

Supplementary Material

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

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Supplementary Table S1. Exposure Variables extracted from NHANES and the UK Biobank

Variables	UKB cohort	NHANES cohort	Definitions
COPD	UK Biobank Category 1712	MCQ160G, MCQ160K, MCQ160O	In the UK Biobank, COPD was defined using ICD-10 codes J40–J44. In NHANES, COPD was defined by self-reported physician diagnosis of emphysema, chronic bronchitis, or COPD.
Cancer	UK Biobank Data-Field 41270, Diagnoses - ICD10	MCQ220	Cancer in the UK Biobank was identified using cancer diagnosis records and ICD-10 codes C00–C97. Lung cancer was identified using ICD-10 code C34 for sensitivity analysis. In NHANES: self-reported diagnosis of cancer or malignancy variable used.

Supplementary Table S2. Covariates extracted from NHANES and the UK Biobank Cohort

Variables	UKB	NHANES	Definition
Age	21003	RIDAGEYR	Continuous variable; Age in years at the baseline assessment.
Sex	31	RIAGENDR	Binary variable; Male or Female.
Ethnicity	21000	RIDRETH1 or RIDRETH3	Binary variable; White or Non-White.
Smoking	20160	SMQ020, SMQ040	Categorized as smoker and non-smoker.
Body mass index	21001	BMXBMI	Continuous variable (kg/m ²); Calculated as body weight (kg) divided by square of height (m ²).
Education	6138	DMDEDUC2	Binary variable. Reclassified as "College or Above" (including college, university degrees, or equivalent) and "Less than college".

TDI/PIR	22189	INDFMPIR	Categorical variable. (Low, Medium, High)
			UKB Townsend Deprivation Index (TDI) was grouped into Low (≤ -3), Medium (> -3 and ≤ 0),
			and High (> 0) deprivation.
			NHANES Poverty Income Ratio (PIR) was grouped into Low (≤ 1), Medium (>1 and <3), and High (≥ 3) income levels.

Supplementary Table S3. Association of COPD with prevalent cancer at baseline

Cohort	COPD status	N	Cancer cases	Cancer prevalence	Model 1 OR (95% CI),	Model 2 OR (95% CI),	Model 3 OR (95% CI),
					P-value	P-value	P-value
UKB	No COPD	468,902	52,093	11.11 %	Ref	Ref	Ref
UKB	COPD	16,578	2,525	15.23 %	1.44 (1.38–1.50), <0.001	1.34 (1.29–1.40), <0.001	1.28 (1.23–1.34), <0.001
NHANES	No COPD	43,041	3,663	8.59 %	Ref	Ref	Ref
NHANES	COPD	3,556	639	18.89 %	2.48 (2.20–2.79), <0.001	1.64 (1.43–1.88), <0.001	1.62 (1.42–1.86), <0.001

Note: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PIR, poverty-income ratio; TDI, Townsend deprivation index; UK, United Kingdom; N=number of participants

Model 1: unadjusted.

Model 2: adjusted for age, sex, and race/ethnicity.

Model 3: adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and socioeconomic status. Socioeconomic status was represented by TDI in the UK Biobank and PIR in US NHANES.

* NHANES analyses were survey-weighted.

Supplementary Table S4. Bidirectional longitudinal associations between COPD and cancer in the UK Biobank

Outcome	Baseline exposure	Participants, n	Events, n	Model 1 HR (95% CI), P-value	Model 2 HR (95% CI), P-value	Model 3 HR (95% CI), P-value
Incident cancer	No COPD at baseline	430,862	105,182	Ref	Ref	Ref
Incident cancer	COPD at baseline	430,862	105,182	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	468,902	20,439	Ref	Ref	Ref
Incident COPD	Cancer at baseline	468,902	20,439	1.53 (1.47–1.59), <0.001	1.39 (1.33–1.44), <0.001	1.31 (1.26–1.36), <0.001

Note: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; UK, United Kingdom.

Model 1: unadjusted.

Model 2: adjusted for age, sex, and race/ethnicity.

Model 3: adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and Townsend deprivation index

**Events indicate the number of incident outcome cases during follow-up. For the incident cancer analysis, events represent new cancer diagnoses; for the incident COPD analysis, events represent new COPD diagnoses.*

Supplementary Table S5. Crude all-cause mortality by COPD and cancer status

Cohort	COPD/cancer status	Participants, n	Deaths, n	Mortality, %
UK Biobank	No COPD and no cancer	416,809	31,429	7.5
	COPD only	14,053	2,797	19.9
	Cancer only	52,093	7,193	13.8
	Coexisting COPD and cancer	2,525	784	31.0
US NHANES	No COPD and no cancer	39,378	4,756	12.1
	COPD only	2,917	745	25.5
	Cancer only	3,663	1,265	34.5
	Coexisting COPD and cancer	639	273	42.7

COPD, chronic obstructive pulmonary disease; NHANES, National Health and Nutrition Examination Survey. Mortality percentage represents crude all-cause mortality within each COPD/cancer status group.

Supplementary Table S6. Association of COPD and cancer status with all-cause mortality across three Cox regression models

Cohort	COPD/cancer status	Model 1 HR (95% CI), P-value	Model 2 HR (95% CI), P-value	Model 3 HR (95% CI), P-value
UK Biobank	No COPD and No Cancer	Ref	Ref	Ref
	Only COPD	2.83 (2.72-2.94), <0.001	2.29 (2.20-2.38), <0.001	1.96 (1.89-2.04), <0.001
	Only Cancer	1.92 (1.88-1.97), <0.001	1.73 (1.69-1.78), <0.001	1.68 (1.64-1.73), <0.001
	Both COPD and Cancer	4.83 (4.50-5.19), <0.001	3.54 (3.30-3.80), <0.001	2.94 (2.74-3.16), <0.001
	No COPD and No Cancer	Ref	Ref	Ref
US NHANES	Only COPD	2.65 (2.40-2.94), <0.001	1.89 (1.71-2.10), <0.001	1.62 (1.46-1.79), <0.001
	Only Cancer	3.74 (3.44-4.08), <0.001	1.28 (1.18-1.39), <0.001	1.31 (1.22-1.42), <0.001
	Both COPD and Cancer	5.92 (4.92-7.13), <0.001	2.24 (1.92-2.60), <0.001	2.03 (1.76-2.34), <0.001
	No COPD and No Cancer	Ref	Ref	Ref

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; PIR, poverty-income ratio; TDI, Townsend deprivation index.

Model 1: unadjusted.

Model 2: adjusted for age, sex, and race/ethnicity.

Model 3: adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and socioeconomic status. Socioeconomic status was represented by TDI in the UK Biobank and PIR in US NHANES. NHANES Cox models were survey-weighted

Sensitivity analysis

Supplementary Table S7. Baseline characteristics of participants after excluding lung cancer patients in the UK Biobank and US NHANES study populations.

Characteristic	UK Biobank						US NHANES					
	Overall 479381	Only COPD 13495	Only Cancer 50939	Both 2296	None 412651	P- value	Overall 46471	Only COPD 2917	Only Cancer 3583	Both 593	None 39378	P-value
Age (Yrs)	56.45 (8.09)	58.82 (7.47)	58.28 (7.59)	60.56 (6.81)	56.13 (8.13)	<0.001	46.60 (16.66)	52.17 (16.11)	61.69 (14.74)	62.29 (14.22)	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)	2.16 (0.84)	2.03 (0.81)	<0.001
Sex						<0.001						<0.001
Female	261,641 (55%)	6,778 (50%)	33,764 (66%)	1,345 (59%)	219,754 (53%)		24,070 (52%)	1,731 (62%)	1,868 (56%)	339 (65%)	20,132 (51%)	
Male	217,740 (45%)	6,717 (50%)	17,175 (34%)	951 (41%)	192,897 (47%)		22,401 (48%)	1,186 (38%)	1,715 (44%)	254 (35%)	19,246 (49%)	
Ethnicity/Race						<0.001						<0.001
Non-White	24,838 (5%)	392 (3%)	2,578 (5%)	56 (2%)	21,812 (5%)		9,695 (14%)	585 (12%)	511 (6%)	61 (4%)	8,538 (15%)	
White	454,543 (95%)	13,10 (97%)	48,361 (95%)	2,240 (98%)	390,839 (95%)		20,937 (86%)	1,679 (88%)	2,462 (94%)	464 (96%)	16,332 (85%)	
Education Level						<0.001						<0.001
College or above	107,953 (27%)	2,650 (27%)	11,551 (28%)	448 (29%)	93,304 (27%)		23,525 (59%)	1,280 (49%)	1,976 (65%)	291 (58%)	19,978 (60%)	
Less than college	290,191 (73%)	7,012 (73%)	29,181 (72%)	1,090 (71%)	252,908 (73%)		22,902 (41%)	1,632 (51%)	1,605 (35%)	302 (42%)	19,363 (40%)	
TDI/PIR						<0.001						<0.001
Low	174,973 (36%)	3,970 (29%)	18,272 (36%)	624 (27%)	152,107 (37%)		9,720 (14%)	824 (22%)	491 (9%)	122 (16%)	8,283 (14%)	

Medium	169,006 (35%)	4,415 (33%)	18,058 (35%)	755 (33%)	145,778 (35%)	19,435 (36%)	1,359 (43%)	1,493 (32%)	294 (44%)	16,289 (36%)
High	135,402 (28%)	5,110 (38%)	14,609 (29%)	917 (40%)	114,766 (28%)	17,316 (50%)	734 (35%)	1,599 (59%)	177 (41%)	14,806 (50%)
Smoking	<0.001									
Non smoker	264,984 (55%)	5,018 (37%)	27,508 (54%)	770 (34%)	231,688 (56%)	25,247 (54%)	920 (32%)	1,712 (48%)	154 (27%)	22,461 (56%)
Smoker	214,397 (45%)	8,477 (63%)	23,431 (46%)	1,526 (66%)	180,963 (44%)	21,224 (46%)	1,997 (68%)	1,871 (52%)	439 (73%)	16,917 (44%)

Note: Data are presented as mean (SD) for continuous variables and n (%) for categorical variables; NHANES values are weighted; COPD = chronic obstructive pulmonary disease; SD = standard deviation; PIR = poverty-income ratio; BMI = body mass index

Supplementary Table S8. Association of COPD with prevalent non-lung cancer at baseline

Cohort	COPD status	Participants, n	Cancer cases, n	Cancer prevalence, %	Model 1 OR (95% CI), P-value	Model 2 OR (95% CI), P-value	Model 3 OR (95% CI), P-value
UKB	No COPD	463,590	50,939	10.99	Ref	Ref	Ref
UKB	COPD	15,791	2,296	14.54	1.38 (1.32–1.44), <0.001	1.29 (1.23–1.35), P<0.001	1.24 (1.18–1.30), <0.001
NHANES	No COPD	42,961	3,583	8.45	Ref	Ref	Ref
NHANES	COPD	3,510	593	17.95	2.37 (2.11–2.67), <0.001	1.57 (1.37–1.79), <0.001	1.57 (1.37–1.80), <0.001

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PIR, poverty-income ratio; TDI, Townsend deprivation index; UK, United Kingdom; **Model 1:** unadjusted; **Model 2:** adjusted for age, sex, and race/ethnicity; **Model 3:** adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and socioeconomic status. Socioeconomic status was represented by TDI in the UK Biobank and PIR in US NHANES; **Note:** NHANES analyses were survey-weighted

Supplementary Table S9. Bidirectional longitudinal associations between COPD and non-lung cancer in the UK Biobank

Outcome	Baseline exposure	Participants, n	Events, n	Model 1 HR (95% CI), P-value	Model 2 HR (95% CI), P-value	Model 3 HR (95% CI), P-value
Incident non-lung cancer	No COPD at baseline	426,146	100,467	Ref	Ref	Ref
Incident non-lung cancer	COPD at baseline	426,146	100,467	1.29 (1.25–1.34), <0.001	1.16 (1.12–1.19), <0.001	1.12 (1.08–1.15), <0.001
Incident COPD	No cancer at baseline	463,590	18,765	Ref	Ref	Ref
Incident COPD	Non-lung cancer at baseline	463,590	18,765	1.50 (1.44–1.56), <0.001	1.37 (1.31–1.43), <0.001	1.30 (1.25–1.35), <0.001

Note: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; UK, United Kingdom; **Model 1**; unadjusted, **Model 2**: adjusted for age, sex, and race/ethnicity, **Model 3**: adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and socioeconomic status. Socioeconomic status was represented by TDI in the UK Biobank and PIR in US NHANES; **Events indicate the number of incident outcome cases during follow-up. For the incident cancer analysis, events represent new cancer diagnoses; for the incident COPD analysis, events represent new COPD diagnoses.*

Supplementary Table S10. Association of COPD and non-lung cancer status with all-cause mortality across three Cox regression models

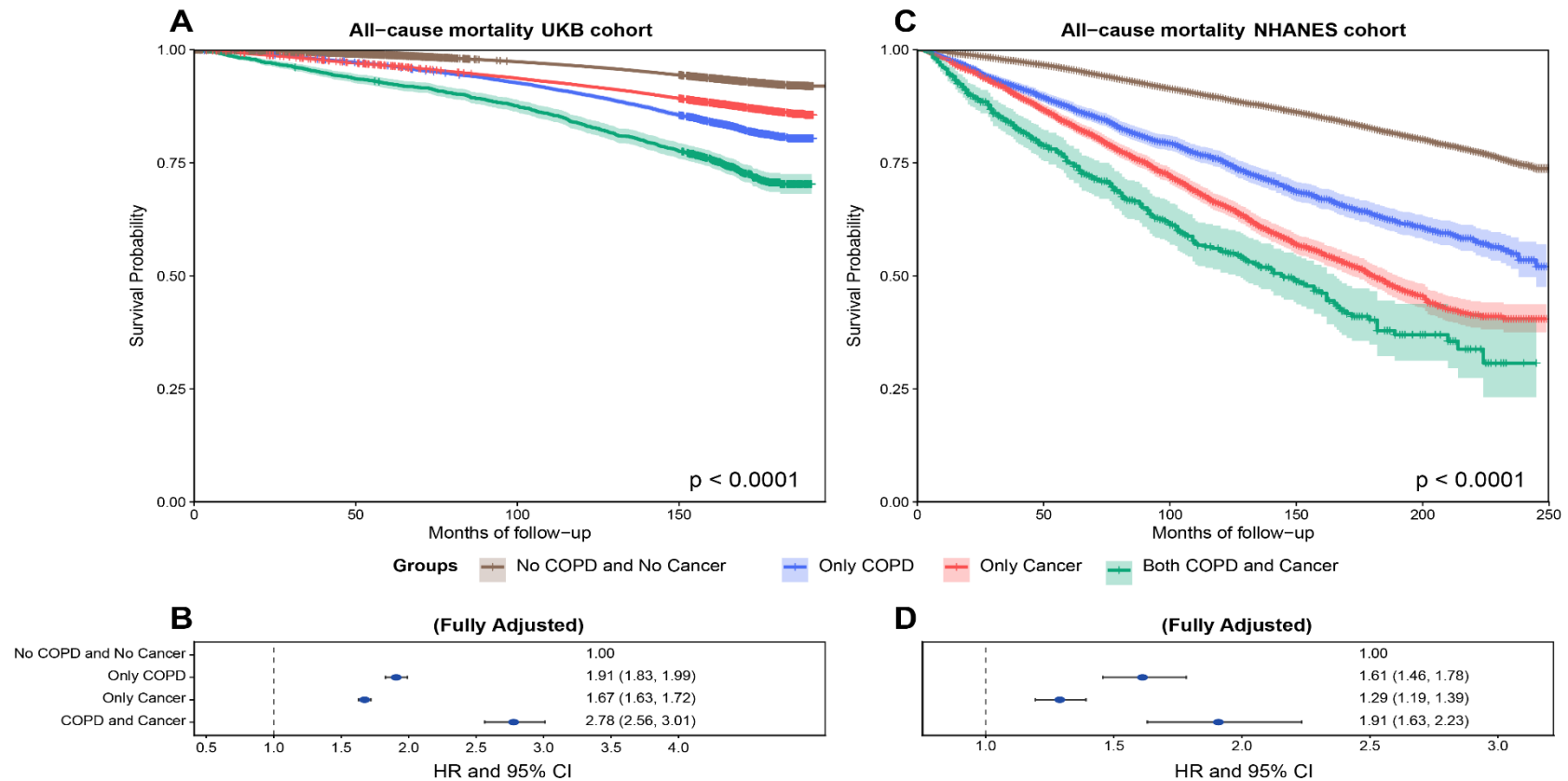
Cohort	COPD/cancer status	Model 1 HR (95% CI),	Model 2 HR (95% CI),	Model 3 HR (95% CI),
		P-value	P-value	P-value
UK Biobank	No COPD and no cancer	Ref	Ref	Ref
	COPD only	2.68 (2.57–2.79), <0.001	2.18 (2.09–2.27), <0.001	1.91 (1.83–1.99), <0.001
	Cancer only	1.90 (1.85–1.95), <0.001	1.71 (1.67–1.76), <0.001	1.67 (1.63–1.72), P<0.001
	Coexisting COPD and non-lung cancer	4.40 (4.07–4.77), <0.001	3.25 (3.00–3.52), <0.001	2.78 (2.56–3.01), <0.001
	No COPD and no cancer	Ref	Ref	Ref
US NHANES	COPD only	2.65 (2.39–2.94), <0.001	1.89 (1.71–2.09), <0.001	1.61 (1.46–1.78), <0.001
	Cancer only	3.67 (3.38–4.00), <0.001	1.25 (1.16–1.35), <0.001	1.29 (1.19–1.39), P<0.001
	Coexisting COPD and non-lung cancer	5.52 (4.59–6.63), <0.001	2.11 (1.79–2.49), <0.001	1.91 (1.63–2.23), <0.001

Note: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; PIR, poverty-income ratio; TDI, Townsend deprivation index; UK, United Kingdom, **Model 1:** unadjusted, **Model 2:** adjusted for age, sex, and race/ethnicity, **Model 3:** adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and socioeconomic status. Socioeconomic status was represented by TDI in the UK Biobank and PIR in US NHANES, **Reference group;** participants with neither COPD nor cancer, **Note;** Lung cancer was excluded in this sensitivity analysis, NHANES analyses were survey-weighted.

Supplementary Table S11. Associations of coexisting COPD and non-lung cancer compared to having Only COPD and Only non-lung Cancer with all-cause mortality and stratified by subgroups.

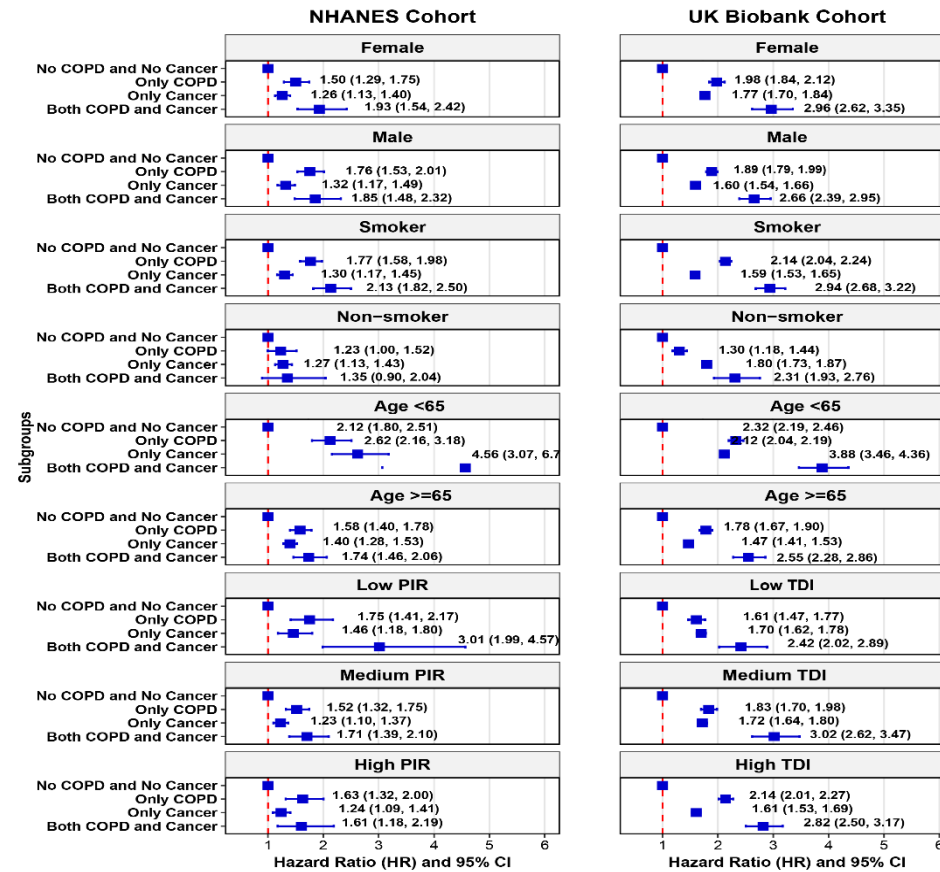
Coexisting COPD and Cancer vs. COPD only, HR (95% CI)			Coexisting COPD and Cancer vs. Cancer only, HR (95% CI)			
Subgroup	Category	Model	UK Biobank	US NHANES	UK Biobank	US NHANES
Overall	Overall	Model 1	1.64 (1.50, 1.79)	2.08 (1.71, 2.53)	2.31 (2.12, 2.51)	1.50 (1.23, 1.84)
		Model 2	1.48 (1.36, 1.62)	1.10 (0.91, 1.33)	1.89 (1.74, 2.05)	1.67 (1.41, 1.98)
		Model 3	1.45 (1.32, 1.58)	1.18 (0.98, 1.41)	1.67 (1.53, 1.81)	1.47 (1.25, 1.73)
Sex	Female	Model 1	1.60 (1.39, 1.84)	1.92 (1.46, 2.53)	2.11 (1.86, 2.39)	1.55 (1.19, 2.02)
		Model 2	1.53 (1.33, 1.75)	1.29 (0.98, 1.70)	1.87 (1.64, 2.12)	1.77 (1.39, 2.26)
		Model 3	1.50 (1.31, 1.72)	1.29 (0.98, 1.69)	1.68 (1.48, 1.91)	1.53 (1.20, 1.95)
	Male	Model 1	1.87 (1.66, 2.10)	2.54 (1.88, 3.41)	2.29 (2.05, 2.56)	1.73 (1.27, 2.34)
		Model 2	1.45 (1.29, 1.63)	0.93 (0.72, 1.21)	1.92 (1.72, 2.14)	1.56 (1.21, 2.02)
		Model 3	1.41 (1.25, 1.58)	1.06 (0.83, 1.35)	1.67 (1.49, 1.86)	1.41 (1.11, 1.79)
Smoking	Smoker	Model 1	1.49 (1.35, 1.65)	2.00 (1.60, 2.50)	2.37 (2.15, 2.60)	1.62 (1.29, 2.05)
		Model 2	1.40 (1.27, 1.55)	1.13 (0.93, 1.37)	2.01 (1.83, 2.21)	1.77 (1.47, 2.14)
		Model 3	1.38 (1.25, 1.52)	1.21 (1.00, 1.46)	1.86 (1.69, 2.04)	1.65 (1.38, 1.97)
	Non-smoker	Model 1	2.07 (1.69, 2.53)	2.07 (1.33, 3.20)	1.57 (1.31, 1.89)	0.97 (0.66, 1.44)
		Model 2	1.80 (1.47, 2.21)	1.02 (0.64, 1.63)	1.34 (1.12, 1.61)	1.09 (0.73, 1.63)
		Model 3	1.77 (1.45, 2.17)	1.09 (0.68, 1.77)	1.29 (1.07, 1.54)	1.06 (0.71, 1.59)

Model 1: Unadjusted; **Model 2:** adjusted for age, sex, and race/ethnicity; **Model 3:** adjusted for age, sex, race/ethnicity, education level, smoking status, BMI category, and socioeconomic status. Socioeconomic status was represented by TDI in the UK Biobank and PIR in US NHANES. *NHANES analyses were survey-weighted; **Note;** Lung cancer was excluded in this sensitivity analysis,



Supplementary Figure S1 a: Kaplan-Meier curves demonstrating survival by COPD and non-lung cancer status (COPD only, non- lung cancer only, coexisting COPD and non- lung cancer, no COPD or non-lung cancer) for all-cause mortality in UKB Cohort. **b:** Results from multivariable Cox proportional hazards models comparing risk of all-cause mortality by COPD and non- lung cancer status groupings (reference: No COPD and No non- lung cancer) in the overall population of UKB Cohort. **c:** Kaplan-Meier curves demonstrating survival by COPD and non-lung cancer status (COPD only, non-lung cancer only, coexisting COPD and non-lung cancer, no COPD or non-lung cancer) for all-cause mortality in US Nhanes. **d:** Results from multivariable Cox proportional hazards models comparing risk of all-cause mortality by COPD and non-lung cancer status (reference: No COPD and No non-lung cancer) in the overall population of US Nhanes. All multivariable models were adjusted for age, sex, race and ethnicity, education, smoking, BMI and PIR/TDI (model 3).

Note: In the panel B and D, cancer is all non-lung cancers



Supplementary Figure S2. Associations of COPD and non-lung cancer status with all-cause mortality stratified by subgroups in the UK Biobank and US NHANES cohorts. 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.

Note: cancer is all non-lung cancers