Association of high-density lipoprotein cholesterol with all-cause and cause-specific mortality in a Chinese population of 3.3 million adults: a prospective cohort study

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Summary

Background High-density lipoprotein cholesterol (HDL-C) has been inversely associated with cardiovascular disease (CVD) risk, but recent evidence suggests that extremely high levels of HDL-C are paradoxically related to increased CVD incidence and mortality. This study aimed to comprehensively examine the associations of HDL-C with all-cause and cause-specific mortality in a Chinese population.

Methods The China Health Evaluation And risk Reduction through nationwide Teamwork (ChinaHEART) project included 3,397,547 participants aged 35–75 years with a median follow-up of 3.9 years. Baseline HDL-C levels were measured, and mortality data was ascertained from the National Mortality Surveillance System and Vital Registration of Chinese Center for Disease Control and Prevention.

Findings This study found U-shaped associations of HDL-C with all-cause, cardiovascular and cancer mortality. When compared with the groups with the lowest risk, the adjusted hazard ratios (95% CIs) for HDL-C <30 mg/dL was 1.23 (1.17–1.29), 1.33 (1.23–1.45) and 1.18 (1.09–1.28) for all-cause, CVD and cancer mortality, respectively. For HDL-C >90 mg/dL, the corresponding HR (95% CIs) was 1.10 (1.05–1.15), 1.09 (1.01–1.18) and 1.11 (1.03–1.19). Similar U-shaped patterns were also found in associations of HDL-C with ischemic heart disease, ischemic stroke, and liver cancer. About 3.25% of all-cause mortality could be attributed to abnormal levels of HDL-C. The major contributor to mortality was ischemic heart disease (16.06 deaths per 100,000 persons, 95% UI: 10.30–22.67) for HDL-C <40 mg/dL and esophageal cancer (2.29 deaths per 100,000 persons, 95% UI: 0.57–4.77) for HDL-C >70 mg/dL.

Interpretation Both low and high HDL-C were associated with increased mortality risk. We recommended 50–79 mg/dL as the optimal range of HDL-C among Chinese adults. Individuals with dyslipidemia might benefit from proper management of both low and high HDL-C.

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Keywords: High-density lipoprotein; All-cause mortality; CVD mortality; Cancer mortality

Research in context

Evidence before this study

We conducted literature search on PubMed using the term "Lipoprotein, HDL" OR "Cholesterol, HDL", combined with terms "mortality" OR "death" up to 30 May, 2023. We limited the records to cohort studies specifically conducted in Chinese adults by adding search terms "cohort studies" AND "adult" AND "China" and their alternatives. Our search yielded a total of 111 studies. After screening the titles and abstracts, we identified ten cohort studies that investigated the association between high-density lipoprotein cholesterol (HDL-C) levels and mortality in Chinese population. Among these, six studies revealed nonlinear associations between HDL-C and all-cause or cardiovascular mortality. These studies encompassed diverse population characteristics, including elderly people, patients with pre-existing cardiovascular disease or type 2 diabetes, as well as subjects from single-site. While the U-shaped association between HDL-C and all-cause mortality has been proposed in European and U.S. population, the available evidence in Chinese lacked representativeness and presented conflicting findings. Additionally, no study comprehensively investigated the specific cause of death attribute to HDL-C in Chinese population.

Added value of this study

To our knowledge, this study is the first to comprehensively examine the associations of HDL-C with all-cause and cause-specific mortality in a population of 3.3 million Chinese adults. We found the optimal range of HDL-C among Chinese adults was 50–79 mg/dL with a U-shaped association with mortality risk. A similar dose-response curve was observed in ischemic heart disease and ischemic stroke, but not hemorrhagic stroke. Liver cancer exhibited U-shaped pattern with HDL-C, which was seldomly reported before. We evaluated the public health effect by HDL-C, and found approximately one in thirty all-cause deaths could be attributed to abnormal level of HDL-C. In addition to low HDL-C, the contribution of high HDL-C to mortality risk cannot be overlooked.

Implications of all the available evidence

Findings from this study provided further evidence on the potential detrimental effect of very high HDL-C, and highlighted the need for a more nuanced understanding of HDL-C and its role in health and disease physiopathology. Development of public health policies focusing on achieving optimal HDL-C levels rather than simply avoiding low HDL-C, should be considered.

Introduction

High-density lipoprotein cholesterol (HDL-C) has a well-established inverse relationship with cardiovascular disease (CVD) risk. However, recent large-scale epidemiological studies in European and U.S. populations have indicated that very high levels of HDL-C were paradoxically related to increased all-cause mortality, similarly to low levels of HDL-C.[1,2] This U-shaped association may explain the negative results in previous randomized controlled trials (RCTs) and mendelian randomization (MR) studies which tested the linear casual association with HDL-C, a key diagnostic criterion for dyslipidemia and risk indicator for CVD.[3,4]

However, comprehensive understanding on the association between HDL-C and mortality is lacking. On the one hand, evidence in non-Westerners was scarce and conflicting. Similar U-shaped associations were observed in Korean population,[5,6] but not in Japanese population.[7] In China, there were only some inconsistent findings from medium-sized cohorts limited in single region, rural areas,[8,9] or specific subpopulation (e.g., patients with hypertension).[10] On the other hand, investigation into the risk pattern of HDL-C levels on cause-specific mortality was limited, with only one recent study which reported the associations within a wide spectrum of outcomes in Norwegian adults.[2] In addition to the subtypes of CVD, there is growing interest in the relationship between HDL-C and cancer, given the effects of lipoproteins on tissue growth and tumorigenesis. Prior observational studies have suggested that low HDL-C was associated with increased cancer mortality,[11] but for extremely high HDL-C levels the studies were scarce. The association between HDL-C and site-specific cancers remains unclear in Asian population.

Therefore, by leveraging a nationwide prospective cohort of over 3.3 million Chinese adults, this study aimed to comprehensively examine the associations of HDL-C with all-cause and cause-specific mortality, and to determine the mortality attributed to high HDL-C in comparison with that to low HDL-C, thereby providing new knowledge and in-depth insights for HDL-C management strategies at populational-level.

Methods

Study cohort

China Health Evaluation And risk Reduction through nationwide Teamwork (ChinaHEART) project is a government-funded public health program designed to identify the high CVD risk factors throughout China. The details of the project have been described previously (formerly named China PEACE MPP).[12] Briefly, from September 2014 to December 2019, 304 county-level regions from all of the 31 provinces in mainland China were selected as study sites, ensuring diversity in geographic distribution, population structure, and exposure to risk factors and disease patterns. Residents aged 35–75 years who had resided in the community for at least 6 of the prior 12 months were recruited. The central ethics committee at the China National Center for Cardiovascular Disease approved this project (2014-574). All enrolled participants provided written informed consent.

During the study period, 3,820,651 participants were recruited. After excluding 66,044 participants from 11 sites having problem with measurements due to abnormal device calibration at site level, 354,954 participants with missing data for lipid measurements or covariates, and 2106 with missing data on follow-up, a total of 3,397,547 participants remained in the final analysis. The study flowchart was provided in the Supplementary Figure S1.

Laboratory tests and covariates measurements

At the baseline visits, each participant had a in-person interview conducted by trained personnel to collect information on socioeconomic status (education, annual household income, health insurance, marital status, and occupation), lifestyles (smoking and alcohol drinking), and self-reported medical history. Specifically, tobacco smoking status was categorized as non-smokers or current smokers, while alcohol use was categorized as never, once or less per month, 2–4 times per month, 2–3 times per week, or more than 4 times per week. Alcohol drinker was defined as participants who had consumed alcohol at least twice per week during the past 12 months.

For each participant, blood lipids, blood glucose, blood pressure, height and weight were measured at baseline. Total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were directly measured with a rapid lipid analyzer using fasting whole blood samples (CardioChek PA Analyzer; Polymer Technology Systems, USA). The levels of LDL-C were calculated with the Friedewald equation,[13] and then converted to milligram per deciliter. Glucose level was measured by a rapid blood glucose analyzer (BeneCheck BK6–20M Multi-Monitoring System, Suzhou Pu Chun Tang Biotechnology, China). Diabetes mellitus was defined as self-reported, the use of antidiabetic medications or fasting glucose levels ≥7 mmol/L.[14]

Blood pressure was measured twice in the right upper arm after a 5-min of rest in a seated position using a standardized electronic monitor (Omron HEM-7430, Omron Corporation, Kyoto, Japan). If the difference between the two systolic blood pressure measurements was larger than 10 mmHg, a third measurement was taken, and the average of the last two readings was used. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or greater, or the use of antihypertensive medications.[15]

Participants were instructed to wear light clothes, no shoes or caps for when measuring height and weight. The measurements were recorded with an accuracy to the nearest 0.1 kg for weight and 0.1 cm for height. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Study outcomes

In this study, participants' vital status and cause of death were collected through passive follow-up, in which, a linkage of data was established between the cohort and the National Mortality Surveillance System and Vital Registration of Chinese Center for Disease Control and Prevention that covers urban and rural areas across the 31 mainland provinces of China,[16] till December 31, 2021. The death records in this system are reported by health care institutions almost in real time, and they are subsequently checked against local residential records and health insurance records on an annual basis.

We considered all-cause mortality, CVD mortality (ICD-10: I01–I99) and cancer mortality (ICD-10: C00–C97) as the primary outcomes, with their respective subtypes as secondary outcomes in our analyses. Specifically, it included ischemic heart disease (ICD-10: I20–I25), stroke (ICD-10: I60–I63), ischemic stroke (ICD-10: I63), and hemorrhagic stroke (ICD-10: I60–I62), as well as certain cancers, such as liver cancer, esophageal cancer, gastric cancer, colorectal cancer, breast cancer and trachea, bronchus, and lung (TBL) cancer. These specific cancers were chosen as they were common causes of death in China,[17] or they had a potential association with HDL-C. The detailed ICD-10 codes for the outcomes were provided in the Supplementary Table S1.

Statistical analyses

Participant characteristics by HDL-C levels are presented as counts and percentages for categorical variables, mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables. Baseline characteristics among different levels of HDL-C were compared by ANOVA, Kruskal–Wallis test and Chi-Square test where appropriate.

The Cox proportional hazards models were used to estimate hazard ratios (HRs) between HDL-C and mortality, along with their corresponding 95%

confidence intervals (CIs), adjusting for age, sex, current smoking, alcohol drinking, BMI, annual household income, education level, systolic blood pressure, the history of diabetes mellitus, LDL-C, triglycerides, and the use of lipid-lowering therapy. HDL-C levels was categorized into eight groups (i.e., <30, 30–39 to 80–89 in increments of 10, and >90 mg/dL), with the group associated with the lowest risk of cause-specific mortality as reference. The proportional hazards (PH) assumption for the Cox models was assessed using the plot of Schoenfeld residual tests, and no violation was found. The linearity assumption of all continuous covariates in the models was evaluated by Martingale residuals plots, revealing a nonlinear association for BMI and LDL-C. Therefore, categorical BMI and LDL-C by quartiles were included as covariates. Fine–Gray sub-distribution hazard model which considered competing risk was used to assess the association with cause-specific mortality. Additionally, interaction analyses were further performed to assess whether the relationship of HDL-C with outcomes differed by sex, alcohol use and smoking status.

Next, we calculated population attributable fractions (PAFs) by sex and death cause using the Levin method (Supplementary Appendix).[18] A Monte Carlo-like approach was used to determine the 95% uncertainty intervals (95% UIs) for the PAFs. According to the Chinese guidelines for lipid management and the theoretical minimum-risk exposure level (TMREL) approach used in Global Burden of Disease study, low and high levels of HDL-C were merged as HDL-C <40 mg/dL and >70 mg/dL, respectively.[19,20] The attributable mortality for low and high levels of HDL-C was calculated by multiplying the aggregated PAF by mortality rate among Chinese aged ≥35 years, using the 2021 data from the National Mortality Surveillance System and Vital Registration.

Sensitivity analyses were performed by examining the associations among individuals without a history of malignancy and CVD and those who did not take lipid-lowering medication at baseline. We also refitted all the regression models after excluding deaths within the first year of follow-up.

SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. Two-sided $P < 0.05$ was considered statistically significant.

Role of the funding source

The funding body had no role in the design of the study and collection, analysis and interpretation of data and in writing the manuscript.

Results

Participant characteristics

A total of 3,397,547 subjects (60.2% women, median age 56, IQR: 48–64) were included in the study. The baseline characteristics of all individuals according to HDL-C categories were presented in Table 1. Around 2.6% of participants (n = 87,359) had extremely high HDL-C (>90 mg/dL), while HDL-C <30 mg/dL was observed in 1.9% (n = 64,137) participants. Participants with higher HDL-C were likely to be older, women, less educated, of lower income, and with lower BMI or diastolic blood pressure ($P < 0.0001$ for all). Individuals with HDL-C >90 mg/dL were more likely to be current alcohol users, non-smokers, without hypertension or diabetes, and had higher total cholesterol or LDL-C, but lower triglyceride ($P < 0.0001$ for all). Also, those with high HDL-C were less likely to take lipid-lowering agents ($P < 0.0001$).

HDL-C and the risk of all-cause, CVD and cancer mortality

During a median follow-up of 1418 (IQR: 1038–2053) days, 74,054 people died leading to a crude mortality of 5.24 per 1000-person years, among which 30,047 were due to CVD, 25,849 were cancer-related, and 18,158 were of other causes (Table 1).

U-shaped associations of HDL-C with all-cause, CVD and cancer mortality were observed after adjustment for potential confounders (Fig. 1). The lowest risk of all-cause and CVD mortality was seen in the group with HDL-C of 50–79 mg/dL. The cancer mortality was lowest at the 40–49 mg/dL group. Although approximately the same shape of associations were observed for both sexes, there were slight differences in the HDL-C range associated with the lowest all-cause mortality: 40–59 mg/dL in men and 50–79 mg/dL in women (Supplementary Figure S2).

Compared with the reference stratum of 50–59 mg/dL, individuals with HDL-C <30 mg/dL had a relatively higher risk of all-cause mortality than those with extremely high HDL-C levels (>90 mg/dL) (HR 1.23, 95% CI: 1.17–1.29 vs HR 1.10, 95% CI: 1.05–1.15). Furthermore, both HDL-C <30 mg/dL and >90 mg/dL were associated with an increased risk of CVD mortality (HR 1.33, 95% CI: 1.23–1.45 and HR 1.09, 95% CI: 1.01–1.18, respectively), and cancer mortality (HR 1.18, 95% CI: 1.09–1.28 and HR 1.11, 95% CI: 1.03–1.19, respectively), when compared to their lowest mortality group.

To test the influence of alcohol drinking and tobacco use on the association between HDL-C and mortality, subgroup analyses were conducted. No significant difference was identified between drinkers and non-drinkers (P for interaction = 0.057 for all-cause mortality, 0.90 for CVD mortality and 0.096 for cancer mortality), or between current smokers and non-smokers (P for interaction = 0.12 for all-cause mortality, 0.75 for CVD mortality, and 0.11 for cancer mortality).

Sensitivity analyses, which excluded patients with CVD and cancer, those taking lipid-lowering drugs or individuals who died within the first year of follow-up, showed similar U-shaped associations (Supplementary Figures S3–S5).

	Overall	<30 mg/dL	30–60 mg/dL	60–90 mg/dL	≥90 mg/dL	*P*-value
Total	3,397,547	64,137	2,171,514	1,074,537	87,359	
Age, median years (IQR)	56 (48–64)	54 (47–62)	56 (48–64)	57 (49–64)	58 (50–65)	<0.0001
Sex						<0.0001
Female, n (%)	2,046,436 (60.2)	20,085 (31.3)	1,207,776 (55.6)	757,415 (70.5)	61,160 (70.0)	
Male, n (%)	1,351,111 (39.8)	44,052 (68.7)	963,738 (44.4)	317,122 (29.5)	26,199 (30.0)	
Household income (RMB)						<0.0001
Last year income <10k, n (%)	604,537 (17.8)	10,596 (16.5)	371,277 (17.1)	204,883 (19.1)	17,781 (20.4)	
Last year income 10–50k, n (%)	1,879,116 (55.3)	34,351 (53.6)	1,203,195 (55.4)	592,896 (55.2)	48,674 (55.7)	
Last year income >50k, n (%)	598,007 (17.6)	13,103 (20.4)	395,616 (18.2)	176,212 (16.4)	13,076 (15.0)	
Unknown, n (%)	315,887 (9.3)	6087 (9.5)	201,426 (9.3)	100,546 (9.4)	7828 (9.0)	
Education						<0.0001
Primary school, n (%)	1,443,681 (42.5)	21,471 (33.5)	873,213 (40.2)	505,106 (47.0)	43,891 (50.2)	
Middle school, n (%)	1,110,544 (32.7)	21,660 (33.8)	728,335 (33.5)	333,750 (31.1)	26,799 (30.7)	
High school, n (%)	463,282 (13.6)	10,718 (16.7)	306,932 (14.1)	135,486 (12.6)	10,146 (11.6)	
College, n (%)	257,812 (7.6)	7834 (12.2)	178,739 (8.2)	66,887 (6.2)	4352 (5.0)	
Unknown, n (%)	122,228 (3.6)	2454 (3.8)	84,295 (3.9)	33,308 (3.1)	2171 (2.5)	
Lifestyle						
Smoking, n (%)	602,357 (17.7)	20,413 (31.8)	429,649 (19.8)	140,666 (13.1)	11,629 (13.3)	<0.0001
Alcohol, n (%)	330,031 (9.7)	6202 (9.7)	204,901 (9.4)	107,470 (10.0)	11,458 (13.1)	<0.0001
Medical history						
Hypertension, n (%)	1,580,618 (46.5)	31,679 (49.4)	1,043,139 (48.0)	468,234 (43.6)	37,566 (43.0)	<0.0001
Diabetes mellitus, n (%)	568,564 (16.7)	14,027 (21.9)	397,371 (18.3)	146,529 (13.6)	10,637 (12.2)	<0.0001
Lipid-lowering therapy, n (%)	87,450 (2.6)	1983 (3.1)	61,215 (2.8)	22,787 (2.1)	1465 (1.7)	<0.0001
BMI, kg/m^2, mean (SD)	24.7 (3.4)	26.0 (3.3)	25.2 (3.3)	23.9 (3.3)	23.0 (3.1)	<0.0001
SBP, mmHg, mean (SD)	135.8 (20.0)	135.6 (19.5)	136.1 (19.9)	135.3 (20.3)	135.6 (20.3)	<0.0001
DBP, mmHg, mean (SD)	81.0 (11.1)	82.8 (11.4)	81.5 (11.1)	79.8 (11.0)	79.6 (11.0)	<0.0001
GLU, mmol/L, mean (SD)	6.2 (1.7)	6.6 (2.0)	6.2 (1.7)	6.0 (1.5)	6.0 (1.5)	<0.0001
TG, median, mg/dL (IQR)	121.3 (88.6–171.8)	169.2 (118.7–244.5)	132.0 (95.7–186)	103.6 (78.8–142.6)	95.7 (72.6–133.7)	<0.0001
HDL-C, mg/dL, mean (SD)	55.4 (15.3)	26.5 (3.2)	47.0 (7.6)	71.0 (7.9)	94.4 (2.9)	<0.0001
LDL-C, mg/dL, mean (SD)	94.6 (33.9)	85.3 (35.7)	93.9 (32.9)	96.5 (35.1)	94.8 (37.3)	<0.0001
TC, mg/dL, mean (SD)	177.4 (39.2)	155.1 (40.0)	171.2 (37.0)	188.9 (39.4)	204.5 (41.8)	<0.0001
Follow-up time, median days (IQR)	1418 (1038–2053)	1709 (1247–2092)	1373 (1023–2047)	1619 (1079–2060)	1684 (1258–2094)	<0.0001
All-cause death, n (%)	74,054 (2.18)	1900 (2.96)	46,005 (2.12)	23,735 (2.21)	2414 (2.76)	<0.0001
Cardiovascular death, n (%)	30,047 (0.88)	816 (1.27)	19,255 (0.89)	9074 (0.84)	902 (1.03)	<0.0001
Cancer death, n (%)	25,849 (0.76)	627 (0.98)	15,843 (0.73)	8517 (0.79)	862 (0.99)	<0.0001
Ischemic heart disease death, n (%)	11,376 (0.33)	330 (0.51)	7393 (0.34)	3317 (0.31)	336 (0.38)	<0.0001
Stroke death, n (%)	10,340 (0.30)	232 (0.36)	6565 (0.30)	3202 (0.30)	341 (0.39)	<0.0001
Ischemic stroke death, n (%)	4015 (0.12)	100 (0.16)	2621 (0.12)	1154 (0.11)	140 (0.16)	<0.0001
Hemorrhagic stroke death, n (%)	6325 (0.19)	132 (0.21)	3944 (0.18)	2048 (0.19)	201 (0.23)	0.0030
TBL cancer death, n (%)	7787 (0.23)	173 (0.27)	4871 (0.22)	2477 (0.23)	266 (0.30)	<0.0001
Gastric cancer death, n (%)	2700 (0.08)	61 (0.10)	1646 (0.08)	904 (0.08)	89 (0.10)	0.0027
Liver cancer death, n (%)	3979 (0.12)	124 (0.19)	2359 (0.11)	1350 (0.13)	146 (0.17)	<0.0001
Colorectal cancer death, n (%)	1945 (0.06)	56 (0.09)	1231 (0.06)	601 (0.06)	57 (0.07)	0.0091
Esophageal cancer death, n (%)	1287 (0.04)	17 (0.03)	700 (0.03)	508 (0.05)	62 (0.07)	<0.0001
Breast cancer death, n (%)	640 (0.02)	13 (0.02)	394 (0.02)	211 (0.02)	22 (0.03)	0.41

IQR, interquartile range; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, blood glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TBL, tracheal, bronchus, and lung cancer.

Table 1: **Baseline characteristics according to HDL cholesterol levels.**

HDL-C and mortality of CVD and cancer subtypes

The U-shaped associations were also found in CVD-specific mortality, including ischemic heart disease and ischemic stroke, but not hemorrhagic stroke (Fig. 2 and Supplementary Table S2). Participants with HDL-C <30 mg/dL (HR 1.40, 95% CI: 1.23–1.59) and >90 mg/dL (HR 1.15, 95% CI: 1.02–1.30) had significantly higher mortality risk for ischemic heart disease compared to the reference group (70–79 mg/dL). Similarly, for ischemic stroke, the corresponding HRs of

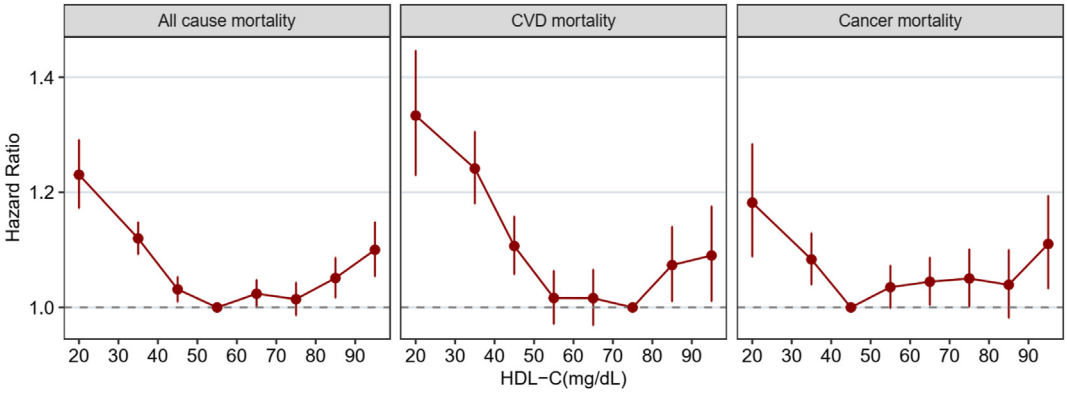

Fig. 1: Multivariable adjusted hazard ratios of HDL-C levels for top causes of death among 3,397,547 Chinese adults. Hazard ratio (solid red dot) with 95% confidence interval (error bar) from Cox regression were adjusted for age, sex, current smoking, alcohol drinking, body mass index (BMI), income, education level, systolic blood pressure, diabetes mellitus, LDL cholesterol, triglycerides, the use of lipid-lowering therapy. The horizontal dashed line referred to a hazard ratio of 1.0.

mortality for those extremely low and high HDL-C were 1.38 (95% CI: 1.09–1.74) and 1.43 (95% CI: 1.17–1.74) with 70–79 mg/dL as the reference.

With regards to site-specific cancers, the U-shaped association was only found between HDL-C and the mortality of liver cancer (Fig. 3). Compared to the reference group (40–49 mg/dL), HDL-C at <30 mg/dL (HR 1.55, 95% CI: 1.28–1.87) and >80 mg/dL (HR above 1.35, 95% CI above 1.10) were associated with higher risk of liver cancer mortality. Additionally, breast cancer mortality was significantly higher in individuals with HDL-C <40 mg/dL (HR above 1.90, 95% CI above 1.20), while esophageal cancer mortality was higher in those with HDL-C >70 mg/dL (HR above 1.90, 95% CI above 1.10). The associations above remained robust in the sensitivity analyses (Supplementary Figures S3–S5).

Attributable burden due to HDL-C

Over 3.25% of all-cause mortality could be attributed to high and low level of HDL-C (Supplementary Table S3, Fig. 4A). Specifically, HDL-C <40 mg/dL led to 34.09 deaths (95% UI: 24.91–44.41) per 100,000 persons, which contributed 2.86% of overall mortality (95% UI: 2.09–3.72), while HDL-C >70 mg/dL contributed to 0.39% (95% UI: 0.02–0.82) of all deaths, with an attributable mortality of 4.64 deaths (95% UI: 0.24–9.76) per 100,000 persons.

Regarding cause-specific mortality, the PAF and attributable mortalities were different across high HDL-C and low HDL-C levels. The largest PAFs were seen in breast cancer, ischemic heart disease and ischemic stroke when HDL-C levels <40 mg/dL. Conversely, for HDL-C >70 mg/dL, the largest PAFs were observed for

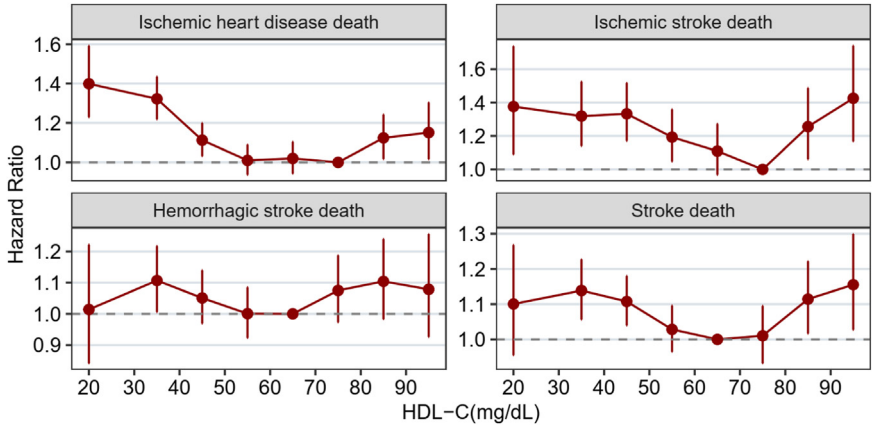

Fig. 2: Multivariable adjusted hazard ratios of HDL-C levels for the mortality of main CVD subtypes among 3,397,547 Chinese adults. Hazard ratio (solid red dot) with 95% confidence interval (error bar) from Cox regression were adjusted for age, sex, current smoking, alcohol drinking, body mass index (BMI), income, education level, systolic blood pressure, diabetes mellitus, LDL cholesterol, triglycerides, the use of lipid-lowering therapy. The horizontal dashed line referred to a hazard ratio of 1.0.

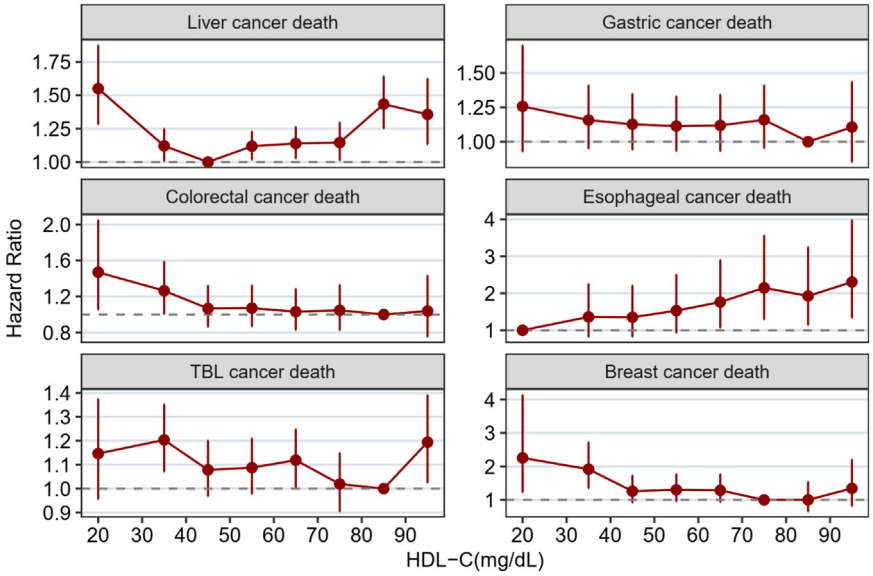

Fig. 3: Multivariable adjusted hazard ratios of HDL-C levels for the mortality of main cancer subtypes among 3,397,547 Chinese adults. Hazard ratio (solid red dot) with 95% confidence interval (error bar) from Cox regression were adjusted for age, sex, current smoking, alcohol drinking, body mass index (BMI), income, education level, systolic blood pressure, diabetes mellitus, LDL cholesterol, triglycerides, the use of lipid-lowering therapy. The horizontal dashed line referred to a hazard ratio of 1.0. TBL referred to tracheal, bronchus, and lung cancer.

esophagus cancer and liver cancer (Supplementary Table S3, Supplementary Figure S6). As shown in Fig. 4, ischemic heart disease (16.06 deaths per 100,000 persons, 95% UI: 10.30–22.67) was the major contributors to mortality associated with HDL-C <40 mg/dL. In contrast, the top ranked attributable mortality due to HDL-C >70 mg/dL was observed in esophageal cancer (2.29 per 100,000 persons, 95% UI: 0.57–4.77).

There were considerable sex differences in the attributable burden due to low or high HDL-C. The all-cause mortality attributed to high HDL-C was smaller in women. Further results regarding sex differences were presented in Fig. 4B and C and Supplementary Table S4 and S5.

Discussion

In this mega cohort of Chinese adults, a U-shaped association was observed between HDL-C and all-cause, overall CVD and cancer mortality. The HDL-C level associated with the lowest all-cause mortality was 50–79 mg/dL. The mortality risk related to HDL-C followed a U-shaped curve in ischemic heart disease, ischemic stroke, and liver cancer. Overall, approximately one in thirty deaths from all-cause could be attributed to high and low level of HDL-C. It is worth noting that, in addition to the well-established association with low HDL-C, high HDL-C also contributed significantly to population mortality, albeit with different patterns across specific causes of death.

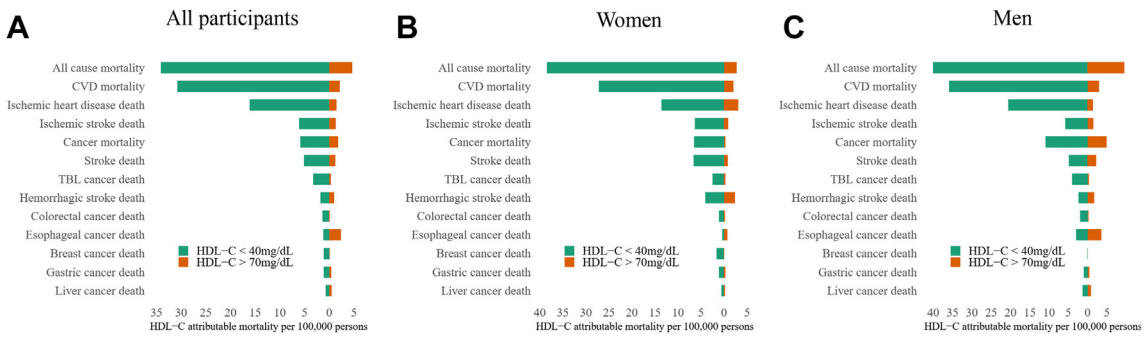

Fig. 4: HDL-C attributable mortality by different causes of death and gender.

In contrast to the inverse association that has been widely recognized, our study revealed a U-shaped association of HDL-C with all-cause and CVD mortality. Prior myth that HDL-C could be referred to as "good cholesterol" has led to some unexplained findings in previous RCTs and MR studies. Over the past two decades, several RCTs investigating lipid regulators have failed to demonstrate the effectiveness of increasing HDL-C in reducing CVD risk.[3,21,22] These disappointing results seem to be within the bounds of reason, as the intervention groups often elevated HDL-C to over 85 mg/dL, which were associated with higher all-cause and CVD mortality according to our findings. Moreover, previous MR studies have shown no linear association of genetically-predicted HDL-C with ischemic heart disease among either Western or East Asian population.[23,24] Although MR studies can overcome the limitations of the reverse causation and reduce the confounding biases from observational studies,[25] the linear exposure-outcome assumption in conventional MR might only provide a blurred effect estimation for nonlinear relationships,[26] which lead to, maybe falsely, the hypothesis that HDL-C is a "marker", rather than a "maker" of CVD risk.

Consistently, among subtypes of CVD, extremely high levels of HDL-C were associated with increased mortality from ischemic heart disease and ischemic stroke. It is highly unlikely that the relationships were observed by accident, since these two subtypes share a similar pathological process of atherosclerosis. This finding was contradicted with previous studies in Western population, which have reported a high risk of these two atherosclerotic cardiovascular diseases only in individuals with low HDL-C levels.[1,27] Nevertheless, more recent researches, such as the NHANES[28] study, have revealed that both extremely low and high HDL-C levels were both associated with higher mortality from ischemic heart disease. Nonetheless, the use of different reference groups to estimate effects of low (with ≥40 mg/dL as reference) and high HDL-C (with 40–79.9 mg/dL as reference) made it difficult to determine the overall dose-effect pattern. Another recent study conducted in the Norwegian population found an association between low HDL-C and stroke, but ischemic and hemorrhagic stroke were combined in the analysis.[2] Notably, our study, in line with most prior studies, did not find any significant relationship with HDL-C and hemorrhagic stroke.[29,30] This heterogeneity is unsurprising, given the different pathological mechanisms between ischemic and hemorrhagic stroke, but further investigation is warranted.

Among the population, a notable proportion of the overall disease burden could be attributed to HDL-C. However, when considering the leading causes of death, the "optimal ranges" of HDL-C for CVD and cancer were different. The HDL-C level associated with the lowest mortality risk of CVD was found to be 50–79 mg/dL, covering 46% of Chinese adults, while the optimal range for the lowest mortality risk of cancer was identified as 40–49 mg/dL, covering 27% of the population, as estimated from latest the China Chronic Disease and Risk Factor Surveillance (CCDRFS) survey. These findings were consistent with a previous study of 15.8 million Korean adults.[5] Furthermore, the optimal range of HDL-C representing the lowest all-cause mortality risk was 50–79 mg/dL, with a slight variation between male (40–59 mg/dL) and female (50–79 mg/dL). This heterogeneity was almost in accordance with the commonly accepted normal range of HDL-C in Western countries, which is 40–60 mg/dL for men and 50–60 for women. These variations in cut-off points of HDL-C for men and women highlighted the importance of considering sex-specific thresholds for identifying individuals at high risk. However, before the causality could be confirmed, it is still too early to recommend HDL-C management target, let alone sex-specific ones.

The fluctuant and non-linear associations between HDL-C and the overall cancer mortality suggested a potentially complex role that HDL-C may be involved in the development of specific cancers. Cause-specific analyses showed inconsistent risk patterns between HDL-C and mortality for different cancer subtypes. In agreement with findings of a study from the UKB,[31] a U-shaped association of HDL-C with liver cancer was found in our study. However, our findings were different from those of a Norwegian study that also explored associations with specific causes of cancers. The Norwegian study observed increased mortality risks for upper digestive cancer in individuals with higher HDL-C and stomach cancer in those with lower HDL-C, while mortality of other specific cancers did not show a statistically significant association with HDL-C.[2] However, it's worth noting that the Cox regression models employed by the Norwegian study did not consider the competing risk of death or adjust for alcohol intake as a potential confounder in their analysis. These may have potentially affected the validity of their estimates. Additionally, differences in the classification of cancers and racial disparities could also have contributed to the inconsistent findings with ours.

Outside the realm of CVD and cancer, emerging evidence has indicated associations between HDL-C and the development of infectious disease,[32] type 2 diabetes,[33] autoimmune disease,[34] and kidney disease.[35] These associations may contribute to the high mortality among individuals with extremely high HDL-C. Although we were not clear about the exact mechanisms of this association, it highlighted that the HDL functionality instead of the cholesterol content might be of greater importance for the pathogenesis of CVD and non-CVD diseases. HDL is a heterogeneous mix of particles that differ in size, shape, and composition. The increased particle sizes and detrimental subspecies such as HDL containing apoC3 among those with high levels

of HDL-C have been found to result in cholesterol deposition and atherosclerosis development, thereby increasing the risk of coronary heart disease.[36,37] Under particular circumstances, the alteration in protein composition could render HDL particles to be "dysfunctional", converting HDLs to be proinflammatory from anti-inflammatory, and with impaired antiatherogenic ability.[38] The presence of dysfunctional HDL was likely to contribute to the development of inflammation-driven diseases such as atherosclerotic cardiovascular disease and diabetes as well as malignancies and infections. Further studies are still warranted to investigate the functions of HDL in the development of specific diseases, and the causal relationship in between.

Our findings have substantial health implications. On the one hand, considering HDL-C a risk "marker" or diagnostic indicator, more comprehensive understanding about its relationships with mortality, which highlighted the nonlinear nature, disease-specific patterns, and subgroup heterogeneities, are essential. Currently, diagnosis of dyslipidemia and most CVD risk stratification tools[39] are based on the assumption of monotonic association, and updates should be considered to incorporate the new insights. Besides, the associations of HDL-C with overall and site-specific cancers in our analysis, especially the U-shaped one aligned with findings in the UKB cohort,[31] call for further research on cholesterol metabolism and synthesis in development and progression of cancer. On the other hand, we still lack the evidence supporting the treatment of HDL-C as a risk "maker" or a treatment target. Further research in this field, such as non-linear MR studies, should be performed to address this knowledge gap. Nevertheless, our findings serve as a reminder that lipid management, particularly the use of medications that could increase HDL-C, should be approached with caution, considering the potentially causal effects of high HDL-C on mortality.

Strengths and limitations

To our knowledge, this study was the largest research of its kind among Chinese population, with over three million community-dwelling individuals recruited from 31 provinces in mainland China. The large sample size in the present study allowed us to comprehensively examine the non-linear associations of HDL-C with mortality risk of major death causes and their subtypes, especially the impact of extreme HDL-C levels. However, several limitations in this study should be considered. Firstly, as an observational study, the causality between HDL-C and mortality could not be confirmed, considering the concerns about reverse causation. Also, although various potential confounders were adjusted for in the Cox models, residual confounding bias, including those arising from unmeasured confounders, could not be totally ruled out. Secondly, the relatively short follow-up (average less than 4 years) may limit the study's statistical power and the presence of events that develop over a long period of time. However, in this circumstance, the baseline HDL-C level could better reflect exposure during the entire follow-up period, which makes its observed association with mortality even closer.

Conclusion

In summary, HDL-C was associated with all-cause, CVD and cancer mortality risk in U-shaped patterns, with the optimal range varying across different diseases. The cause of death attributed to high HDL-C was distinct from those attributed to low HDL-C. Individuals with dyslipidemia should be cautious about target management and treatment regimens related to HDL-C.

Contributors

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All authors read and approved the final manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author Xi Li, upon reasonable request.

Declaration of interests

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100874.

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