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Association of Remnant Cholesterol with All-Cause and Cause-Specific Mortality in Patients with Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study

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Abstract

Background

Although remnant cholesterol (RC) has been established as a causal risk factor for atherosclerotic cardiovascular disease in the general population, whether this pro-atherogenic lipid component holds the same prognostic significance in patients with chronic obstructive pulmonary disease (COPD)—a group characterized by systemic inflammation and metabolic disorders—remains unexplored.

Methods

This cohort study utilized data from ten consecutive cycles (1999–2018) of the National Health and Nutrition Examination Survey (NHANES), linked to National Death Index (NDI) mortality records through December 31, 2019. Adults with self-reported COPD diagnosis and complete fasting lipid profiles were included. RC was calculated as total cholesterol minus HDL-C minus LDL-C estimated via the Sampson formula. Analyses employed complex sampling-weighted Cox regression (with stepwise covariate adjustment), restricted cubic splines (RCS), Kaplan-Meier survival analysis, and pre-specified subgroup and sensitivity analyses.

Results

Among 1,563 eligible patients (431 deaths, median follow-up 7.4 years, IQR 3.5–12.3), after full adjustment, the highest RC quartile (Q4) was associated with a significantly lower risk of all-cause mortality compared to the lowest quartile (Q1) (HR 0.62; 95% CI 0.42–0.91; P = 0.014; P-trend = 0.028). The association was most pronounced for chronic lower respiratory disease (CLRD) mortality (HR 0.29; 95% CI 0.10–0.88; P = 0.029). Cardiovascular mortality showed a similar direction but did not reach statistical significance (HR 0.68; P = 0.274). The RCS model identified a non-linear dose-response curve (P-nonlinear < 0.001), with the steepest risk reduction observed below 20 mg/dL. Subgroup analyses suggested potential effect modification by sex (male: HR 0.70, P = 0.036) and diabetes status (diabetes: HR 0.54, P = 0.026), although no formal interaction terms reached significance. Results were consistent across four sensitivity analyses (Q4 HR range 0.60–0.67; all P < 0.05).

Conclusions

In this nationally representative cohort, higher RC levels were independently and inversely associated with all-cause and respiratory mortality in COPD patients—a finding that reverses the established detrimental role of RC in the general population and parallels the metabolic paradox described in other wasting diseases. If prospectively validated, RC may serve as an inexpensive and routinely accessible prognostic marker in COPD.

Clinical trial number:

not applicable.

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by persistent airflow limitation and systemic inflammation. Statistically, COPD has become the third leading cause of death globally, accounting for over 3 million deaths annually [1]. The global mortality burden among COPD patients remains substantial, with prognosis influenced not only by airflow limitation itself but also by systemic comorbidities including cardiovascular disease, diabetes, and sarcopenia [2]. Standard risk stratification tools such as the BODE index incorporate limited metabolic information [3], highlighting the need for simple and inexpensive biomarkers to improve prognostic assessment. Remnant cholesterol (RC), defined as total cholesterol minus HDL-C minus LDL-C, represents the cholesterol content of triglyceride-rich lipoproteins [4]. Mendelian randomization studies have established RC as a causal risk factor for ischemic heart disease [5, 6], and recent population-based studies have linked elevated RC to increased all-cause and cardiovascular mortality in the general population [8–11]. However, COPD is characterized by chronic airway inflammation, accelerated catabolism, and metabolic disorders [7, 12, 13]—conditions under which the “obesity paradox” and “cholesterol paradox” have been repeatedly reported [14–17]. Whether RC exhibits a similar paradoxical association in COPD patients remains unknown.

As a dynamic parameter reflecting the metabolism of triglyceride-rich lipoproteins, RC can be conveniently calculated from routine lipid panels without additional cost. Clinical studies have confirmed associations between RC and various diseases and outcomes [5, 8, 9]. In recent years, several NHANES-based studies have explored the relationship between RC and mortality in the general population [10, 11], but no study has examined this association in a specific disease population characterized by catabolism. Furthermore, the relationship between RC and cause-specific mortality, including cardiovascular disease mortality and chronic lower respiratory disease mortality, in COPD patients has not been explored.

Therefore, the primary objective of this study was to evaluate the associations between RC levels and all-cause, cardiovascular disease (CVD), and CLRD mortality among COPD patients, using data from ten consecutive cycles of NHANES (1999–2018) linked to the National Death Index through December 31, 2019. Cox proportional hazards regression, Kaplan-Meier survival curves, restricted cubic spline models, and multiple sensitivity strategies were employed to investigate these associations.

Methods

Study Design and Data Source

NHANES is a cross-sectional survey of the non-institutionalized civilian U.S. population using a stratified, multistage probability sampling design. Data from ten 2-year cycles between 1999 and 2018 were pooled. The NCHS Research Ethics Review Board approved all protocols; all participants provided written informed consent. As the data are publicly available and de-identified, this secondary analysis required no additional ethical approval.

Study Population

Eligible participants were adults aged ≥ 20 years with self-reported physician diagnosis of emphysema (variable MCQ160G) or chronic bronchitis (MCQ160K), valid measurements of fasting total cholesterol, HDL-C, and triglycerides, and linkage to mortality follow-up files. Pregnant individuals, those with triglycerides exceeding 400 mg/dL (due to unreliable LDL-C estimation [18]), and those missing key covariates were excluded. The final analytical cohort comprised 1,563 patients (Fig. 1).

Exposure Variable: Remnant Cholesterol

LDL-C was uniformly recalculated for all cycles using the Sampson formula [18] (which outperforms the Friedewald formula at higher triglyceride levels): LDL-C = TC/0.948 − HDL-C/0.971 − (TG/8.56 + TG×non-HDL-C/2140 − TG²/16100) − 9.44. RC = TC − HDL-C − LDL-C (Sampson). RC was categorized into quartiles for primary analysis, with Q1 as the reference group.

Outcome Variables

The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular mortality (UCOD_LEADING codes 1 and 5, corresponding to heart disease and cerebrovascular disease) and chronic lower respiratory disease (CLRD) mortality (UCOD_LEADING code 3). Follow-up extended from the NHANES examination date to the date of death or the administrative censoring date of December 31, 2019.

Covariates

Covariates were selected a priori based on directed acyclic graph reasoning and previous NHANES literature [19]. Demographic variables included age (continuous), sex, and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Other). Behavioral variables included education level, smoking status (never/former/current), alcohol consumption, and body mass index (BMI). Comorbidities included hypertension, diabetes (self-reported diagnosis, fasting glucose ≥ 126 mg/dL, or HbA1c ≥ 6.5%), coronary heart disease, congestive heart failure, stroke, and chronic kidney disease (eGFR < 60 mL/min/1.73 m², CKD-EPI 2021 formula). Statin use was obtained from the prescription medication questionnaire.

Statistical Analysis

All analyses adhered to NHANES analytical guidelines, accounting for the complex sampling design with sample weights, strata, and clusters. Fasting subsample weights were divided by 10 to accommodate pooling across ten cycles. All respondent data were weighted using the recommended NHANES examination weights to account for differential sampling probabilities and non-response. Comparisons of baseline characteristics used weighted linear regression (continuous variables) and Rao-Scott chi-square tests (categorical variables).

Weighted Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) at three adjustment levels: Model 1 (unadjusted), Model 2 (age, sex, race/ethnicity), Model 3 (all aforementioned covariates). The proportional hazards assumption was verified via Schoenfeld residuals (global P = 1.00). Restricted cubic splines with 4 knots were used to explore continuous dose-response relationships and test for non-linearity. P-for-trend was obtained by modeling the median RC value within each quartile as a continuous variable in the fully adjusted model.

Pre-specified subgroup analyses were stratified by sex, age (< 65 vs ≥ 65 years), smoking status, BMI category, hypertension, diabetes, and statin use; P-for-interaction was calculated using multiplicative interaction terms. Four sensitivity analyses tested robustness: (i) excluding participants who died within the first two years of follow-up, (ii) restricting to non-statin users, (iii) additionally adjusting for C-reactive protein, (iv) modeling RC as a continuous variable per 10 mg/dL increment. All analyses were performed in R 4.3 using the survey, survival, and rms packages. A two-sided $P < 0.05$ was considered the threshold for statistical significance.

Results

Participant Characteristics

The screening process (Fig. 1) ultimately included 1,563 COPD patients; their weighted baseline characteristics are presented in Table 1. With increasing RC quartiles, participants were more likely to have diabetes (Q1: 5.2% vs Q4: 19.2%; $P < 0.001$), had higher BMI (28.1 vs 31.7 kg/m²; $P < 0.001$), and had higher statin use (17.6% vs 29.1%; $P = 0.007$). Non-Hispanic whites were also more prevalent in the higher quartiles (73.4% vs 82.4%; $P < 0.001$). No significant difference in mean age was observed across groups ($P = 0.149$).

Table 1
Weighted baseline characteristics stratified by RC quartiles

Characteristic	Q1 (n = 391)	Q2 (n = 391)	Q3 (n = 391)	Q4 (n = 390)	P
Age, years	52.3 ± 1.0	54.7 ± 0.9	54.9 ± 1.0	54.8 ± 1.1	0.149
Male, %	33.4	30.8	43.3	38.8	0.031
NH White, %	73.4	74.5	78.9	82.4	< 0.001
NH Black, %	16.1	11.3	6.8	4.7	
Other race, %	10.5	14.2	14.3	12.9	
BMI, kg/m²	28.1 ± 0.7	30.0 ± 0.6	31.9 ± 0.5	31.7 ± 0.5	< 0.001
Current smoker, %	32.0	35.2	32.7	33.4	0.347
Diabetes, %	5.2	10.9	10.7	19.2	< 0.001
Hypertension, %	45.4	48.2	52.3	53.4	0.331
CHD, %	8.1	11.8	9.2	8.7	0.562
CHF, %	8.2	8.3	9.8	9.8	0.848
Statin use, %	17.6	31.0	27.4	29.1	0.007
TC, mg/dL	184.6	190.4	193.8	218.9	< 0.001
HDL-C, mg/dL	65.4	56.3	49.7	42.7	< 0.001
TG, mg/dL	63.3	98.7	144.0	258.1	< 0.001
RC, mg/dL	12.1 ± 2.1	17.8 ± 1.6	25.5 ± 2.6	45.4 ± 20.5	< 0.001
CRP, mg/L	3.4	2.4	2.3	2.6	0.825
Follow-up, yrs	8.2 ± 5.7	8.5 ± 5.5	8.9 ± 5.5	9.6 ± 5.6	0.165
Death, n(%)	102(22.0%)	100(20.0%)	121(25.0%)	108(22.2%)	0.595

Values are weighted mean ± SE or weighted proportion. P from survey-weighted regression or Rao-Scott χ^2.

RC and All-Cause Mortality

During a median follow-up of 7.4 years (IQR 3.5–12.3), a total of 431 deaths were accumulated (Q1: 102; Q2: 100; Q3: 121; Q4: 108). In the fully adjusted model, all-cause mortality in Q4 was 38% lower compared to Q1 (HR 0.62; 95% CI 0.42–0.91; P = 0.014), with a significant trend across quartiles (P-trend = 0.028). The intermediate quartiles showed directionally consistent but non-significant reductions (Q2 HR 0.77; Q3 HR 0.85). Analyzed as a continuous exposure variable, each 10 mg/dL increase in RC was associated with a 10% reduction in mortality (HR 0.90; 0.82–1.00; P = 0.040). Complete results from the multivariable models are shown in Table 2.

Table 2
Survey-weighted Cox regression: RC quartiles and mortality

Outcome / Model	Q1	Q2 HR (95%CI)	Q3 HR (95%CI)	Q4 HR (95%CI)	P Q4
All-cause mortality					
Model 1	Ref	0.88 (0.54–1.41)	1.06 (0.73–1.53)	0.86 (0.56–1.33)	0.508
Model 2	Ref	0.78 (0.50–1.21)	0.87 (0.63–1.21)	0.72 (0.49–1.06)	0.094
Model 3	Ref	0.77 (0.49–1.21)	0.85 (0.60–1.20)	0.62 (0.42–0.91)	0.014
CVD mortality					
Model 1	Ref	1.69 (0.84–3.39)	1.38 (0.55–3.49)	1.16 (0.52–2.57)	0.723
Model 2	Ref	1.48 (0.79–2.78)	1.17 (0.51–2.67)	1.02 (0.51–2.03)	0.953
Model 3	Ref	1.30 (0.70–2.41)	0.93 (0.40–2.16)	0.68 (0.34–1.36)	0.274
CLRD mortality					
Model 1	Ref	0.93 (0.30–2.93)	1.35 (0.57–3.21)	0.55 (0.17–1.79)	0.322
Model 2	Ref	0.85 (0.26–2.74)	1.10 (0.44–2.73)	0.44 (0.15–1.27)	0.128
Model 3	Ref	1.09 (0.33–3.65)	1.02 (0.42–2.50)	0.29 (0.10–0.88)	0.029

Model 1: unadjusted. Model 2: age, sex, race. Model 3: all covariates.

RC and Cause-Specific Mortality

Cardiovascular mortality (151 events) did not show an inverse association in the crude model (Q4 HR 1.16; P = 0.723). After full adjustment, the point estimate shifted to 0.68 (P = 0.274), a pattern consistent with positive confounding by diabetes and statin use. For CLRD mortality (78 events), the fully adjusted HR for Q4 was 0.29 (0.10–0.88; P = 0.029; P-trend = 0.010), representing the strongest cause-specific finding in this study.

Dose-Response Analysis

Restricted cubic spline modeling confirmed a significant overall association (P < 0.001) and a significant deviation from linearity (P-nonlinear < 0.001; Fig. 3). The curve was steepest below approximately 20 mg/dL, crossed the reference line (HR = 1.0) around 20–25 mg/dL, and continued to decline gradually at higher RC levels.

Subgroup and Sensitivity Analyses

The protective association was most pronounced in males (HR 0.70; P = 0.036) and in patients with comorbid diabetes (HR 0.54; P = 0.026), although no interaction term reached formal significance (all P-interaction > 0.05; Table 3). Sensitivity analyses consistently confirmed the primary finding: Q4 HRs

ranged from 0.60 to 0.67 and remained significant regardless of excluding early deaths, removing statin users, or adjusting for CRP (Table 4).

Table 3
Subgroup analyses: high vs low RC and all-cause mortality

Subgroup	N	Events	HR (95% CI)	P	P-interaction
Male	622	239	0.70 (0.50–0.98)	0.036	0.151
Female	941	192	1.21 (0.81–1.81)	0.360	
Age < 65	963	117	0.88 (0.60–1.28)	0.502	0.874
Age ≥ 65	600	314	0.93 (0.68–1.26)	0.631	
Diabetes: No	1322	344	0.88 (0.65–1.19)	0.404	0.257
Diabetes: Yes	241	87	0.54 (0.32–0.93)	0.026	
HTN: No	700	142	1.04 (0.64–1.69)	0.882	0.661
HTN: Yes	863	289	0.81 (0.59–1.09)	0.165	
Statin: No	1127	297	0.84 (0.59–1.20)	0.338	0.232
Statin: Yes	436	134	1.14 (0.66–1.96)	0.634	

High RC = above median. Adjusted for age, sex, race, smoking, BMI (minus stratification variable).

Table 4
Sensitivity analyses: Q4 vs Q1 and all-cause mortality

Analysis	N	Events	Q4 HR (95% CI)	P
Main analysis	1,563	431	0.62 (0.42–0.91)	0.014
Exclude death < 2 yr	1,471	339	0.67 (0.48–0.94)	0.020
Exclude statin users	1,127	297	0.60 (0.39–0.93)	0.022
Adjusted for CRP	1,240	366	0.62 (0.43–0.90)	0.011
RC per 10 mg/dL	1,563	431	0.90 (0.82–1.00)	0.040

Discussion

In this large population-based cohort study utilizing US NHANES data from 1999–2018, a clear independent inverse association was demonstrated between RC and both all-cause mortality (Q4 vs Q1: HR 0.62, P = 0.014) and CLRD-related mortality (HR 0.29, P = 0.029) in COPD patients. Conversely, the association between RC and CVD mortality was directionally consistent but did not reach statistical significance (HR 0.68, P = 0.274). Further exploratory subgroup analyses indicated that the protective

association was most prominent in male patients and those with comorbid diabetes, with no significant interactions observed. Our analysis also identified a non-linear dose-response relationship between RC and all-cause mortality, with the steepest risk reduction observed at lower RC levels. Furthermore, four sensitivity analyses confirmed the robustness of the primary findings (Q4 HR range: 0.60–0.67, all $P < 0.05$).

These findings appear superficially paradoxical in light of RC's established role as a causal atherogenic factor in the general population [5, 8]. In the Copenhagen General Population Study, elevated RC was associated with a doubling of cardiovascular mortality [8], and Mendelian randomization data have confirmed that genetically elevated RC promotes ischemic heart disease [5, 6]. However, accumulating evidence suggests that the direction of the lipid-mortality association can reverse once chronic catabolic disease is established, a phenomenon termed the "cholesterol paradox" or "obesity paradox" [20]. In advanced heart failure, higher total cholesterol independently predicts better survival, likely because lipoproteins buffer endotoxins and serve as an energy substrate [21]. A similar pattern has been reported following COPD exacerbations, where survivors had significantly higher mean total cholesterol than non-survivors [16]. These results align with our findings, suggesting that RC may play a different prognostic role in COPD patients compared to the general population. Interestingly, a recent Mendelian randomization study demonstrated that genetically elevated RC increases the risk of developing COPD [29], yet our findings suggest that once COPD is established, higher RC levels are associated with improved survival—a pattern consistent with the risk–survival paradox observed across multiple chronic diseases.

To our knowledge, the underlying mechanisms primarily involve the following aspects. COPD is characterized by accelerated catabolism, with resting energy expenditure 15–20% higher than predicted even during stable periods [12]. Up to 40% of patients with moderate-to-severe COPD experience fat-free mass depletion, an independent predictor of mortality regardless of BMI [13, 22]. The European Respiratory Society has positioned nutritional status as an intervenable determinant of COPD prognosis [23]. In this context, higher RC may reflect preserved hepatic synthetic capacity and adequate caloric reserves. RC is carried by VLDL and chylomicron remnants and is closely linked to the flux of triglyceride-rich lipoproteins, which reflect recent dietary fat absorption and hepatic VLDL secretion [4]. Therefore, very low RC levels may signal advanced cachexia, reduced oral intake, or impaired liver function, all of which increase mortality risk in COPD.

The particularly strong protective association in the COPD subgroup with diabetes (HR 0.54) warrants attention. COPD patients with diabetes represent a phenotype with a significantly elevated mortality risk [2, 24]. Insulin resistance promotes hepatic VLDL overproduction and is a major determinant of circulating RC concentration [25]. Paradoxically, in the setting of COPD-related catabolism, the ability to sustain high VLDL output may signify relative metabolic resilience. This interpretation is consistent with data from the NHANES 1999–2018 diabetic sub-cohort, which showed a U-shaped RC-mortality curve with the lowest risk at moderately elevated levels [26].

The sex-specific pattern—significant protection in males (HR 0.70) but not in females (HR 1.21)—may reflect multiple interacting factors. Male COPD patients are more likely to have an emphysema-dominant phenotype, associated with more severe lean mass depletion and metabolic stress [27]. Estrogen modulates hepatic lipase and VLDL clearance, potentially altering the metabolic significance of a given RC level in premenopausal women [28]. Furthermore, female COPD patients tend to have a greater burden of airway disease with less parenchymal destruction and thus may be less susceptible to the catabolic pathways through which RC exerts its apparent protective effect. Given that the interaction term did not reach statistical significance (P = 0.151), this sex difference should be interpreted with caution.

The reversal of the CVD mortality point estimate between adjustment models—from a non-significant positive association (crude HR 1.16) to a non-significant negative association (adjusted HR 0.68)—merits methodological comment. Diabetes and statin use were positively associated with RC but independently predicted CVD death; their inclusion in Model 3 attenuated the positive confounding effect, revealing an underlying (albeit underpowered) negative trend. With only 151 cardiovascular events distributed across four quartiles, our study was underpowered for CVD-specific effects. Larger cohorts or pooled analyses are needed to address this issue.

This study has several notable strengths. First, to our knowledge, it is the first to explore the association between RC and mortality in COPD patients. Second, our study included a large, nationally representative sample from ten consecutive NHANES cycles with a follow-up period of up to 20 years and employed weighted analyses accounting for the complex sampling design. Third, we examined three distinct mortality endpoints (all-cause, CVD, and CLRD) and utilized multiple analytical approaches including Cox regression, Kaplan-Meier survival curves, and restricted cubic spline modeling. Furthermore, comprehensive subgroup and sensitivity analyses, including CRP adjustment and exclusion of statin users and early deaths, were conducted, enhancing the credibility of the findings.

Nevertheless, several limitations should be acknowledged. First, COPD was defined by self-report rather than spirometry, potentially introducing misclassification bias. However, this definition is widely used in NHANES-based COPD studies and has been successfully implemented elsewhere [14]. Second, single-timepoint RC measurement cannot capture longitudinal trajectories or treatment-induced changes. Third, data on COPD severity (FEV1, GOLD stage), inhaled corticosteroid use, and exacerbation frequency were lacking. Fourth, CRP data were unavailable for the 2011–2014 NHANES cycles; however, sensitivity analyses adjusting for CRP yielded results consistent with the main analysis. Fifth, despite efforts to adjust for relevant confounders in multivariable models, residual confounding from unmeasured or unknown factors cannot be entirely excluded. Finally, generalizability is limited to the non-institutionalized US adult population. Future well-designed prospective multicenter studies with spirometry-confirmed COPD are needed to validate these findings.

Conclusions

In this large cohort of US adult COPD patients, higher RC levels were found to be inversely associated with all-cause mortality and CLRD-related mortality after adjusting for various potential confounders. The protective association was particularly prominent in male patients and those with comorbid diabetes. Further exploratory subgroup and sensitivity analyses showed consistent results, supporting the robustness of these findings. Therefore, measuring RC from routine lipid panels may aid in risk assessment and prognosis prediction for COPD patients. Prospective studies with spirometry-confirmed COPD and serial RC measurements are warranted to validate these results.

Declarations

Ethics approval and consent to participate

The National Center for Health Statistics (NCHS) Research Ethics Review Board approved all NHANES protocols. All participants provided written informed consent. As NHANES data are publicly available and de-identified, this secondary analysis did not require additional ethical approval.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

WZY conceptualized the study, performed data curation and formal analysis, and wrote the original draft. XY and XWD contributed to data collection and methodology. SMT, WC and WZY participated in data interpretation and manuscript revision. SJL and WHB supervised the research and provided critical revision. All authors read and approved the final manuscript.

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contributions. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the NCHS or the Centers for Disease Control and Prevention.

Data Availability

All data analyzed in this study are publicly available from the NHANES website (https://www.cdc.gov/nchs/nhanes) and the NCHS linked mortality files (https://www.cdc.gov/nchs/linked-data/mortality-files/index.html).

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Figures

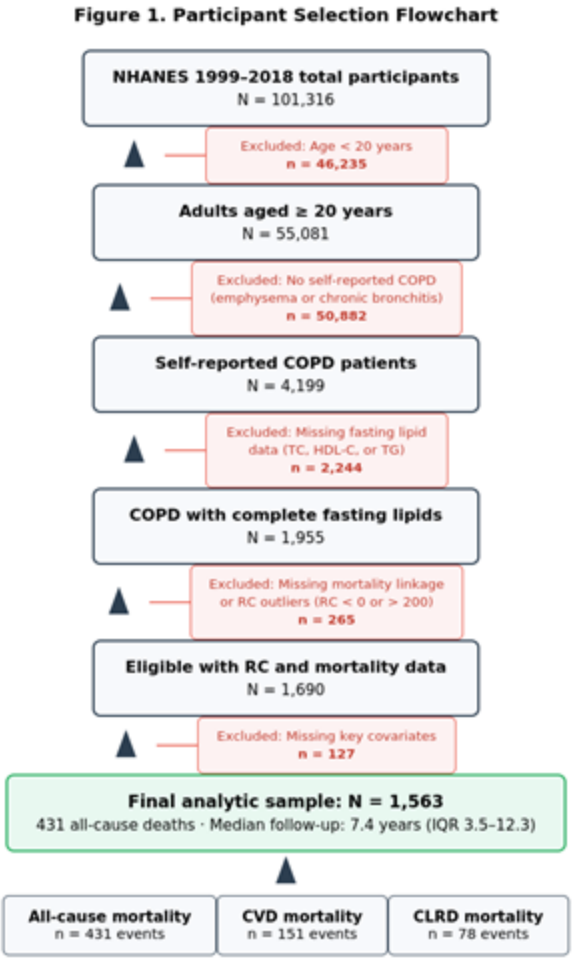


Figure 1

Participant selection flowchart. NHANES 1999–2018, from 101,316 participants to 1,563 eligible COPD patients with complete data.

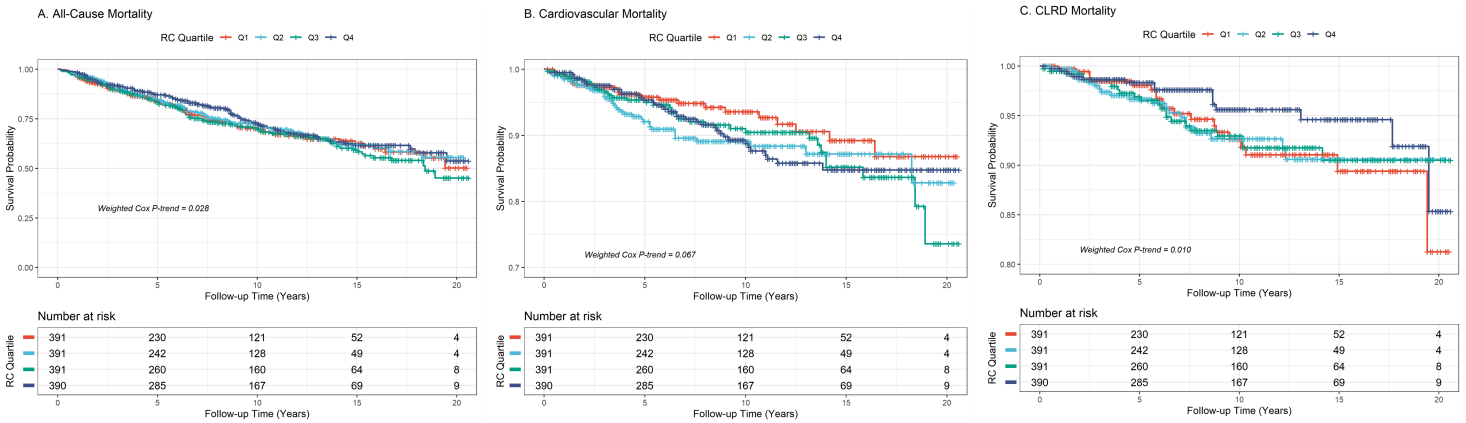


Figure 2

A. Kaplan–Meier curves for all-cause mortality by RC quartile. Survey-weighted Cox P-trend = 0.028.

B. Kaplan–Meier curves for cardiovascular mortality by RC quartile. Survey-weighted Cox P-trend = 0.067.

C. Kaplan–Meier curves for CLRD mortality by RC quartile. Survey-weighted Cox P-trend = 0.010.



Figure 3

A. Restricted cubic spline of the dose–response relationship between RC and all-cause mortality (fully adjusted). P-nonlinearity < 0.001.

B. Restricted cubic spline: RC and CVD mortality. P-nonlinearity = 0.342.

C. Restricted cubic spline: RC and CLRD mortality. P-nonlinearity = 0.262.

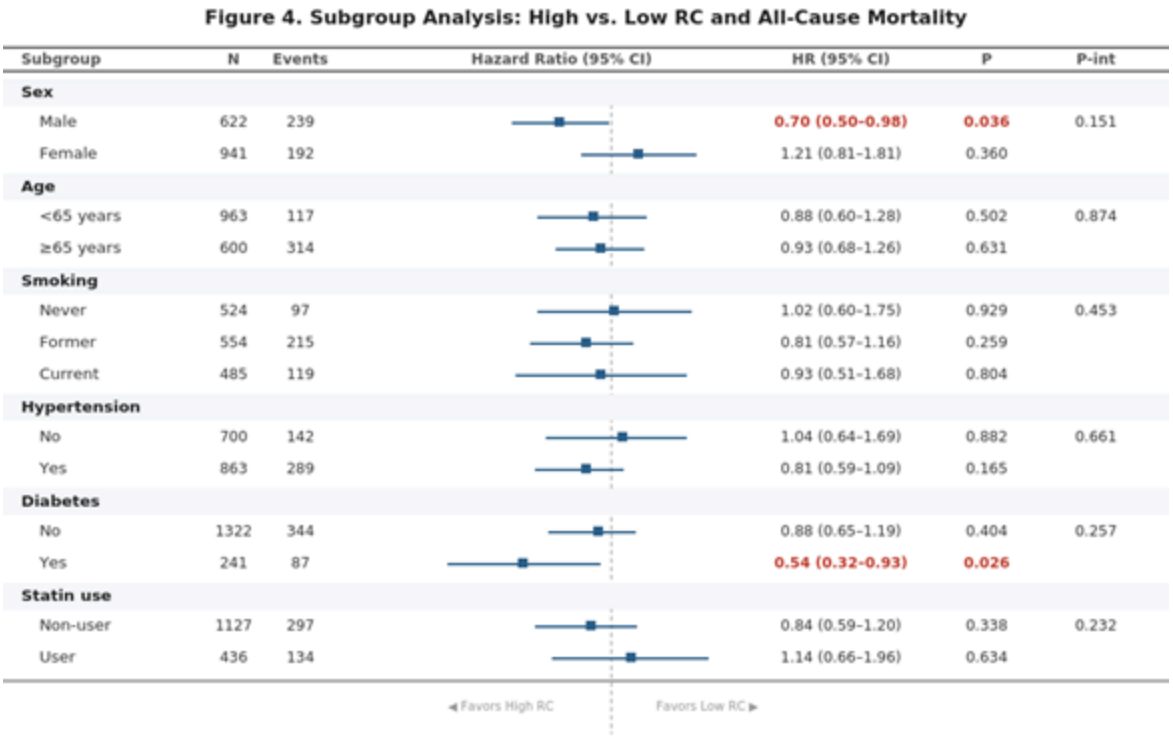


Figure 4

Forest plot of subgroup analyses for the association between high vs low RC and all-cause mortality.