.46)	<0.0001	1.68 (1.13, 2.49)	0.01
Age, y				
20–60	1.66 (0.73, 3.75)	0.23	1.09 (0.48, 2.49)	0.84
>60	2.18 (1.54, 3.07)	<0.0001	2.00 (1.29, 3.09)	0.00
Follow-up time				
<50th percentile (9.6 y)	2.24 (1.50, 3.35)	<0.0001	1.86 (1.17, 2.96)	0.01
≥50th percentile (9.6 y)	3.57 (1.63, 7.82)	0.00	3.42 (1.86, 6.28)	<0.0001
BZDs only vs neither				
All participants	1.48 (0.74, 2.93)	0.27	1.15 (0.58, 2.27)	0.69
Age, y				
20–60	2.60 (1.01, 6.65)	0.05	4.29 (1.27, 14.55)	0.02
>60	1.16 (0.51, 2.63)	0.72	0.94 (0.39, 2.26)	0.9
Follow-up time				
<50th percentile (9.6 y)	2.02 (1.18, 3.45)	0.01	1.63 (1.05, 2.55)	0.03
≥50th percentile (9.6 y)	1.97 (0.34, 11.48)	0.45	3.39 (0.72, 15.97)	0.12
Opioids plus BZDs vs neither				
All participants	2.30 (1.35, 3.91)	0.00	1.76 (1.11, 2.78)	0.02
Age, y				
20–60	1.27 (0.51, 3.20)	0.61	1.38 (0.36, 5.29)	0.64
>60	3.26 (1.83, 5.79)	<0.0001	1.89 (1.20, 2.97)	0.01
Follow-up time				
<50th percentile (9.6 y)	1.99 (0.94, 4.23)	0.07	1.45 (0.82, 2.56)	0.2
≥50th percentile (9.6 y)	4.59 (0.87, 24.18)	0.07	3.19 (0.79, 12.95)	0.1

Notes: *Adjusted covariates including age group (20–60, >60), sex, race, body mass index group (<30, ≥30), poverty ratio, educational attainment, insurance status, hypertension, coronary heart disease, congestive heart failure, hyperlipidemia, stroke, diabetes, asthma, cancer, and chronic kidney disease. #Survey-weighted.
Abbreviations: BZD, benzodiazepine; HR, hazard ratio.

risk was not statistically significant (adjusted HR 1.38; [95% CI, 0.36–5.29]). A similar pattern emerged for those prescribed opioids only, with older participants showing an adjusted HR of 2.00 (95% CI, 1.29–3.09) compared to 1.09 (95% CI, 0.48–2.49) for younger individuals. However, an increase in mortality risk was noted with benzodiazepine-only prescriptions in this younger group, a trend that was absent in the older cohort (Table 2).

This study categorized participants by follow-up duration, using the median duration to differentiate between short- and long-term follow-up. In the short-term follow-up subgroup, opioid use was associated with a lower but nonetheless significantly elevated mortality risk (adjusted HR 1.86 [95% CI, 1.17–2.96]). This risk increased in the long-term follow-up subgroup (adjusted HR 3.42 [95% CI, 1.86–6.28]). Conversely, opioid and benzodiazepine coprescription did not significantly increase mortality risk across the different follow-up durations ($P > 0.05$). Benzodiazepine-only use was associated with increased mortality in the short-term follow-up subgroup (adjusted HR 1.63 [95% CI, 1.05–2.55]), but this association was not observed in the long-term follow-up subgroup (adjusted HR 3.39 [95% CI, 0.72–15.79]).

An absolute standardized difference less than 0.1 to indicate minimal covariate imbalance between opioid-only group and control group (Figure S1). This analysis involved 648 participants, revealing consistently larger effect sizes in all comparisons (Table S3). The weighted hazard ratios for mortality associated with opioids indicated a slight increase (adjusted HR, 1.87 [95% CI, 1.25–2.81]). Furthermore, a sensitivity analysis included participants who survived less than one year post-recruitment. These analyses revealed greater mortality hazards in the short-term follow-up than in the analyses excluding individuals who died within the first year (Table S4).

Discussion

This research demonstrated that opioid use, with or without benzodiazepine use, significantly increased all-cause mortality risk among individuals with COPD older than 60 years, compared to nonusers of these drugs. Specifically, concurrent use of benzodiazepines and opioids slightly increased all-cause mortality, even after adjusting for socio-demographic factors, health behaviors and comorbidities.

According to our weighted analyses, benzodiazepines did not significantly impact all-cause mortality overall. However, they were associated with increased mortality risk in COPD patients during shorter follow-up periods. This finding contrasts with that in previous research suggesting that benzodiazepines increase adjusted mortality risk in patients with respiratory failure related to COPD (with a short median follow-up of 1.1 years).[15] This points to a complex interplay between benzodiazepine use and mortality in COPD patients, possibly modulated by factors such as the stage or severity of COPD and other concurrent medical conditions. Recent literature indicates that benzodiazepines can exacerbate respiratory depression, particularly in patients with advanced COPD, leading to increased short-term mortality risk.[16] This risk may be more pronounced in the presence of other respiratory or systemic conditions that compromise respiratory function. Interestingly, our participant-based data indicate that benzodiazepines may be safe for COPD patients concerning long-term survival. This could reflect a healthy user effect, where healthier individuals are more likely to continue long-term use, or developed tolerance to the respiratory effects of this drug. However, the difference between short-term and long-term outcomes suggests that the impact of benzodiazepines may vary based on the duration of use and the overall health status of the patient.[16] Further research is needed to understand the varying impacts of benzodiazepine use over different time frames and in various COPD subpopulations. This will aid in developing more precise guidelines for the safe use of benzodiazepines in managing COPD.

Clinical concern about the association between opioid use and respiratory depression in elderly patients appears to be justified, as we found increases in mortality with the use of opioids with or without benzodiazepines in this consecutive cohort, and the risk of death was significant after a short or longer follow-up period. These findings align with those of the literature that identifies a strong association between opioid use and increased risk of death in COPD patients.[17] The augmented mortality risk in patients cotreated with opioids and benzodiazepines is primarily attributable to opioids. This finding aligns with prior studies suggesting that concurrent use of opioids and sedatives significantly heightens the risk of respiratory events and death in COPD patients.[16] One study found that opioid use in advanced COPD patients was associated with an increased risk of hospitalization for respiratory issues and higher overall mortality.[18] Another study reported that benzodiazepine use in COPD patients led to a higher incidence of adverse respiratory events, including pneumonia and acute exacerbations.[19] The immediate risk of co-prescribing opioids and benzodiazepines is a critical concern. Additionally, the long-term effects on respiratory function, immune response, physical and mental health, and increased risk of falls also significantly contribute to mortality.[20–24] We acknowledge that smoking significantly increases mortality in COPD patients.[25] Furthermore, opioid use in lung cancer patients may further elevate mortality risk,[26] and frailty is also a contributing factor to increased mortality rates.[27]

Age-stratified analysis was also conducted for COPD patients, particularly since previous studies indicated that older COPD patients were more likely to receive sedatives and analgesics and that the risk of death associated with them was more significant.[16,28] This demographic discrepancy in research is noteworthy because older adults may have different physiological responses to opioids, coupled with a greater likelihood of concurrent use of other medications and comorbidities. These factors could alter the risk profile of opioid or benzodiazepine use in this age group. Our findings corroborated an increased all-cause mortality risk associated with the coprescription of benzodiazepines and opioids in COPD patients older than 60 years.

The strengths of this study lie in its robust methodology applied to the data and minimal loss during extended follow-up. To minimize confounding, we implemented several measures. Initially, individuals who died within one year were excluded to eliminate the influence of end-of-life cases, where opioids and benzodiazepines might be justifiably prescribed. Furthermore, our analysis included 16 covariates, many of which were related to health behaviors and comorbidities, such as cancer and coronary heart disease, that could influence mortality associated with opioids or benzodiazepines.[17] Additionally, we employed propensity score weighting in our sensitivity analyses to further mitigate observed confounding. Notably, our study also included a longer follow-up than did similar studies, which exhibited a median duration of approximately 10 years.[15]

Several limitations of this study need to be considered. The observational design raises concerns about residual confounding and reverse causality. The NHANES does not provide detailed data on the indication, duration, or dosage of drug use, limiting our ability to distinguish between new and long-term users, high and low dosages, or short and long-term exposure to benzodiazepines or opioids. Moreover, as each participant was interviewed only once, assessing changes in drug usage patterns over time was not feasible. Due to the high number of missing post-bronchodilator FEV_1 values, we could not achieve the statistical reliability required for stratification according to the GOLD criteria, as the remaining sample size would be insufficient (less than 420 participants). Therefore, we were unable to stratify patients according to COPD severity.

Conclusions

This cohort study revealed that opioid use, with or without benzodiazepine use, was associated with higher long-term all-cause mortality in individuals with COPD older than 60 years compared to nonusers of these drugs. Additionally, we observed that benzodiazepine use alone increased mortality risk only in individuals 60 years or younger. Given the lack of comprehensive opioid prescribing guidelines for COPD patients using sedatives and hypnotics, managing the coprescription of opioids and benzodiazepines is a major challenge for physicians. To address this, collaborative efforts involving clinicians, scientists, and policy-makers are essential to reduce the overprescription of these drugs for COPD patients, identify high-risk individuals, and develop specific interventions.

Abbreviations

BMI, Body mass index; BZDs, Benzodiazepines; CDC, Centers for Disease Control and Prevention; CI, Confidence interval ; COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in 1 s ; FVC, Forced vital capacity; HR, Hazard ratio; IPTW, Inverse probability treatment weighting; IRB, Institutional Review Boards ; MEC, Mobile examination center; NCHS, National Center for Health Statistics; NDI, National Death Index; NHANES, National Health and Nutrition Examination Survey; OW, Overlap weighting ; PA, PA weighting; PSM, Propensity score matching ; SMRW, Standardized mortality ratio weighting; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Data Sharing Statement

This study utilized publicly accessible datasets, which can be downloaded from the following website: https://www.cdc.gov/nchs/nhanes/.

Ethics Approval and Consent to Participate

The NHANES protocols were approved by the Institutional Review Boards (IRBs) of both the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC). All participants provided informed consent, and the Ethics Review Committee of Harbin Medical University Cancer Hospital granted an exemption for the study (ethic-number: 2024-0012).

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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 declare no competing interests in this work.

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