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Association of high-density lipoprotein cholesterol with all-cause and cause-specific mortality in the general population: insights from NHANES 1999–2018

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Abstract

Background Previous studies have shown that extremely high levels of high-density lipoprotein (HDL) cholesterol are paradoxically associated with adverse outcomes in certain clinical settings. We aimed to test the hypothesis that extremely high levels of HDL cholesterol are associated with increased all-cause and cause-specific mortality in the general population.

Methods We included 51,235 individuals from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2018 with a median follow-up of 9.3 years. Baseline HDL cholesterol levels were measured, and mortality data were ascertained from National Death Index (NDI) records through December 31, 2019. Weighted Cox proportional hazards regression, restricted cubic spline curves, and cumulative incidence analyses were performed.

Results A U-shaped association was observed between HDL cholesterol levels and all-cause, cardiovascular and non-cardiovascular mortality in the general population. Compared with individuals with HDL cholesterol levels between 50 and 59 mg/dL, the adjusted hazard ratios (95% CIs) for those with extremely high HDL cholesterol levels (≥ 80 mg/dL) were 1.24 (1.08–1.43), 1.18 (1.03–1.36) and 1.27 (1.09–1.49) for all-cause, cardiovascular and non-cardiovascular mortality, respectively. Similar U-shaped patterns were replicated in both men and women. Further analyses of cause-specific mortality subcategories showed that extremely high HDL cholesterol levels were also associated with increased mortality from heart disease, respiratory disease, endocrine disease, and cancer.

Conclusion Extremely high levels of HDL cholesterol were associated with an increased risk of all-cause, cardiovascular, and non-cardiovascular mortality in the general population. Future studies should investigate the causal factors leading to the association of elevated HDL cholesterol and mortality.

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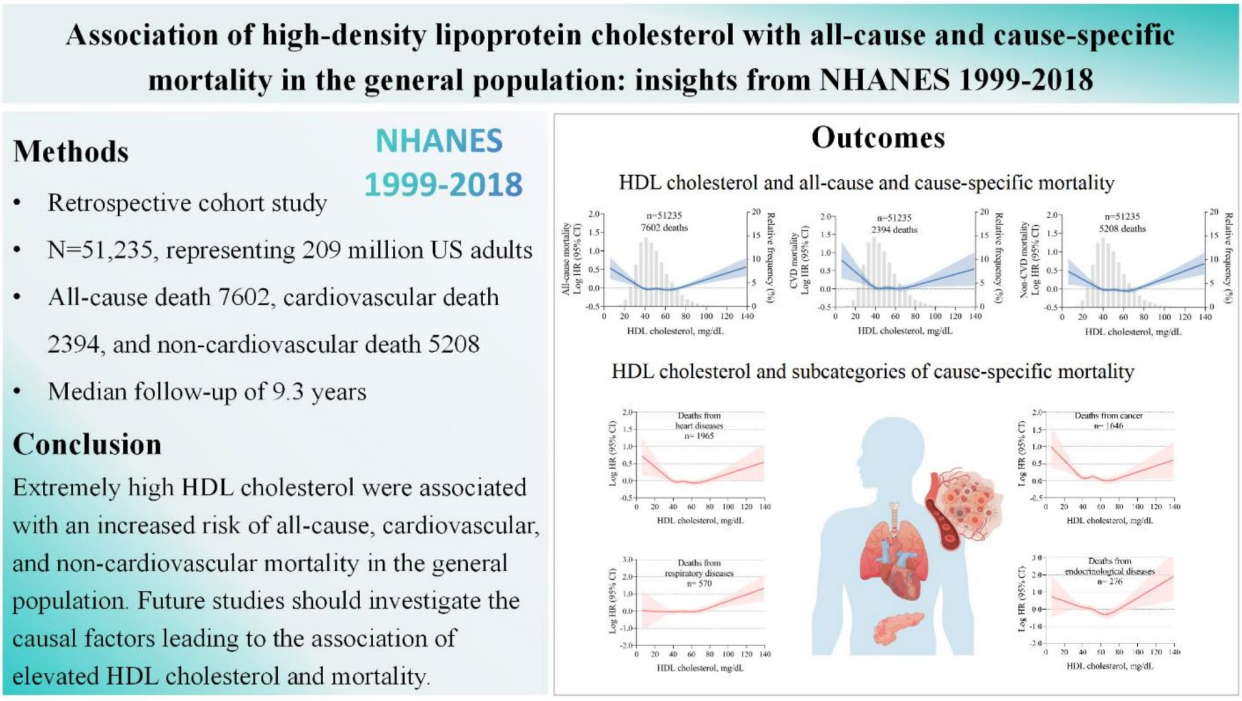
Graphical Abstract



Keywords High-density lipoprotein cholesterol, All-cause mortality, Cardiovascular mortality, Non-cardiovascular mortality, Lipid

Introduction

The inverse association between HDL cholesterol levels and the risk of atherosclerotic cardiovascular disease (ASCVD) has been well documented in epidemiological studies [1]. As a result, HDL cholesterol has been incorporated into the ASCVD risk pooled cohort equation and recognized as a promising therapeutic target [2, 3]. However, subsequent randomized controlled trials have been terminated due to futility in demonstrating the cardiovascular benefit of high-dose niacin or cholesteryl ester transfer protein (CETP) inhibitors, despite significant increases in HDL cholesterol concentrations [4–6]. Furthermore, Mendelian randomization studies have shown that genetically determined high HDL cholesterol levels are not linearly associated with a reduced risk of cardiovascular events, suggesting that HDL cholesterol may not be a causative factor in cardiovascular disease [7, 8].

Recently, several large-scale observational studies have demonstrated a U-shaped association between HDL cholesterol levels and mortality risk in European and U.S. populations that included participants from a single ethnicity or were confined to a specific clinical setting [9–11]. However, the association between HDL cholesterol and all-cause mortality in the general population has not been comprehensively investigated, and the available evidence on cause-specific mortality is also underrepresented or provides conflicting results. While genetic studies are effective in confirming causality, traditional Mendelian randomization designs assume linear effects and have many difficulties in detecting non-linear effects that require more statistical power [12]. In addition, the Mendelian randomization method is not suitable for exploring extreme phenotypes of HDL cholesterol because it requires very large sample sizes and often does not allow the construction of a genetic instrument to reflect the extreme phenotype [13]. Therefore, replicated observational studies in diverse populations are warranted to validate these associations.

We conducted this study using the National Health and Nutrition Examination Survey (NHANES) cohort with three objectives: first, to investigate the dose-response associations between continuous HDL cholesterol and all-cause, cardiovascular, and non-cardiovascular mortality in the general population; second, to examine this association in men and women separately to account for sex differences in HDL cholesterol levels; and third, to explore the association of HDL cholesterol with more detailed subcategories of cause-specific mortality.

Methods

Study population

NHANES is a nationally representative survey which is conducted and maintained by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC), the survey employs multistage stratified probability sampling to reflect the demographics of the contemporaneous U.S. census. NHANES has been described in detail previously [14]. We extracted NHANES data from 1999 to 2018, covering 10 survey cycles. The study adhered to the Declaration of Helsinki. The Ethical Review Board of the National Center for Health Statistics approved the study protocol for each NHANES cycle. Written informed consent was obtained from all adult participants. Of the 101,316 participants, 50,081 were excluded because of age younger than 18 years ($n = 42{,}112$), pregnancy ($n = 1{,}596$), loss to follow-up ($n = 2{,}874$), missing HDL cholesterol measurements ($n = 3{,}461$), and extreme HDL cholesterol levels (> 140 mg/dL) ($n = 38$). A total of 51,235 individuals were finally included in the analysis (Supplementary material Figure S1).

Endpoints

The primary outcomes were all-cause mortality, cardiovascular disease (CVD) mortality and non-CVD mortality. The secondary outcomes were the subcategories of CVD and non-CVD mortality. Data on deaths were obtained by matching the NHANES survey with NDI records through December 31, 2019, using a probabilistic matching method. The NCHS recoded the underlying classification of death (UCOD) according to the International Classification of Diseases, 10th Revision (ICD-10). CVD deaths included deaths from heart diseases (054–068) and cerebrovascular diseases (070). Non-CVD deaths included deaths from cancer (019–043), deaths from neurological diseases (052), deaths from endocrine diseases (046), deaths from respiratory diseases (076–078 and 082–086), deaths from renal diseases (097–101), and deaths from all residual causes (010).

Laboratory measurements

Enzymatic measurements of serum HDL cholesterol, total cholesterol, and triglycerides were performed at the University of Minnesota using Roche/Hitachi Cobas 6000 analyzer. Both fasting (≥ 8 h from the last meal) and non-fasting measurements were included in the analysis because postprandial effects do not substantially affect lipid profiles [15]. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula in the case of triglycerides less than 4.0 mmol/L (352 mg/dL), otherwise measured directly. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16]. Individuals were categorized into five predefined clinically meaningful groups based on HDL-C concentrations: <40, 40–49, 50–59, 60–79, and ≥ 80 mg/dL. Eight more granular groups based on percentiles were also generated to account for the highest and lowest HDL-C levels. The HDL-C levels associated with the lowest risk of death served as the reference.

Covariates

Self-reported sociodemographic information was obtained through a computer-assisted interview system, including age, sex, ethnicity/race, smoking status, alcohol consumption, education level, marital status and family income. Alcohol consumption was categorized by the number of drinks per week. One drink was defined as at least 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor. Cumulative alcohol consumption during the past 12 months was also adjusted in the sensitivity analysis to account for the increase in HDL cholesterol with alcohol consumption [17]. Systolic blood pressure, height and weight (used to calculate body mass index [BMI]) were measured using standardized methods at a mobile examination center (MEC). Medical history including coronary artery disease, stroke, diabetes, heart failure, chronic obstructive pulmonary disease (COPD) and cancer, was determined by self-report, physician diagnosis, and current use of prescription medications. Chronic kidney disease was defined as eGFR < 60 mL/min as assessed by the CKD-EPI equation. Aspirin and statin use was obtained from the Prescription Drug Questionnaire.

Statistical analysis

In accordance with the CDC recommendations, sampling weights, strata, and clusters were incorporated into the analyses to account for unequal sampling and nonresponse probabilities. The four-year sample weights for the NHANES cycles (1999–2002) and the two-year sample weights for the NHANES cycles (2003–2018) were combined to provide 20-year weights for the 1999–2018 survey periods. Continuous variables were presented as weighted mean (95% CI), and categorical variables were presented as weighted % (95% CI). Data on covariates were more than 95% complete, and missing data (4.9% for systolic blood pressure, 1.7% for BMI, 4.6% for LDL cholesterol, 0.2% for triglycerides, and 0.3% for eGFR) were interpolated using the chained equation multiple imputation method (number of imputations = 5). Statistical analyses were performed with R, version 4.2.0 (R Project) and EmpowerStats (X&Y Solutions, Inc., Boston, MA). Statistical significance was defined as a two-tailed P value < 0.05.

The Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) between categorical HDL

cholesterol and risk of mortality, adjusting for age, sex, ethnicity, systolic blood pressure, BMI, smoking status, alcohol consumption, LDL cholesterol, triglycerides, fasting status, coronary artery disease, stroke, diabetes, heart failure, COPD, cancer, chronic renal disease, aspirin and statin use. The proportional hazards assumption was assessed using Schoenfeld residuals and log time plots, and no violation was found. Two types of HDL cholesterol grouping based on concentration cutpoints and percentiles (to account for extremely high or extremely low levels) were assessed, respectively. Because the average HDL cholesterol concentration was higher in women than in men, men and women were also analyzed separately. Interactions of very high HDL cholesterol levels with covariates on all-cause mortality and cause-specific mortality were tested by introducing two-factor interaction terms to account for the potential effect modification by covariates.

The restricted cubic splines were used to examine the association between continuous HDL cholesterol and risk of mortality, adjusting for all predefined covariates. Four knots were chosen to balance best fit and overfitting according to Akaike's information criterion. The HDL cholesterol concentrations associated with the lowest risk of death were those with the lowest HRs on the spline curve, and 95% CIs were generated by bootstrap resampling with 1000 repetitions. Restricted cubic splines were also used to visualize the nonlinear association of HDL cholesterol with cause-specific mortality subcategories, using the same knots for comparisons. The penalized splines based on the generalized additive models were used to generate the dose-response curves between continuous HDL cholesterol and disease endpoints.

Cumulative all-cause mortality for each HDL cholesterol group was estimated using the Kaplan-Meier method and compared using the log-rank test. Entry age-adjusted age with delayed entry (left truncation) was used as the underlying time scale, which mitigates survival probability bias and is considered a superior model for epidemiological studies [18]. Fine and Gray competing risk models were used to estimate cumulative cause-specific mortality, with the Gray's test for comparison.

Sensitivity analyses were performed to examine the impact of (i) using follow-up time as the potential time scale for survival analysis, (ii) reverse causality, by excluding individuals with less than 2 years of follow-up, (iii) additional adjustment for cumulative alcohol consumption during the past 12 months, (iv) additional adjustment for education level, marital status, and poverty income ratio, (v) plotting the spline curve based on the generalized additive model, (vi) unweighted models, (vii) exclusion of ASCVD, diabetes mellitus, heart failure, renal disease, COPD, cancer, or any underlying disease at baseline, and (viii) inclusion of all participants with HDL cholesterol data (in the main analysis we excluded 38 participants with extreme HDL cholesterol levels [> 140 mg/dL] to avoid wide confidence intervals).

Results

A total of 51,235 individuals were analyzed, weighted to represent 209 million US adults. During a median follow-up of 9.3 years, there were 7602 (14.8%) all-cause deaths, 2394 (4.7%) CVD deaths, and 5208 (10.2%) non-CVD deaths, respectively. Baseline characteristics of the overall population across HDL cholesterol categories are shown in Table 1. The mean HDL cholesterol concentration in the entire population was 52.9 (95% CI, 52.6–53.2) mg/dL, which was higher in women (58.0, 95% CI 57.6–58.4 mg/dL) than in men (47.6, 95% CI 47.3–47.9 mg/dL). Individuals with HDL cholesterol concentrations greater than 80 mg/dL comprised 5.9% of this cohort and were more likely to be older, female, non-Hispanic white, have greater alcohol consumption and less smoking, higher triglyceride levels, lower prevalence of diabetes, coronary heart disease, and heart failure, and higher prevalence of cancer, compared with those with lower HDL cholesterol concentrations. Baseline characteristics of men and women are shown in Supplementary material Table S1 and S2.

HDL cholesterol and all-cause mortality

In the general population, the association between continuous HDL cholesterol and all-cause mortality was apparently U-shaped. This dose-response pattern was also observed in men and women separately. The lowest risk of all-cause mortality occurred at HDL cholesterol concentrations of 54 mg/dL (95% CI, 51–57 mg/dL) in the general population, 51 mg/dL (95% CI, 48–53 mg/dL) in men, and 59 mg/dL (95% CI, 56–62 mg/dL) in women, respectively (Fig. 1).

Similar results were found in multivariable adjusted analyses of categorical HDL cholesterol based on concentration cutpoints. Compared with the reference category of HDL cholesterol 50–59 mg/dL, individuals with low HDL cholesterol (< 40 mg/dL) had an expected higher risk of all-cause mortality in the overall cohort (HR, 1.17; 95% CI, 1.05–1.31). Importantly, the risk of death was also higher in those with extremely high HDL cholesterol (≥ 80 mg/dL) (HR, 1.24; 95% CI, 1.08–1.43). These associations were evident in both sexes. The adjusted HRs for men and women with HDL cholesterol ≥ 80 mg/dL were 1.29 (95% CI, 1.09–1.49) and 1.20 (95% CI, 1.02–1.41), respectively (Fig. 2). Percentile-based analyses showed higher HRs for HDL cholesterol extremes. Compared with the reference groups (71st-90th percentile, 58–72 mg/dL), the multivariable adjusted HRs for all-cause mortality for the top percentile (99th-100th percentile, ≥ 91 mg/dL) were 1.30 (95% CI, 1.09–1.52) in the

Table 1 Baseline characteristics of individuals by HDL cholesterol category

Characteristics	HDL cholesterol					*P* value
	< 40 mg/dL	40–49 mg/dL	50–59 mg/dL	60–79 mg/dL	≥ 80 mg/dL	
Age, years	44.6 (44.1–45.1)	45.4 (44.9–45.9)	45.6 (45.1–46.1)	47.8 (47.2–48.4)	52.0 (51.2–52.8)	< 0.0001
Male, %	73.0 (71.9–74.0)	59.2 (58.2–60.2)	43.4 (42.0–44.7)	29.8 (28.6–31.0)	20.1 (18.5–21.9)	< 0.0001
Ethnicity, %						< 0.0001
Non-Hispanic White	68.6 (66.0–71.0)	66.7 (64.5–68.9)	67.2 (64.9–69.6)	70.1 (67.9–72.1)	74.1 (71.5–76.4)	
Non-Hispanic Black	7.5 (6.6–8.5)	10.2 (9.2–11.3)	11.9 (10.7–13.3)	12.2 (10.9–13.6)	13.5 (11.8–15.4)	
Hispanic	16.7 (14.8–18.8)	16.2 (14.5–18.2)	13.7 (12.3–15.4)	11.1 (9.9–12.4)	6.6 (5.6–7.7)	
Other	7.2 (6.4–8.1)	6.9 (6.2–7.6)	7.1 (6.3–8.0)	6.6 (5.9–7.4)	5.9 (4.9–7.0)	
Body mass index, kg/m^2	31.3 (31.0–31.5)	29.9 (29.8–30.1)	28.2 (28.1–28.4)	26.4 (26.2–26.5)	24.7 (24.5–25.0)	< 0.0001
Systolic blood pressure, mmHg	124 (123–124)	123 (123–124)	122 (122–123)	122 (122–123)	125 (124–126)	< 0.0001
Smoking status, %						< 0.0001
Never smoker	48.5 (47.1–50.0)	54.4 (52.9–55.9)	57.7 (56.4–59.1)	59.9 (58.6–61.2)	55.5 (53.2–57.7)	
Former smoker	23.7 (22.6–24.9)	23.4 (22.3–24.5)	23.6 (22.5–24.7)	23.3 (22.2–24.5)	26.1 (24.0–28.3)	
Current smoker	27.8 (26.3–29.2)	22.2 (21.2–23.3)	18.7 (17.7–19.8)	16.7 (15.9–17.6)	18.4 (16.6–20.4)	
Alcohol consumption*, %						< 0.0001
Never	39.5 (38.1–41.0)	37.9 (36.3–39.4)	37.4 (35.8–38.9)	35.0 (33.7–36.3)	32.0 (29.9–34.2)	
Less than once a week	57.6 (56.1–59.2)	58.9 (57.4–60.5)	58.9 (57.3–60.5)	60.3 (59.0–61.6)	63.4 (61.0–65.8)	
More than once a week	2.8 (2.2–3.6)	3.2 (2.8–3.7)	3.7 (3.1–4.4)	4.7 (3.7–5.8)	4.6 (3.4–6.1)	
Cumulative times of alcohol consumption, per year	8.2 (7.0–9.4)	8.4 (7.5–9.4)	8.5 (7.4–9.5)	10.3 (9.1–11.5)	11.2 (8.6–13.7)	< 0.0001
LDL cholesterol, mgl/dL	112 (110–113)	117 (116–117)	115 (114–116)	111 (110–112)	107 (105–109)	< 0.0001
Triglycerides, mgl/dL	247 (241–253)	157 (154–160)	123 (122–125)	100 (98–102)	84 (82–86)	< 0.0001
Fasting status†, %	(48.3–51.4)	54.6 (53.4–55.8)	55.1 (53.8–56.4)	55.2 (53.8–56.5)	54.4 (51.9–56.9)	< 0.0001
Diabetes mellitus, %	13.3 (12.4–14.2)	10.5 (9.8–11.2)	7.1 (6.6–7.7)	5.4 (4.9–6.0)	3.7 (3.0–4.5)	< 0.0001
Coronary artery disease, %	4.9 (4.4–5.5)	4.0 (3.5–4.5)	2.8 (2.5–3.2)	2.2 (1.8–2.6)	2.3 (1.8–3.1)	< 0.0001
Stroke, %	3.2 (2.8–3.7)	2.8 (2.5–3.1)	2.5 (2.2–2.8)	2.3 (2.0–2.7)	2.9 (2.2–3.8)	0.0004
Heart failure, %	3.6 (3.1–4.1)	2.4 (2.2–2.7)	1.9 (1.6–2.2)	1.7 (1.4–2.0)	1.7 (1.3–2.3)	< 0.0001
COPD, %	6.6 (5.9–7.5)	5.8 (5.3–6.3)	5.4 (4.8–6.1)	5.4 (4.8–6.0)	7.3 (6.1–8.5)	< 0.0001
Cancer, %	7.9 (7.2–8.7)	8.9 (8.3–9.6)	8.5 (7.9–9.3)	9.7 (9.0–10.4)	13.1 (11.6–14.6)	< 0.0001
Chronic renal disease (eGFR < 60 ml/min), %	6.3 (5.8–6.8)	6.4 (6.0–6.9)	6.2 (5.7–6.7)	6.3 (5.8–6.8)	7.3 (6.0–8.9)	< 0.0001
Aspirin use, %	9.1 (8.1–10.2)	8.7 (8.0–9.6)	8.1 (7.4–8.8)	8.7 (7.9–9.7)	9.8 (8.0–12.1)	0.0103
Statin use, %	15.8 (14.7–17.0)	15.5 (14.7–16.4)	14.2 (13.3–15.2)	12.9 (12.0–13.8)	12.2 (10.6–14.0)	< 0.0001
Education level, %						< 0.0001
Under high school	20.6 (19.5–21.8)	18.3 (17.2–19.5)	15.9 (14.8–17.1)	13.4 (12.5–14.4)	11.9 (10.5–13.5)	
High school graduate	26.3 (24.9–27.7)	24.6 (23.6–25.6)	22.6 (21.4–23.9)	20.4 (19.2–21.5)	20.6 (18.7–22.7)	
Above high school/unknown	53.1 (51.3–54.9)	57.1 (55.6–58.6)	61.5 (59.8–63.1)	66.2 (64.6–67.8)	67.4 (64.9–69.9)	
Marital status, %						< 0.0001
Married/cohabiting	64.3 (62.6–65.9)	61.9 (60.7–63.0)	60.1 (58.7–61.5)	58.7 (57.1–60.2)	59.4 (57.1–61.7	
Separated/divorced/widowed	14.6 (13.7–15.6)	16.3 (15.5–17.0)	17.7 (16.8–18.7)	20.7 (19.6–21.7)	24.5 (22.7–26.4)	
Never married/unkown	21.1 (19.5–22.8)	21.9 (20.6–23.1)	22.2 (20.9–23.5)	20.7 (19.2–22.3)	16.1 (14.5–17.8)	
Poverty income ratio (PIR)#	2.8 (2.7–2.8)	2.9 (2.8–3.0)	3.0 (2.9–3.1)	3.2 (3.1–3.2)	3.4 (3.3–3.5)	< 0.0001
All-cause mortality, %	12.3 (11.5–13.2)	10.9 (10.3–11.6)	9.5 (8.7–10.2)	10.4 (9.6–11.2)	13.4 (12.0–14.8)	< 0.0001
CVD mortality, %	3.8 (3.4–4.3)	3.2 (2.9–3.6)	2.8 (2.5–3.2)	3.1 (2.7–3.5)	3.5 (2.9–4.1)	0.0005
Non-CVD mortality, %	8.5 (7.8–9.1)	7.7 (7.2–8.2)	6.7 (6.1–7.3)	7.3 (6.7–7.9)	9.9 (8.7–11.1)	< 0.0001

†Fasting status, indicated by fasting time ≥ 8 h. *One drink means at least 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor. #PIR is calculated by dividing family income by family size, year, and geographic location, as measured by the Department of Health and Human Services. CVD, cardiovascular disease. HDL, high-density lipoprotein. LDL, low-density lipoprotein. COPD, chronic obstructive pulmonary disease

total population, 1.33 (95% CI, 1.02–1.62) in men, and 1.29 (95% CI, 1.06–1.60) in women, respectively (Fig. 2).

Cumulative mortality analysis showed that the group with HDL cholesterol ≥ 80 mg/dL had the highest all-cause mortality, followed by the group with HDL cholesterol < 40 mg/dL, while the group with HDL cholesterol of 50–59 mg/dL had the lowest mortality. Cumulative all-cause mortality at age 75 years was 14.9% for individuals with HDL cholesterol < 40 mg/dL, 12.5% for 40–49 mg/dL, 10.4% for 50–59 mg/dL, 10.5% for 60–79 mg/dL, and 18.6% for ≥ 80 mg/dL (Fig. 3).

In groups stratified by prespecified covariates, individuals with HDL cholesterol ≥ 80 had a significantly increased risk of all-cause mortality compared with those

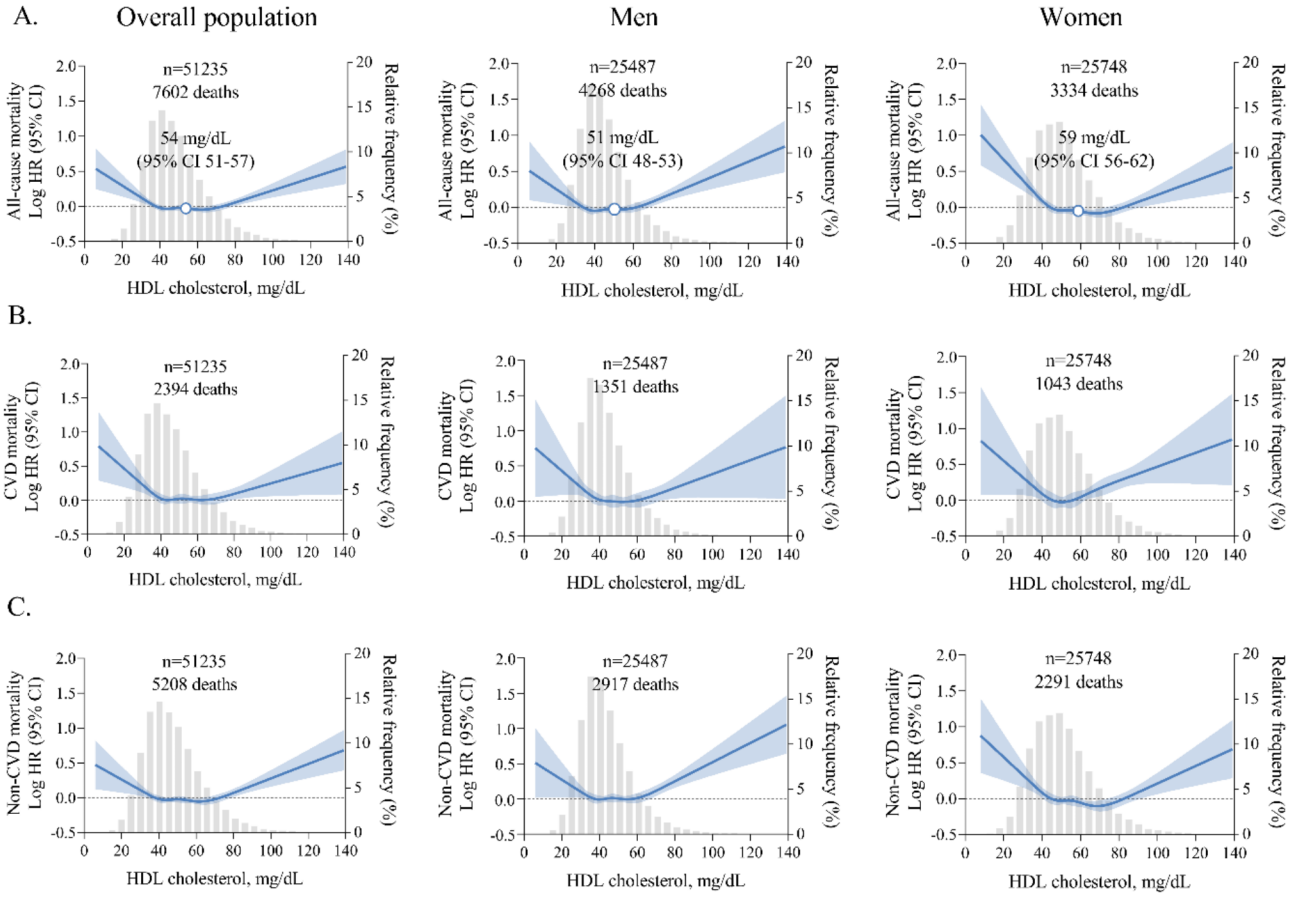


Fig. 1 All-cause and cause-specific mortality by HDL cholesterol on continuous scales. All-cause mortality, (**B**) cardiovascular mortality, (**C**) non-cardiovascular mortality. Model was adjusted for age, sex, ethnicity, systolic blood pressure, BMI, smoking status, alcohol consumption, LDL cholesterol, triglycerides, fasting status, coronary artery disease, stroke, diabetes, heart failure, COPD, cancer, chronic renal disease, aspirin and statin use. Not adjusted for sex when sex stratified analysis was performed. HDL, high-density lipoprotein. LDL, low-density lipoprotein. COPD, chronic obstructive pulmonary disease. Solid blue lines are adjusted hazard ratios, with shaded areas showing 95% confidence intervals derived from restricted cubic spline regressions

with HDL cholesterol of 50–59 mg/dL, and no significant effect modification was found (Fig. 4, Supplementary material Table S3).

HDL cholesterol and cause-specific mortality

In the overall population, continuous HDL cholesterol showed analogous U-shaped associations with CVD mortality and non-CVD mortality. These associations were equally present in men and women (Fig. 1). These findings were further confirmed using cut points for HDL cholesterol concentration. Compared with the reference category of 50–59 mg/dL, individuals in both the lowest (< 40 mg/dL) and the highest (≥ 80 mg/dL) HDL cholesterol groups had a significantly higher risk of death. For CVD mortality, individuals with HDL cholesterol ≥ 80 mg/dL had multivariable adjusted HRs of 1.18 (95% CI, 1.03–1.36) in the overall cohort, 1.19 (95% CI, 1.01–1.52) in men, and 1.19 (95% CI, 1.03–1.40) in women, respectively. For non-CVD mortality, the corresponding HRs were 1.27 (95% CI, 1.09–1.49) in the total population, 1.40 (95% CI, 1.09–1.68) in men, and 1.20 (95% CI, 1.02–1.43) in women. Similar results were found in percentile-based analyses (Fig. 2).

Cumulative mortality estimated by HDL cholesterol category also showed that individuals with HDL cholesterol ≥ 80 mg/dL had significantly increased CVD mortality and non-CVD mortality. Cumulative CVD mortality at age 75 years was 4.4% for individuals with HDL cholesterol < 40 mg/dL, 2.9% for 40–49 mg/dL, 2.7% for 50–59 mg/dL, 2.8% for 60–79 mg/dL, and 5.6% for ≥ 80 mg/dL. The corresponding cumulative mortality for non-CVD deaths were 10.8%, 9.9%, 7.9%, 8.0%, and 13.5%, respectively (Fig. 3).

In stratified analyses for CVD mortality and non-CVD mortality, individuals with HDL cholesterol ≥ 80 had a significantly higher risk of death when compared with those with HDL cholesterol of 50–59 mg/dL, and there was no convincing evidence of an interaction across the strata (Fig. 4, Supplementary material Table S4 and S5).

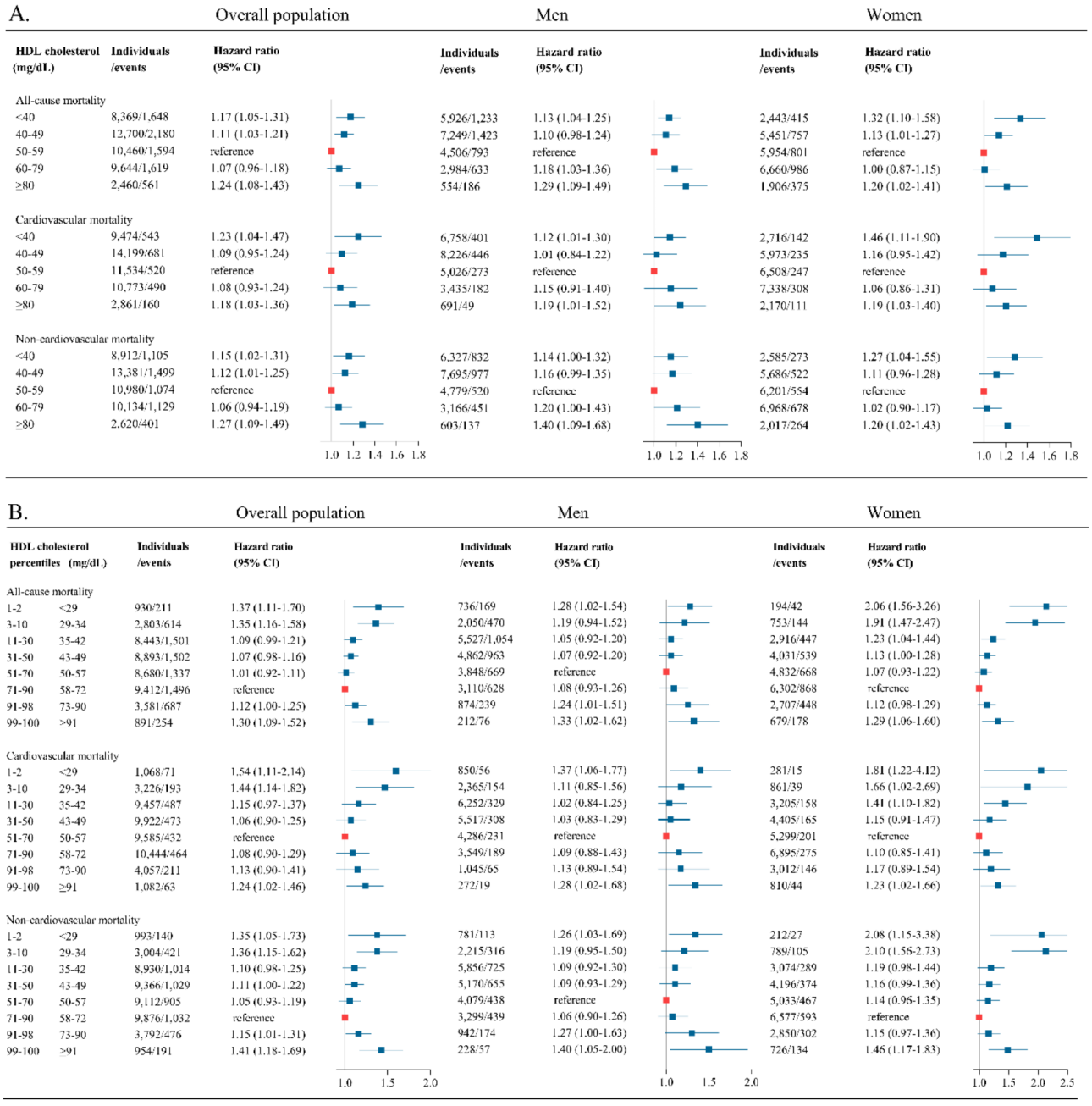


Fig. 2 All-cause and cause-specific mortality for categorical HDL cholesterol based on concentration and percentile cutpoints. (**A**) HDL cholesterol concentration cutpoints, (**B**) HDL cholesterol percentile cutpoints. Model was adjusted for age, sex, ethnicity, systolic blood pressure, body mass index, smoking status, alcohol consumption, LDL cholesterol, triglycerides, fasting status, coronary artery disease, stroke, diabetes, heart failure, COPD, cancer, chronic renal disease, aspirin and statin use. Not adjusted for sex when sex stratified analysis was performed. CVD, cardiovascular disease. HDL, high-density lipoprotein. LDL, low-density lipoprotein. COPD, chronic obstructive pulmonary disease

HDL cholesterol and subcategories of cause-specific mortality

In subcategory analyses of CVD mortality and non-CVD mortality, a U-shaped association was observed between HDL cholesterol and death from heart disease and death from cancer. For death from respiratory disease and death from endocrinological disease, high levels of HDL cholesterol were associated with higher risk. The risk of death from renal disease showed a negative association with HDL cholesterol. No significant association was found for death from cerebrovascular disease, neurological disease, and death from accidents. For death from all other residual causes, HDL cholesterol showed an apparent U-shaped pattern with death (Fig. 5).

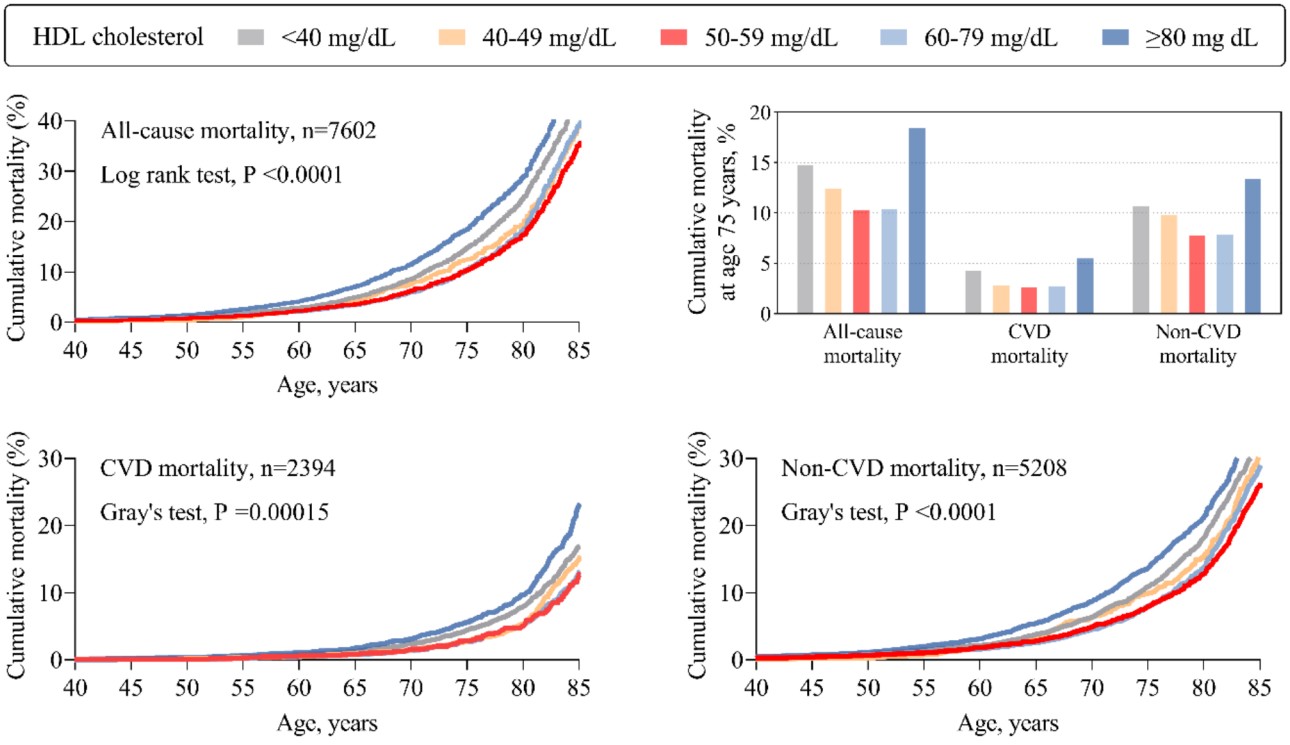


Fig. 3 Cumulative all-cause and cause-specific mortality by HDL cholesterol group. All-cause and cause-specific mortality were followed through December 31, 2019. The Fine and Gray competing risk models were used for cause-specific mortality, with deaths from the remaining cause as competing risk

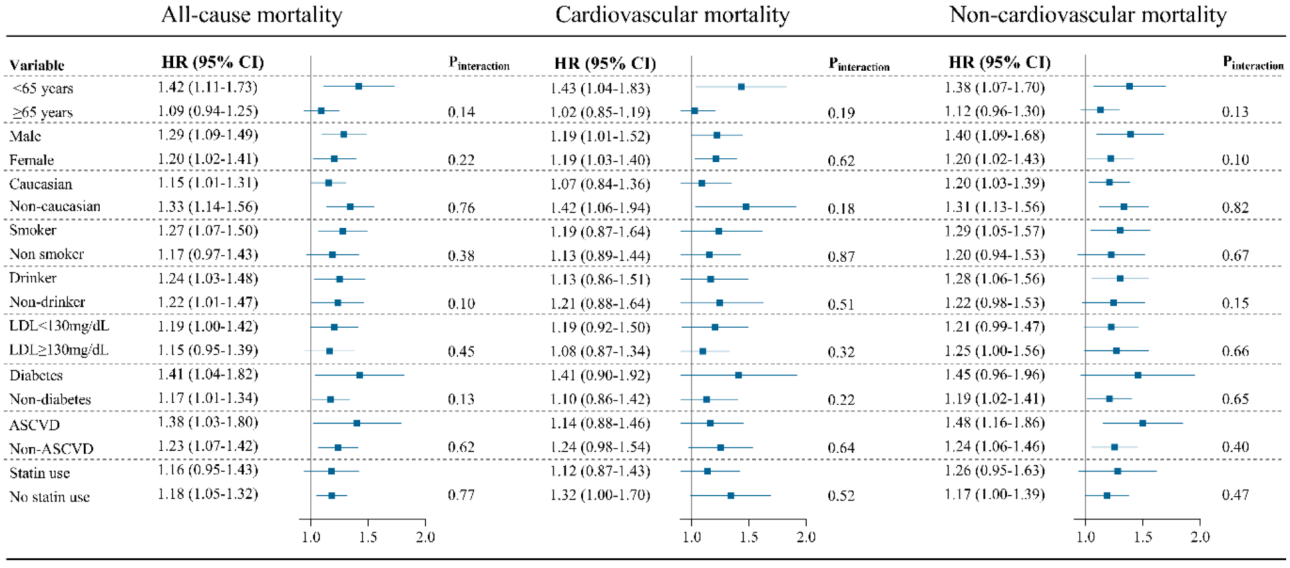


Fig. 4 Forest plot of HDL cholesterol ≥ 80 mg/dL compared with reference HDL cholesterol 40–60 mg/dL. Model was adjusted for age, sex, ethnicity, systolic blood pressure, body mass index, smoking status, alcohol consumption, LDL cholesterol, triglycerides, fasting status, coronary artery disease, stroke, diabetes, heart failure, COPD, cancer, chronic renal disease, aspirin and statin use. Not adjusted for stratified variables. ASCVD, atherosclerotic cardiovascular disease, includes coronary artery disease and stroke. HDL, high-density lipoprotein. BMI, body mass index. LDL, low-density lipoprotein. COPD, chronic obstructive pulmonary disease

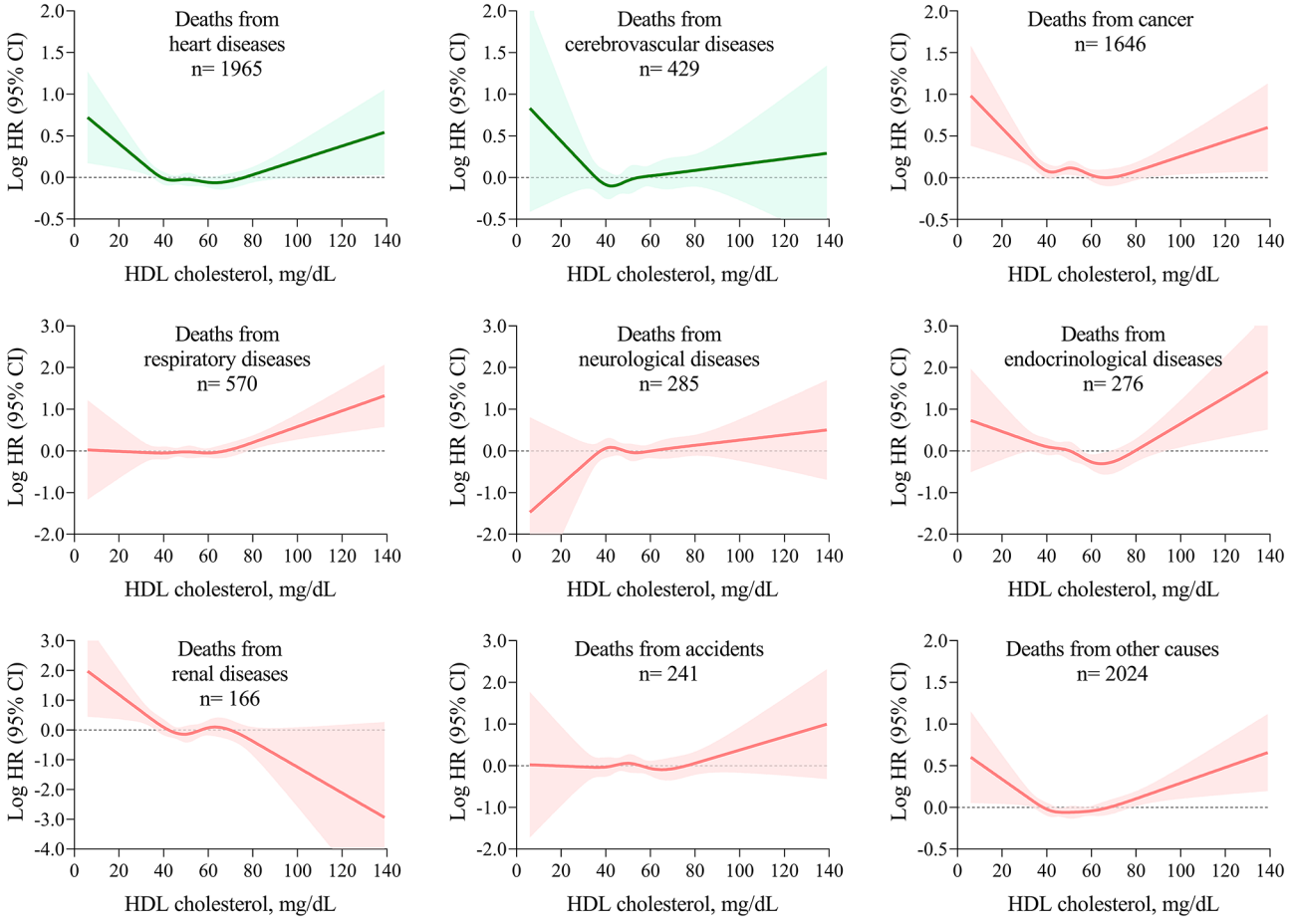


Fig. 5 Subcategory of cause-specific mortality by HDL cholesterol on continuous scales. Model was adjusted for age, sex, ethnicity, systolic blood pressure, BMI, smoking status, alcohol consumption, LDL cholesterol, triglycerides, fasting status, coronary artery disease, stroke, diabetes, heart failure, COPD, cancer, chronic renal disease, aspirin and statin use. Solid green lines and shaded areas are hazard ratios and 95% confidence intervals for CVD mortality subcategory. Solid red lines and shaded areas are hazard ratios and 95% confidence intervals for non-CVD mortality subcategory

HDL cholesterol and specific diseases

A higher risk of coronary artery disease, stroke, heart failure and chronic kidney disease was observed with low HDL cholesterol levels. The risk reached a plateau around an HDL cholesterol concentration of about 60 mg/dL, thereafter no further change in risk as the HDL cholesterol concentrations increased. For COPD and cancer, the opposite pattern of association was observed, with high levels of HDL cholesterol associated with higher risk (Supplementary material Figure S2).

Sensitivity analysis

Results were similar when using follow-up time as the timescale for cumulative mortality analysis (Supplementary material Figure S3). The U-shaped associations between HDL cholesterol and all-cause mortality and non-CVD mortality were similar when excluding individuals with less than 2 years of follow-up (Supplementary material Figure S4), when additionally adjusting for cumulative alcohol consumption (Supplementary material Figure S5), when additionally adjusting for education level, marital status, and poverty income ratio (Supplementary material Figure S6), when generating spline curves based on generalized additive models (Supplementary material Figure S7), and when performing unweighted models (Supplementary material Figure S8). However, the association between high HDL cholesterol levels and risk of CVD death was slighted attenuated or lost statistical significance (Supplementary material Figure S4-S8). When excluding ASCVD, diabetes mellitus, heart failure, renal disease, COPD, cancer, or any underlying disease at baseline, the statistically significant U-shaped association between HDL cholesterol and all-cause mortality was consistent with the primary analysis (Supplementary material Figure S9). The results did not change significantly when all participants with HDL cholesterol data (including 38 participants with HDL cholesterol levels between 141 and 226 mg/dL) were analyzed (Supplementary material Figure S10).

Discussion

In this nationally representative cohort, a U-shaped association was observed between HDL cholesterol levels and all-cause, cardiovascular and non-cardiovascular mortality in the US adults. This association was consistent in both men and women. The concentration of HDL cholesterol associated with the lowest risk of all-cause mortality was 54 mg/dL (51–57 mg/dL). Extremely high levels of HDL cholesterol were also associated with an increased risk of death from heart disease, respiratory disease, endocrine disease, and cancer. These findings lend further credence of the potentially deleterious effects of extremely high HDL cholesterol, which contrasts with its widely recognized cardioprotective effects and suggests the need for more appropriate strategies for managing HDL cholesterol in clinical practice.

Emerging observational evidence has shown a paradoxical association between extremely high HDL cholesterol levels and increased mortality in various populations. These studies have been conducted in specific clinical settings, including hypertension, coronary artery disease, or without pre-existing cardiovascular conditions [10, 11, 19], or in selected groups of elderly or primary care populations [20, 21], or in ethnically homogeneous populations, such as Northern European whites or Asians [9, 22, 23], limiting the extrapolation of the findings to the general population. In addition, some studies had limited sample sizes that did not cover the extremes of the HDL cholesterol concentration spectrum, or categorized HDL cholesterol into quartiles or quintiles without specifically examining individuals with extremely high concentrations [1]. Therefore, evidence on the association between HDL cholesterol and mortality in the general population was lacking. NHANES is a multiethnic population-based cohort that offers a unique opportunity to extend existing knowledge by reevaluating the dose-response relationship between HDL cholesterol covering extreme concentrations and risk of mortality. Major strengths of our study were the ability to investigate a large ethnically heterogeneous population of 51,235 participants, weighted to represent 209 million U.S. adults, and the ability to examine the extremes of the HDL cholesterol concentration spectrum, thereby extending the generalizability of the current findings.

We found a U-shaped association of HDL cholesterol levels with all-cause, cardiovascular and non-cardiovascular mortality. This pattern was consistent in men and women, despite the fact that estrogen causes elevated HDL cholesterol [24]. In addition, this association persisted after accounting for reverse causality, cumulative alcohol consumption, more comorbidities, and additional socioeconomic factors, suggesting the robustness of the results. Notably, in several sensitivity analyses, the association between HDL cholesterol and cardiovascular death appeared to be slightly attenuated in the extremely high concentration range, indicating that the high mortality risk at high HDL cholesterol concentrations was primarily driven by non-cardiovascular mortality. In parallel with our findings, a large population-based cohort in Canada have reported that the association between high HDL cholesterol and increased mortality appeared to be driven mainly by deaths from causes other than cardiovascular and cancer [11]. These results highlight an area of strongly recommended concern, the pleiotropic effects of HDL cholesterol on organs other than the cardiovascular system, which challenges the plausibility of HDL cholesterol as a specific cardioprotective biomarker.

The HDL cholesterol concentrations associated with the lowest risk of all-cause mortality in our study were found to be 54 mg/dL (51–57 mg/dL), which varied slightly between 51 mg/dL (48–53 mg/dL) for men and 59 mg/dL (56–62 mg/dL) for women. These concentrations were far below those in the Copenhagen cohort, which were 73 mg/dL (95% CI, 42–77 mg/dL) for men and 93 mg/dL (95% CI, 66–239 mg/dL) for women [9]. Possible reasons include differences in the laboratory quantification methods and study populations, since blacks generally have lower HDL cholesterol levels than whites [25], and the Copenhagen cohort included only northern European whites. Our results are consistent with a pooled analysis of 37 prospective cohort studies, which revealed that the risk of all-cause mortality was lowest at HDL cholesterol concentrations of 54–58 mg/dL [26]. In addition, the nadir in the Copenhagen cohort was quite broad and covered a large proportion of the population, and the risk of death did not increase until HDL cholesterol greater than 80 mg/dL, whereas in our study the risk began to increase slightly once HDL cholesterol exceeded 60 mg/dL, especially in men. A contemporary cohort study of patients with coronary artery disease in the United States also showed that there was an increased all-cause mortality not only in individuals with HDL cholesterol levels above 80 mg/dL, but also in those with HDL cholesterol levels of 60–80 mg/dL [10]. Our findings extend the results of the Copenhagen general population study by including a large number of ethnically diverse individuals and are therefore more representative. Importantly, individuals with HDL cholesterol concentrations above 60 mg/dL represent a substantial proportion of the general population, which may be a potential explanation for the futility of most HDL cholesterol-targeted intervention strategies, as the intervention arms in these trials often raised HDL cholesterol levels to above 80 mg/dL, which our findings suggest is associated with higher mortality.

Mechanically, HDL is a large family of heterogeneous particles composed of subspecies that vary in size, shape, density, and composition, and exert pleiotropic biological

effects, including reverse cholesterol transport, bacterial lipopolysaccharide binding, coagulation homeostasis, inflammation and immune regulation, endothelial barrier integrity, and stimulation of angiogenesis [27]. Moreover, the compositional complexity of HDL determines its properties of highly dynamic conformation and functionality in the circulation. There are several possible explanations for the association between high HDL cholesterol and increased mortality. First, individuals carry rare genetic variants that result in elevated HDL cholesterol, but also have concomitant detrimental effects on health status [28]. Second, the effects of HDL are highly dependent on its normal conformation and functionality, and extremely high HDL cholesterol may signal HDL dysfunction, e.g. from anti-atherogenic to pro-atherogenic, from anti-inflammatory to pro-inflammatory, and reduced capacity to elicit cholesterol efflux from macrophages [29]. Third, the pleiotropic effects of HDL depend on either entire particles or specific components, not just cholesterol, and circulating concentrations of HDL cholesterol may not be an optimal indicator of functionality [27].

Previous European and US studies have reported heterogeneous results regarding high HDL cholesterol and cardiovascular mortality [9, 10], and we found a U-shaped dose-effect pattern between HDL cholesterol and death from heart disease in the general population. Genetic evidence suggests that very high HDL cholesterol may arise from certain genetic variants that are also linked to increased cardiovascular risk [28], which may partly explain this counterintuitive association. We did not find any significant association between HDL cholesterol and death from cerebrovascular disease (mainly stroke), which may be due to the inability to distinguish between stroke subtypes in our cohort. Ischemic and hemorrhagic strokes have distinct pathological mechanisms, so this finding is not surprising and further studies of these two subtypes are warranted. Respiratory disease deaths were predominantly deaths from infectious diseases, and our results are consistent with those of a large cohort study in which very high HDL cholesterol was associated with an increased risk of not only infectious diseases but also subsequent mortality [30]. Possible mechanisms include a variety of processes caused by HDL dysfunction, such as dysregulation of inflammatory responses, disturbances in complement activation, and disruption of coagulation homeostasis [27]. Our findings on the association between high HDL cholesterol levels and increased cancer mortality contrast with those of the Copenhagen cohort, which suggested no substantial association [9]. This may be due to the heterogeneity of the cancer types or other unclear reasons. Emerging evidence suggests a potentially complex effect of HDL cholesterol on the development of site-specific cancers, leading to inconsistent dose-effect patterns between HDL cholesterol and mortality for different cancer subtypes [31]. The observed association between high HDL cholesterol and death from endocrine diseases, primarily diabetes, may be due to the adverse effects of HDL dysfunction on pancreatic β-cells, the insulin signaling pathway, and glucose metabolism [27]. The apparent inverse association between HDL cholesterol and renal disease death was consistent with existing observational and genetic evidence that low HDL cholesterol is associated with reduced renal function and adverse outcomes [32, 33]. Finally, we reproduced a U-shaped pattern in the association of HDL cholesterol with death from all residual causes. Several recent studies have demonstrated the association between high HDL cholesterol and an increased risk of fractures [34], dementia [35], infectious diseases [30], and age-related macular degeneration [36]. Accumulating evidence outside the realm of cardiovascular disease highlights the complexity of the physiological effects of HDL. Although the exact mechanisms remain to be elucidated, these pleiotropic effects of HDL suggest that HDL functionality, rather than cholesterol content, may play a more important role in the pathogenesis of specific disease. These associations still need to be validated in genetic studies, but the results of large-scale observational studies are of great importance in extending existing knowledge, as traditional Mendelian randomized designs cannot provide convincing effect estimates for nonlinear relationships.

Our findings have profound implications for public health and clinical practice. First, HDL cholesterol has been widely incorporated into cardiovascular risk algorithms [37–39], which assume a monotonic inverse relationship, rewarding high levels and penalizing low levels of HDL cholesterol. The modified risk algorithm should eliminate the use of HDL cholesterol as a linear factor to minimize misclassification. Second, the development of CETP inhibitors to raise HDL cholesterol was discontinued due to increased mortality, initially thought to be due to unintended effects on blood pressure and the aldosterone hormone [5]. However, the current findings suggest an alternative hypothesis that very high HDL cholesterol itself may contribute to increased mortality. Mechanically, raising HDL cholesterol by pharmacological intervention would not be beneficial if dysfunctional HDL particles increase. Our results support that appropriate HDL cholesterol management, rather than simply avoiding low concentrations, may benefit individuals. Third, efforts should be initiated to investigate novel biomarkers representing HDL functionality, such as HDL particle number, proteomic composition, and cholesterol efflux capacity, which can be obtained by nuclear magnetic resonance lipoprotein analysis and mass spectrometry [40]. The future prospects of using HDL as a therapeutic target

will depend on the availability of causal biomarkers that reflect the direct contribution of HDL in the pathogenesis of specific diseases.

Strengths and limitations

A major strength of our study is the large sample size, which allowed to analyze individuals at the extremes of the concentration spectrum. Second, the large number of endpoint events ensured statistical power. Third, a nationally representative and ethnically heterogeneous population enhances the extrapolation of results.

Our study has several limitations. First, because of the observational design of this study, causality could not be determined. These associations may be due to reverse causality. However, the results of the analyses excluding individuals with less than 2 years of follow-up were generally consistent with those of the primary analysis. Second, despite adjustment for many important confounders known to affect mortality, unmeasured confounders could not be excluded. However, the E-values of 1.64–2.14 for the mortality risk associated with high HDL cholesterol exposure (≥ 80 mg/dL) implied that the association of unmeasured confounders with both the mortality risk and high HDL cholesterol exposure should be equivalent to these values in the context of adjustment for measured confounders. Third, half of the blood samples were obtained in a non-fasting state. Although fasting lipid measurements are the most commonly used method, the European consensus suggests that fasting is not routinely necessary for lipid measurements [15]. Finally, despite the very large sample size, the relatively small number of individuals with very high HDL cholesterol levels may affect the model fit at these extremes, especially in the stratified analyses and cause-specific mortality subcategory analyses. However, we compensated for this limitation as much as possible using weighted methods.

Conclusion

Extremely high levels of HDL cholesterol were associated with an increased risk of all-cause, cardiovascular, and non-cardiovascular mortality, as well as mortality from specific diseases.

Abbreviations

HDL	High levels of high-density lipoprotein
NHANES	National health and nutrition examination survey
NDI	National death index
ASCVD	Atherosclerotic cardiovascular disease
CETP	Cholesteryl ester transfer protein
NCHS	National center for health statistics
CDC	Centers for disease control and prevention
CVD	Cardiovascular disease
UCOD	Underlying classification of death
LDL	Low-density lipoprotein
eGFR	Estimated glomerular filtration rate
CKD-EPI	Chronic kidney disease epidemiology collaboration
MEC	Mobile examination center
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease

Supplementary Information

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Supplementary Material 1

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Author contributions

S.L. contributed to the design of the study. S.L. and W.Z. wrote the main manuscript text. Z.F. prepared Figs. 1, 2, 3, 4 and 5. S.L. revised the manuscript for important intellectual content. All authors reviewed the manuscript.

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Data availability

The data underlying this article are available on the Center for Disease Control web site (https://wwwn.cdc.gov/nchs/nhanes/default.aspx).

Declarations

Ethical approval

The NHANES study protocol was approved by the National Center for Health Statistics ethics review board (Protocol #2005-06, effective beginning October 26, 2004; Protocol #2011-17, effective beginning October 26, 2010; Protocol #2018-01, effective beginning October 26, 2017). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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