

Survival impact of comorbid COPD and cancer: insights from the UK Biobank and US NHANES cohorts

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) is associated with substantial global morbidity and mortality. However, its bidirectional relationship with cancer development and overall survival remains incompletely understood.

Methods

We analyzed data from 485,480 UK Biobank and 46,597 US NHANES participants. At baseline, participants were classified into four mutually exclusive groups: neither condition, COPD only, cancer only, or both. Logistic regression assessed baseline associations between COPD and prevalent cancer. Kaplan–Meier and Cox proportional hazards models evaluated incident cancer, incident COPD, and all-cause mortality, excluding individuals with the respective condition at baseline. Multivariable models adjusted for sociodemographic, lifestyle, and anthropometric factors.

Results

At baseline, COPD was associated with higher odds of prevalent cancer in the UK Biobank (OR 1.28, 95% CI 1.23–1.34) and NHANES (OR 1.62, 95% CI 1.42–1.86). In longitudinal analyses, baseline COPD predicted a higher risk of incident cancer (HR 1.18, 95% CI 1.15–1.22), while baseline cancer predicted a higher risk of incident COPD (HR 1.31, 95% CI 1.26–1.36). Coexisting COPD and cancer conferred the highest all-cause mortality risk in both cohorts (UK Biobank: HR 2.94, 95% CI 2.74–3.16; NHANES: HR 2.03, 95% CI 1.76–2.34), compared with those with neither condition.

Conclusion

COPD and cancer share a robust bidirectional relationship characterized by an increased joint disease burden and substantially poorer survival outcomes. The coexistence of both conditions identifies a highly vulnerable clinical phenotype with a compounded mortality risk, supporting the need for integrated risk assessment and coordinated care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic obstructive pulmonary disease (COPD) is characterized by systemic inflammation and is epidemiologically linked to an increased risk of lung cancer, though its relationship with non-lung cancer burden remains incompletely understood.

What this study adds

Across the UK Biobank and US NHANES, COPD was associated with a higher prevalence of cancer, while UK Biobank analyses showed bidirectional longitudinal associations between COPD and cancer. Participants with both conditions had the highest all-cause mortality risk, and the associations persisted after excluding lung cancer.

How this study might affect research, practice or policy

These findings underscore the clinical necessity for systemic non lung cancer surveillance and integrated multidisciplinary care for patients presenting with COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and cancer are major non-communicable diseases that contribute substantially to global morbidity and mortality. COPD is the fourth leading cause of death worldwide and accounted for approximately 3.5 million deaths in 2021, while cancer caused nearly 10 million deaths in 2022 ^{1,2}. COPD is increasingly recognized not only as a respiratory disorder but also as a systemic disease characterized by multimorbidity and adverse outcomes ^{3,4}. Cancer is therefore a clinically important comorbidity because of its frequency, prognostic significance and the growing evidence that people with COPD experience an excess cancer burden ^{5,6}.

The relationship between COPD and cancer is biologically plausible. Shared risk factors, including smoking, ageing, adverse lifestyles, environmental exposures and socioeconomic disadvantage, partly explain the association, although common exposures are unlikely to account for it fully ⁷. COPD is characterized by chronic airway and systemic inflammation, oxidative stress, recurrent epithelial injury and

abnormal tissue repair, which promote carcinogenesis⁸. Consistent with these mechanisms, COPD has been associated with increased lung cancer risk, including among never-smokers, suggesting that COPD-related pathways contribute independently of smoking^{9,10}. Evidence also indicates that this excess risk extends beyond lung cancer. Population-based studies have reported higher rates of extrapulmonary malignancies in individuals with COPD^{11,12}, with similar findings in Korean cohorts and outpatient COPD populations^{13,14}. Coexisting COPD and cancer worsen prognosis because COPD reduces pulmonary reserve, increases frailty and systemic inflammation, and limits tolerance to cancer treatment. Conversely, cancer and its treatment accelerate functional decline, increase infection risk and worsen respiratory outcomes. Previous studies suggest that COPD contributes to mortality among patients with cancer, while comorbidities in COPD are associated with poorer survival and quality of life^{15,16}. COPD also influence cancer-related mortality patterns¹⁷.

However, previous research has generally examined cancer risk in COPD or survival in selected cancer populations separately, rather than assessing cancer burden, bidirectional disease development and mortality within one framework. It also remains unclear whether these associations persist after excluding lung cancer. We therefore investigated prevalent cancer, incident cancer, incident COPD and all-cause mortality using the UK Biobank and US National Health and Nutrition Examination Survey. We also performed sensitivity analyses excluding lung cancer to determine whether the associations extended to non-lung cancer outcomes.

METHODS

Study population

We conducted a retrospective cohort analysis using prospectively collected data from two large population-based resources: the UK Biobank (UKB) and the US National Health and Nutrition Examination Survey (NHANES). The UKB is a prospective cohort that recruited approximately 502,128 participants aged 40–69 years from England, Wales and Scotland. Baseline assessments included questionnaire data, physical measurements, biological samples and linkage to national health records¹⁸. NHANES is a nationally representative, complex, stratified, multistage survey of the non-institutionalized US population that collects interview, examination and laboratory data¹⁹.

Inclusion and exclusion criteria

For the UKB, participants were eligible if information was available on COPD status, cancer status, key covariates and mortality follow-up. For NHANES, we included 10 survey cycles conducted between 1999 and 2018, with mortality follow-up available through 2019 from the public-use Linked Mortality Files. Participants were excluded if information on COPD history, cancer history, mortality status or covariates required for the main analyses was missing. The participant selection process for both cohorts is shown in Fig. 1.

After applying the exclusion criteria, the final analytical sample comprised 485,480 participants from the UKB and 46,597 from NHANES. Participants were classified into four mutually exclusive groups according to baseline COPD and cancer status: neither COPD nor cancer, COPD only, cancer only, and coexisting COPD and cancer.

Ascertainment of COPD and cancer

COPD and cancer were identified using cohort-specific data sources. In the UKB, COPD was ascertained from self-reported information, primary care records and hospital admission records linked to National Health Service data²⁰. COPD was defined using International Classification of Diseases, 10th Revision (ICD-10) codes J40–J44. Cancer diagnoses were obtained from hospital inpatient records coded using ICD-10²¹.

In NHANES, COPD and cancer were identified from self-reported physician diagnoses recorded in the Medical Conditions Questionnaire. COPD was defined by an affirmative response for emphysema (MCQ160G), chronic bronchitis (MCQ160K) or COPD (MCQ160O); the COPD-specific question was available in the 2013–2018 cycles. Participants who answered yes to any applicable question were classified as having COPD. Cancer was defined by an affirmative response to whether a doctor or other health professional had ever diagnosed cancer or malignancy (MCQ220)²². Detailed definitions are provided in supplementary table S1.

Follow-up and outcomes

All-cause mortality was the primary outcome in both cohorts. In the UKB, mortality data were obtained through linkage to records maintained by the National Health Service in England and Wales and by the NHS Central Register and National Records of Scotland, with follow-up available until 19 December 2022²³. In NHANES, baseline data from the 1999–2018 survey cycles were linked to the National Death Index, with follow-up available until 31 December 2019²⁴.

For mortality analyses, follow-up time was calculated from the baseline assessment date to death, loss to follow-up or the cohort-specific end of follow-up, whichever occurred first. Secondary longitudinal outcomes included incident cancer and incident COPD and were evaluated only in the UKB. For the incident cancer analysis, the sample was restricted to participants without cancer at baseline, and incident events were defined as new cancer diagnoses occurring after the baseline assessment. For the incident COPD analysis, the sample was restricted to participants without COPD at baseline, and incident events were defined as new COPD diagnoses during follow-up. For both analyses, follow-up extended from baseline to the occurrence of the relevant outcome or the end of follow-up.

Covariates

Potential confounders were selected from demographic, socioeconomic, anthropometric and lifestyle-related factors available in both cohorts. This included age (continuous variable); sex (Male/Female); race/ethnicity (White/non-White); education (college or above/less than college); smoking status (smoker/non-smoker); body mass index (BMI); and socioeconomic status (SES). In the UKB, SES was represented by the Townsend deprivation index (TDI), which is derived from postcode-level information on unemployment, car and home ownership, and household overcrowding; higher scores indicate greater socioeconomic deprivation²⁵. In NHANES, SES was assessed using the family poverty-income ratio (PIR), categorized as low, medium or high²⁶. Further details of the variables used in both cohorts are provided in supplementary table S2.

Statistical analysis

Baseline characteristics were summarized as mean (SD) for continuous variables and number (%) for categorical variables. Survey weights were applied to all NHANES analyses to account for the complex, stratified, multistage sampling design. The proportional hazards assumption was assessed using Schoenfeld residuals and was considered satisfied in both cohorts²⁷. Variance inflation factors and correlation matrices were examined to assess multicollinearity, and no substantial multicollinearity was detected (all VIFs < 5). The Benjamini–Hochberg false discovery rate method was applied to account for multiple testing²⁸. A complete-case approach was used, and participants with missing data for any covariate included in a model were excluded from that analysis.

Logistic regression was used to estimate ORs and 95% CIs for the association between COPD and prevalent cancer at baseline. Kaplan–Meier curves were generated to compare survival across the four COPD and cancer groups, and differences were assessed using log-rank tests. Cox proportional hazards models were used to estimate HRs and 95% CIs for all-cause mortality, with participants who had neither COPD nor cancer as the reference group.

In the UKB, Cox proportional hazards models were also used to examine the bidirectional longitudinal associations between COPD and cancer. First, baseline COPD was evaluated as the exposure and incident cancer as the outcome among participants without cancer at baseline. Second, baseline cancer was evaluated as the exposure and incident COPD as the outcome among participants without COPD at baseline. To estimate the additional mortality burden associated with coexisting COPD and cancer, participants with both conditions were also compared with participants having COPD only and with participants having cancer only as alternative reference groups. For all logistic and Cox regression analyses, three models were fitted. Model 1 was unadjusted. Model 2 adjusted for age, sex and race/ethnicity. Model 3 additionally adjusted for education, smoking status, BMI and SES, represented by TDI in the UKB and PIR in NHANES.

Subgroup analyses examined the association between coexisting COPD and cancer and all-cause mortality according to sex, smoking status, age (< 65 and ≥ 65 years) and SES. SES was defined using TDI in the UKB and PIR in NHANES. Cox proportional hazards models were fitted within each subgroup to assess the consistency of the associations across population subgroups and the possible variation in effect estimates. The same three-model framework was applied to the subgroup analyses. The stratifying variable was excluded from the corresponding adjusted models to avoid adjustment for the variable defining the subgroup.

Sensitivity analyses

Sensitivity analyses excluded participants with primary lung cancer (ICD-10 code C34) to determine whether the observed associations persisted for non-lung cancer outcomes. The analyses of prevalent cancer, incident cancer, incident COPD and all-cause mortality were repeated after excluding primary lung cancer.

All statistical analyses were performed using R version 4.5.1. The survival package was used for time-to-event analyses, and the survey package was used for survey-weighted NHANES analyses. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Out of 502,128 participants recruited from UKB, 485,480 were included after excluding participants aged < 40 years and those with missing covariate data.

Table 1
Baseline characteristics of participants in the UK Biobank and US NHANES study populations

UK Biobank (UKB)							US National Health and Nutrition Examination Survey (US NHANES)					
Characteristic	Overall	Only COPD	Only Cancer	Both	None	P-value	Overall	Only COPD	Only Cancer	Both	None	P-value
N	485,480	14,053	52,093	2525	416809		46,597	2,917	3,663	639	39,378	
Age (Years)	56.52 (8.08)	58.96 (7.43)	58.36 (7.57)	60.73 (6.74)	56.18 (8.12)	< 0.001	46.64 (16.68)	52.17 (16.11)	61.73 (14.70)	62.67 (14.00)	44.56 (15.95)	< 0.001
BMI	1.92 (0.75)	2.03 (0.77)	1.96 (0.76)	2.07 (0.79)	1.91 (0.74)	< 0.001	2.05 (0.82)	2.21 (0.82)	2.04 (0.80)	2.14 (0.84)	2.03 (0.81)	< 0.001
Sex						< 0.001	< 0.001					
Female	264,66 (55%)	7,039 (50%)	34,418 (66%)	1,451 (57%)	221,754 (53%)		24,123 (52%)	1,731 (62%)	1,902 (56%)	358 (64%)	20,132 (51%)	
Male	220,818 (45%)	7,014 (50%)	17,675 (34%)	1,074 (43%)	195,055 (47%)		22,474 (48%)	1,186 (38%)	1,761 (44%)	281 (36%)	19,246 (49%)	
Ethnicity						< 0.001	< 0.001					
Non-White	25,008 (5%)	402 (3%)	2,613 (5%)	65 (3%)	21,928 (5%)		25,577 (31%)	1,238 (24%)	1,150 (14%)	143 (12%)	23,046 (34%)	
White	460,472 (95%)	13,651 (97%)	49,480 (95%)	2,460 (97%)	394,881 (95%)		21,020 (69%)	1,679 (76%)	2,513 (86%)	496 (88%)	16,332 (66%)	
Education						< 0.001						< 0.001
College or above	109,167 (27%)	2,741 (28%)	11,783 (28%)	494 (30%)	94,149 (27%)		23,575 (59%)	1,280 (49%)	2,010 (65%)	307 (56%)	19,978 (60%)	
Less than college	292,829 (73%)	7,182 (72%)	29,680 (72%)	1,167 (70%)	254,800 (73%)		22,977 (41%)	1,632 (51%)	1,650 (35%)	332 (44%)	19,363 (40%)	
TDI/PIR*						< 0.001						< 0.001
Low	176,562 (36%)	4,051 (29%)	18,580 (36%)	667 (26%)	153,264 (37%)		9,744 (14%)	824 (22%)	511 (9%)	126 (15%)	8,283 (14%)	
Medium	170,903 (35%)	4,555 (32%)	18,422 (35%)	805 (32%)	147,121 (35%)		19,499 (36%)	1,359 (43%)	1,529 (32%)	322 (45%)	16,289 (36%)	
High	138,015 (28%)	5,447 (39%)	15,091 (29%)	1,053 (42%)	116,424 (28%)		17,354 (50%)	734 (35%)	1,623 (59%)	191 (40%)	14,806 (50%)	
Smoking						< 0.001						< 0.001
Non smoker	265,994 (55%)	5,035 (36%)	27,783 (53%)	783 (31%)	232,393 (56%)		25,263 (54%)	920 (32%)	1,728 (48%)	154 (26%)	22,461 (56%)	
Smoker	219,486 (45%)	9,018 (64%)	24,310 (47%)	1,742 (69%)	184,416 (44%)		21,334 (46%)	1,997 (68%)	1,935 (52%)	485 (74%)	16,917 (44%)	

Data are presented as mean (SD) for continuous variables and n (%) for categorical variables; NHANES (weighted); COPD, chronic obstructive pulmonary disease; SD, standard deviation; PIR, poverty-income ratio; BMI, body mass index; TDI, Townsend deprivation index; TDI for UKB and PIR for NHANSE

Out of 101,316 NHANES participants, 46,597 adults remained after exclusions for age, missing disease history, mortality information, BMI and PIR (Fig. 1).

In the UKB, 14053 participants had COPD only, 52093 had cancer only, 2525 had both conditions and 416809 had neither condition. The corresponding numbers in NHANES were 2917, 3663, 639 and 39378 respectively. Coexisting COPD and cancer were therefore present in 0.52% of UKB participants and 1.37% of NHANES participants (Table 1).

Baseline characteristics differed across the four groups in both cohorts (all $P < 0.001$). Participants with coexisting COPD and cancer were older and more likely to be smokers than those with neither condition. In the UKB, the mean age was 60.73 years and 69% were smokers in the coexisting group, compared with 56.18 years and 44%, respectively, in the reference group. A similar pattern was observed in NHANES, where the corresponding values were 62.67 versus 44.56 years and 74% versus 44%. Participants with both conditions also had less favourable socioeconomic profiles.

Association of COPD with prevalent cancer

Cancer prevalence was higher among participants with COPD than among those without COPD in both cohorts (Table 2 and supplementary table S3). In the UKB, cancer prevalence was 15.23% among participants with COPD and 11.11% among those without COPD. The OR decreased from 1.44 (95% CI 1.38 to 1.50) in the unadjusted model to 1.34 (95% CI 1.29 to 1.40) after adjustment for age, sex and race/ethnicity. The association remained significant after further adjustment for education, smoking, BMI and TDI (OR 1.28, 95% CI 1.23 to 1.34).

A similar pattern was observed in NHANES, where cancer prevalence was 18.89% among participants with COPD and 8.59% among those without COPD. The survey-weighted OR decreased from 2.48 (95% CI 2.20 to 2.79) in the unadjusted model to 1.64 (95% CI 1.43 to 1.88) after partial adjustment and 1.62 (95% CI 1.42 to 1.86) after full adjustment (all $P < 0.001$).

Bidirectional associations between COPD and cancer

Longitudinal analyses in the UKB demonstrated associations in both directions (Table 3 and supplementary table S4). Among 430,862 participants without cancer at baseline, 105,182 incident cancer events occurred during follow-up. Baseline COPD was associated with a higher risk of incident cancer, with the HR decreasing from 1.40 (95% CI 1.36 to 1.44) in the unadjusted model to 1.24 (95% CI 1.21 to 1.28) after partial adjustment and 1.18 (95% CI 1.15 to 1.22) after full adjustment.

Among 468,902 participants without COPD at baseline, 20,439 incident COPD events occurred. Baseline cancer was associated with a higher subsequent risk of COPD, with HRs of 1.53 (95% CI 1.47 to 1.59), 1.39 (95% CI 1.33 to 1.44) and 1.31 (95% CI 1.26 to 1.36) across models 1–3, respectively. All associations remained statistically significant ($P < 0.001$).

Table 2
Association of chronic obstructive pulmonary disease (COPD) with prevalent cancer at baseline in the UK Biobank and US NHANES cohorts

Cohort	COPD status	Model 1 OR (95%CI) ^a ,	Model 2 OR (95%CI) ^b ,	Model 3 OR (95%CI) ^c ,
		P-value	P-value	P-value
UK Biobank	No COPD	Ref	Ref	Ref
	COPD	1.44 (1.38–1.50), < 0.001	1.34 (1.29–1.40), < 0.001	1.28 (1.23–1.34), < 0.001
US NHANES	No COPD	Ref	Ref	Ref
	COPD	2.48 (2.20–2.79), < 0.001	1.64 (1.43–1.88), < 0.001	1.62 (1.42–1.86), < 0.001

US, United States; UK, United Kingdom; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ^a Model 1, unadjusted; ^b Model 2, adjusted for age, sex, race and ethnicity; ^c Model 3, adjusted for age, sex, race/ethnicity, education, body mass index, pir/tdi, and smoking status; NHANES analyses were survey-weighted

Table 3
Bidirectional longitudinal associations between COPD and cancer in UK biobank

Outcome	Baseline Exposure	Model 1 HR (95%CI) ^a , P-value	Model 2 HR (95%CI) ^b , P-value	Model 3 HR (95%CI) ^c , P-value
Incident Cancer	No COPD at baseline	Ref	Ref	Ref
	COPD at baseline	1.40 (1.36–1.44), < 0.001	1.24 (1.21–1.28), < 0.001	1.18 (1.15–1.22), < 0.001
Incident COPD	No Cancer at baseline	Ref	Ref	Ref
	Cancer at baseline	1.53 (1.47–1.59), < 0.001	1.39 (1.33–1.44), < 0.001	1.31 (1.26–1.36), < 0.001

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ^a Model 1, unadjusted; ^b Model 2, adjusted for age, sex, race and ethnicity; ^c Model 3, adjusted for age, sex, race/ethnicity, education, BMI, PIR/TDI, and smoking status; NHANES analyses were survey-weighted

Association of COPD and cancer with all-cause mortality

During a mean follow-up of 13.7 years, 42203 deaths occurred in the UKB. Crude mortality increased from 7.5% among participants with neither condition to 13.8% among those with cancer only, 19.9% among those with COPD only and 31.0% among those with both conditions. Kaplan–Meier curves remained clearly separated across follow-up, with the lowest survival probability among participants with coexisting COPD and cancer (log-rank $P < 0.001$; Fig. 2a).

The mortality gradient persisted after multivariable adjustment. Compared with participants with neither condition, the fully adjusted HR was highest for coexisting COPD and cancer (HR 2.94, 95% CI 2.74 to 3.16), followed by COPD only (HR 1.96, 95% CI 1.89 to 2.04) and cancer only (HR 1.68, 95% CI 1.64 to 1.73; Fig. 2b).

In NHANES, 7,039 deaths occurred during a mean follow-up of 9.7 years. Crude mortality was 12.1% among participants with neither condition, 25.5% among those with COPD only, 34.5% among those with cancer only and 42.7% among those with both conditions. Survival differed significantly across the four groups (log-rank $P < 0.001$; Fig. 2c). Fully adjusted HRs were 2.03 (95% CI 1.76 to 2.34) for coexisting COPD and cancer, 1.62 (95% CI 1.46 to 1.79) for COPD only and 1.31 (95% CI 1.22 to 1.42) for cancer only (Fig. 2d and supplementary tables S5–S6).

Subgroup analyses

Coexisting COPD and cancer were associated with increased mortality across most population subgroups (Fig. 3). The point estimates were higher among participants aged < 65 years than among those aged ≥ 65 years in both the UKB (HR 4.14 vs 2.70) and NHANES (HR 4.81 vs 1.86). Estimates were also modestly higher among females than males in the UKB (HR 3.14 vs 2.82) and NHANES (HR 2.09 vs 1.98).

Among smokers, the fully adjusted HR was 3.12 (95% CI 2.88 to 3.37) in the UKB and 2.30 (95% CI 1.97 to 2.70) in NHANES. Among non-smokers, the association remained significant in the UKB (HR 2.31, 95% CI 1.94 to 2.75) but not in NHANES (HR 1.37, 95% CI 0.93 to 2.02). Elevated risks were observed across all socioeconomic strata. In the UKB, HRs ranged from 2.51 in the low TDI group to 3.12 in the medium TDI group. In NHANES, estimates decreased from 3.03 in the low PIR group to 1.89 and 1.72 in the medium and high PIR groups, respectively.

Participants with both conditions also had higher mortality than those with either condition alone (Table 4). Compared with the COPD only group, the HR was 1.50 (95% CI 1.38 to 1.62) in the UKB and 1.25 (95% CI 1.06 to 1.49) in NHANES. Compared with the cancer-only group, the corresponding HRs were 1.76 (95% CI 1.63 to 1.90) and 1.54 (95% CI 1.32 to 1.80).

Table 4
Associations of coexisting COPD and cancer compared with having only COPD and only cancer with all-cause mortality in the overall sample and stratified by subgroups

Coexisting COPD and Cancer vs. COPD only, HR (95% CI) Coexisting COPD and Cancer vs. Cancer only, HR (95% CI)						
Subgroup	Category	Model	UK Biobank	US NHANES	UK Biobank	US NHANES
Overall	Overall	Model 1	1.70 (1.57–1.85)	2.23 (1.83–2.72)	2.50 (2.33–2.70)	1.58 (1.29–1.94)
		Model 2	1.54 (1.42–1.67)	1.18 (0.99–1.41)	2.04 (1.90–2.20)	1.75 (1.48–2.06)
		Model 3	1.50 (1.38–1.62)	1.25 (1.06–1.49)	1.76 (1.63–1.90)	1.54 (1.32–1.80)
Sex	Female	Model 1	1.64 (1.45–1.86)	2.07 (1.61–2.66)	2.31 (2.06–2.58)	1.65 (1.27–2.13)
		Model 2	1.56 (1.38–1.77)	1.41 (1.11–1.77)	2.04 (1.82–2.28)	1.88 (1.51–2.35)
		Model 3	1.53 (1.35–1.73)	1.38 (1.10–1.74)	1.78 (1.59–2.00)	1.63 (1.31–2.02)
	Male	Model 1	1.94 (1.75–2.15)	2.69 (2.01–3.61)	2.46 (2.23–2.71)	1.79 (1.31–2.44)
		Model 2	1.52 (1.37–1.68)	1.00 (0.78–1.27)	2.06 (1.87–2.28)	1.61 (1.26–2.07)
		Model 3	1.46 (1.32–1.62)	1.13 (0.89–1.43)	1.75 (1.59–1.94)	1.46 (1.15–1.84)
Smoking	Smoker	Model 1	1.57 (1.44–1.71)	2.16 (1.73–2.69)	2.53 (2.32–2.74)	1.71 (1.37–2.14)
		Model 2	1.46 (1.34–1.59)	1.22 (1.00–1.47)	2.14 (1.97–2.33)	1.85 (1.53–2.24)
		Model 3	1.44 (1.32–1.57)	1.30 (1.08–1.56)	1.96 (1.81–2.13)	1.73 (1.45–2.07)
	Non-smoker	Model 1	2.08 (1.70–2.54)	2.07 (1.35–3.17)	1.54 (1.29–1.84)	0.96 (0.65–1.42)
		Model 2	1.81 (1.49–2.21)	1.04 (0.68–1.59)	1.31 (1.10–1.57)	1.08 (0.73–1.60)
		Model 3	1.78 (1.46–2.17)	1.10 (0.70–1.72)	1.26 (1.06–1.51)	1.05 (0.71–1.55)

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Model 1, unadjusted; Model 2, adjusted for age, sex (male, female), and race and ethnicity (White and Non-white); Model 3, adjusted for age, sex, race/ethnicity, education, BMI, PIR/TDI, and smoking status; COPD, chronic obstructive pulmonary disease; NHANES analyses were survey-weighted

Sensitivity analyses

After excluding 6099 UKB participants and 126 NHANES participants with primary lung cancer, 479381 UKB participants and 46471 NHANES participants remained. The principal findings were unchanged throughout all analysis (supplementary tables S7–S11).

COPD remained associated with prevalent non-lung cancer in the UKB (OR 1.24, 95% CI 1.18 to 1.30) and NHANES (OR 1.57, 95% CI 1.37 to 1.80). In the UKB, COPD remained associated with incident non-lung cancer (HR 1.12, 95% CI 1.08 to 1.15), while baseline non-lung cancer remained associated with incident COPD (HR 1.30, 95% CI 1.25 to 1.35). Coexisting COPD and non-lung cancer also remained associated with the highest mortality risk in the UKB (HR 2.78, 95% CI 2.56 to 3.01) and NHANES (HR 1.91, 95% CI 1.63 to 2.23; all $P < 0.001$).

DISCUSSION

In two large population-based cohorts, COPD was associated with a greater cancer burden and poorer survival. Three findings were particularly important. First, COPD was associated with prevalent cancer in both the UKB and NHANES after adjustment for demographic, socioeconomic and lifestyle factors. Second, the UKB analyses showed bidirectional longitudinal associations: COPD predicted incident cancer, while cancer predicted incident COPD. Third, participants with both conditions had the highest all-cause mortality, exceeding the risk observed with COPD or cancer alone. These patterns were consistent across most subgroups and persisted after exclusion of lung cancer.

Our findings extend previous epidemiological evidence linking COPD with cancer risk. Although this association is best established for lung cancer^{9,10}, population-based studies have also reported increased risks of extrapulmonary malignancies^{11,12}, including in Korean cohorts and outpatient COPD populations^{13,14}. By examining prevalent cancer, incident cancer, incident COPD and mortality within one framework, and by evaluating the principal findings in two independent cohorts, our study provides a broader assessment of the COPD–cancer relationship than studies focused on a single outcome. Consistency across cohorts with different designs supports the robustness of the cross-sectional and mortality associations despite differences in disease ascertainment.

Several mechanisms contribute to these associations. Smoking is an important shared determinant, but it is unlikely to explain the relationship fully because COPD has also been associated with lung cancer among never-smokers^{9,10}. COPD is characterized by persistent airway and systemic inflammation, oxidative stress, epithelial injury, abnormal repair and immune dysregulation^{8,29}. These processes promote cellular senescence, impaired DNA repair and immune escape, thereby creating a pro-carcinogenic environment^{29–31}. The persistence of the association after excluding lung cancer further suggests that systemic rather than exclusively pulmonary mechanisms contribute to the excess cancer burden. Shared genetic susceptibility, environmental exposures and metabolic dysfunction also contribute, although these pathways were not directly evaluated in the present study.

The bidirectional association observed in the UKB also warrants consideration. COPD increase cancer risk through chronic inflammation, cumulative environmental exposures and repeated tissue injury, while more frequent clinical assessment and imaging increase cancer detection. Conversely, cancer and its treatment accelerate respiratory decline through infection, inflammation, reduced physical activity, cardiopulmonary toxicity and functional deterioration. Cancer-related deconditioning also reveals previously unrecognized COPD. These findings remain observational and should therefore be interpreted as associations rather than evidence that either condition directly causes the other. Future studies using repeated lung-function measurements, treatment information and time-updated exposures could help clarify the temporal and biological pathways underlying this relationship.

The mortality findings are clinically important. COPD can reduce pulmonary reserve, increase frailty and limit tolerance of surgery, chemotherapy, radiotherapy or immunotherapy, whereas cancer may add cachexia, infection risk, metabolic stress and functional decline. These combined effects explain why participants with both conditions had substantially poorer survival than those with either disease alone. This pattern is consistent with evidence that comorbidity worsens long-term outcomes in COPD^{3,4,15,32} and that COPD contributes to mortality among patients with cancer^{16,17}. The higher mortality observed when the coexisting group was compared directly with the COPD-only and cancer-only groups further indicates that the coexistence of both diseases carries risk beyond that associated with either condition separately.

Subgroup findings were broadly consistent but should be interpreted cautiously. Relative mortality estimates were higher among younger participants, which partly reflect lower baseline mortality in younger age groups. Differences according to smoking and socioeconomic status reflect variation in cumulative exposure, disease severity, healthcare access or statistical power. The absence of a significant association among non-smokers in NHANES is related to the smaller number of participants with both conditions. These analyses are therefore more useful for identifying potentially vulnerable groups than for establishing definitive effect modification.

Sensitivity analyses excluding lung cancer strengthened the interpretation of the main findings. COPD remained associated with prevalent and incident non-lung cancer, and coexisting COPD and non-lung cancer remained associated with the highest mortality. The observed relationship is therefore unlikely to be explained solely by the established connection between COPD and lung cancer^{10,33}. Clinically, COPD should be considered within a broader multimorbidity framework³⁴. Individuals with COPD represent a population with higher cancer burden and poor long-term outcomes, while the coexistence of COPD and cancer identifies a particularly high-risk subgroup for all-cause mortality. These findings highlight the importance of coordinated clinical care, careful risk stratification, and greater attention to cancer burden among individuals with COPD.

Strengths and limitations

This study used two large cohorts with complementary designs, longitudinal linked records in the UKB and nationally representative survey-weighted analyses in NHANES. It also examined several related outcomes and tested the robustness of the findings after excluding lung cancer. However, causality cannot be inferred and residual confounding may remain. Disease ascertainment differed between cohorts, and NHANES relied on self-reported diagnoses. Information on cancer stage, treatment, COPD severity, lung function, medication use and cause-specific mortality was unavailable. Bidirectional incident analyses were limited to the UKB, and complete-case analysis may have introduced selection bias.

CONCLUSIONS

COPD was associated with a greater cancer burden and poorer survival in both cohorts. Coexisting COPD and cancer identified the group at highest mortality risk, and these associations persisted after excluding lung cancer. These findings support integrated risk assessment and coordinated care for individuals with COPD and cancer.

Declarations

Competing interests

None declared

Ethics approval

The UK Biobank received ethical approval from the relevant UK ethics committees, and all participants provided written informed consent. This research was conducted using the UK Biobank Resource under application number 300880. NHANES protocols were approved by the National Centre for Health Statistics Research Ethics Review Board, and all participants provided informed consent.

Patient consent for publication

Not applicable.

Supplementary data

Supplementary data are available.

Author Contribution

SS designed the study, collected and analyzed the data, interpreted the results, prepared the tables and figures, and wrote the manuscript. PL provided guidance on data collection and analysis. QAN reviewed the manuscript and provided scientific comments. XC and YG assisted with data collection and organization. JP supervised the study and is responsible for the overall content as the guarantor. All authors reviewed the manuscript.

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Data Availability

The data were obtained from the UK Biobank and US NHANES databases.

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Figures

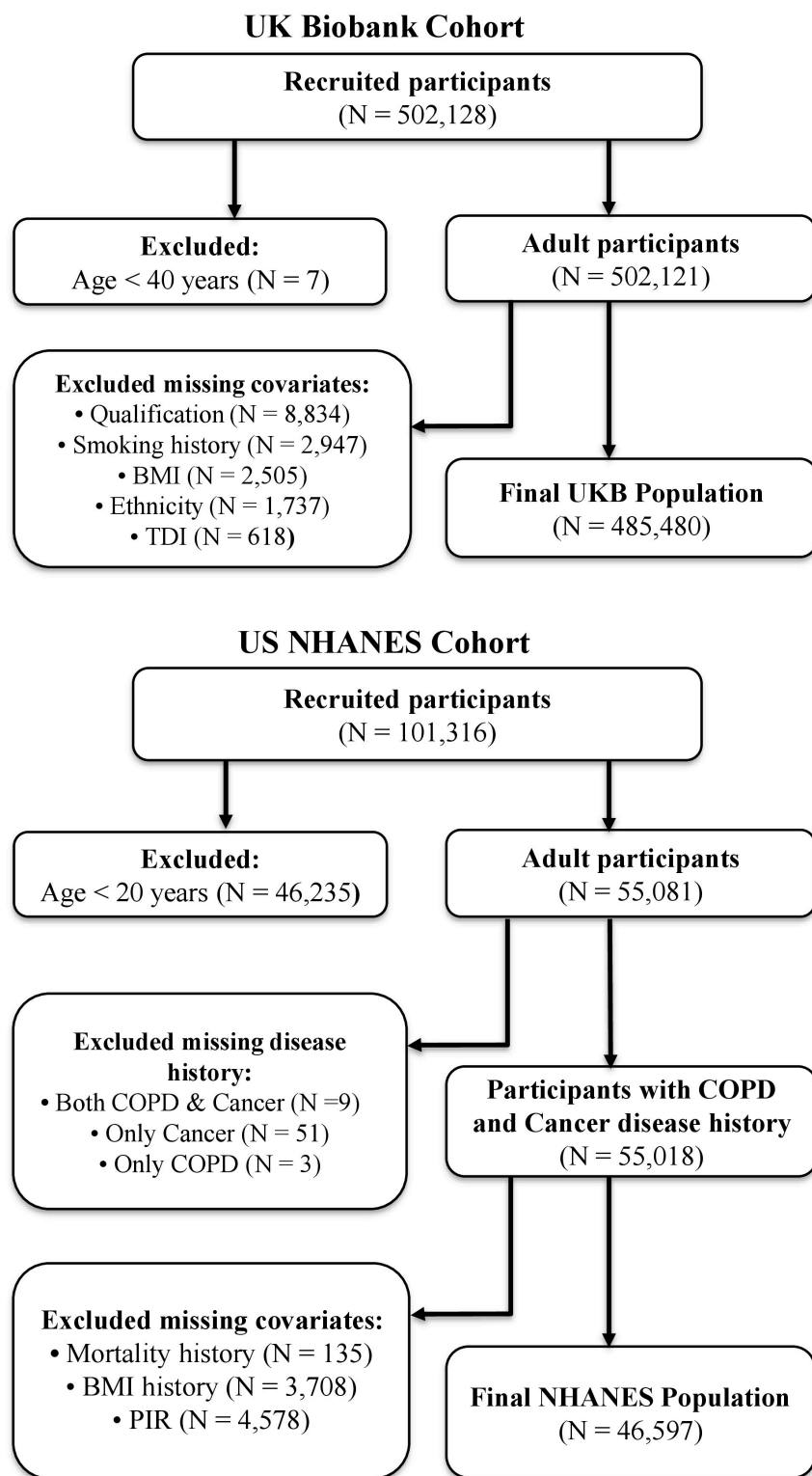


Figure 1

Participant selection flowchart

Flowchart of participants from US NHANES and UK Biobank in this study. COPD, chronic obstructive pulmonary disease; US, United States; UK, United Kingdom; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; PIR, poverty income ratio; TDI, Townsend deprivation index

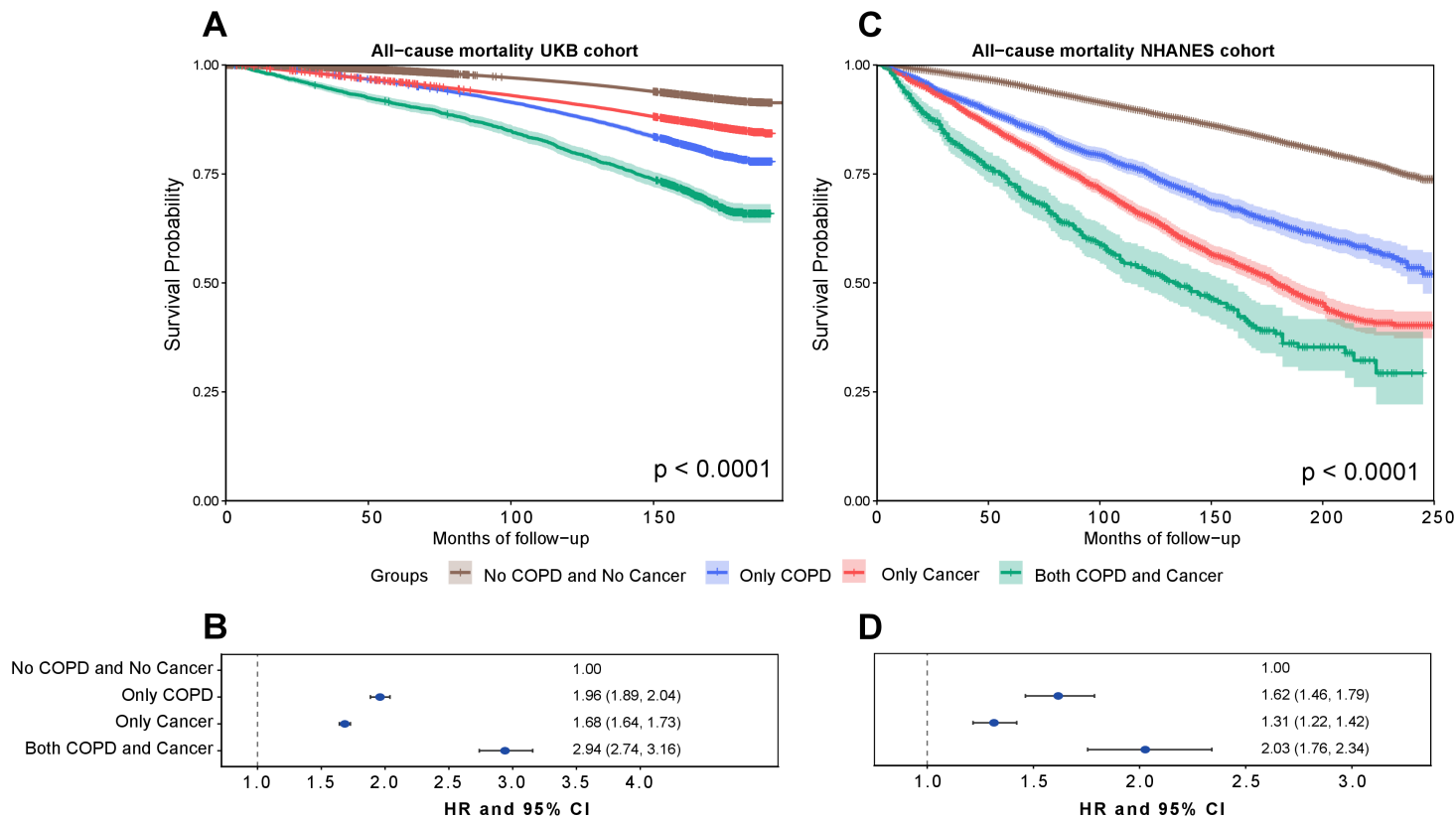


Figure 2

Survival and mortality risk by COPD and cancer status

Kaplan–Meier survival curves and multivariable Cox proportional hazards models showing all-cause mortality according to COPD and cancer status in the UK Biobank and US NHANES cohorts. Participants were classified into four groups: no COPD and no cancer, COPD only, cancer only, and coexisting COPD and cancer; **a** Kaplan–Meier survival curves for all-cause mortality in the UK Biobank cohort; **b** Fully adjusted Cox proportional hazards models comparing mortality risk across COPD/cancer status groups in the UK Biobank cohort, using participants with no COPD and no cancer as the reference group; **c** Kaplan–Meier survival curves for all-cause mortality in the US NHANES cohort; **d** Survey-weighted, fully adjusted Cox proportional hazards models comparing mortality risk across COPD/cancer status groups in the US NHANES cohort, using participants with no COPD and no cancer as the reference group. Fully adjusted models included age, sex, race/ethnicity, education level, smoking status, body mass index, and cohort-specific socioeconomic status, represented by Townsend Deprivation Index in the UK Biobank and Poverty Income Ratio in US NHANES. COPD, chronic obstructive pulmonary disease; NHANES, National Health and Nutrition Examination Survey; TDI, Townsend Deprivation Index; PIR, poverty income ratio.

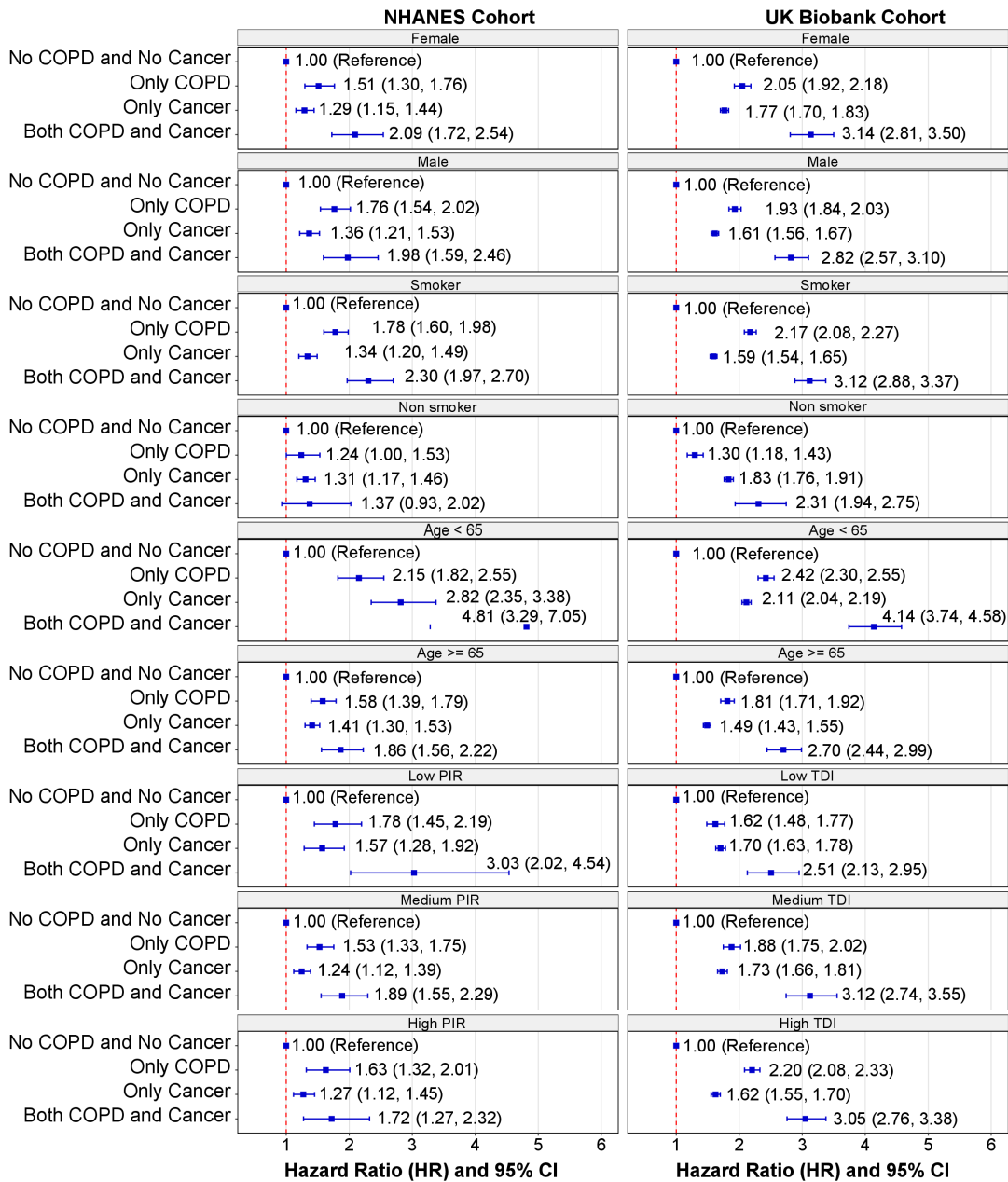


Figure 3

Subgroup associations of coexisting COPD and cancer with mortality

Multivariate Cox proportional hazards models showing the association between COPD/cancer status and all-cause mortality in the UK Biobank and US NHANES cohorts. Participants were classified as having no COPD and no cancer, COPD only, cancer only, or coexisting COPD and cancer. The reference group included participants with no COPD and no cancer. Analyses were stratified by sex, smoking status, age group (<65 and ≥65 years), and socioeconomic status. Socioeconomic status was defined using Townsend Deprivation Index categories in the UK Biobank and poverty income ratio categories in US NHANES. All models were fully adjusted for baseline age, sex, race/ethnicity, education level, smoking status, body mass index, and cohort-specific socioeconomic status. In each subgroup analysis, the stratifying variable was

excluded from the adjustment set to avoid collinearity. COPD, chronic obstructive pulmonary disease; NHANES, National Health and Nutrition Examination Survey; TDI, Townsend Deprivation Index; PIR, poverty income ratio.

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