Full research paper

European Journal of Preventive Cardiology

ESC European Society of Cardiology

European Journal of Preventive Cardiology
2020, Vol. 27(11) 1187–1203
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DOI: 10.1177/2047487320914756
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HDL-C is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose-response fashion: a pooled analysis of 37 prospective cohort studies

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Abstract

Objective: The association between high-density lipoprotein cholesterol (HDL-C) levels and mortality remains controversial. We aimed to investigate the potential dose–response associations between HDL-C levels and mortality from all causes, cardiovascular disease and cancer in the general population.

Methods: PubMed and Embase were searched through April 2019. Prospective cohort studies reporting risk estimates of HDL-C levels and mortality were included. Linear and non-linear dose–response analyses were conducted. A random-effects model was employed to calculate pooled hazard ratio.

Results: Thirty-seven studies, involving 3,524,505 participants and more than 612,027 deaths, were included. HDL-C level was found to be associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose–response pattern, with the lowest risk observed at HDL-C levels of 54–58 mg/dL, 68–71 mg/dL and 64–68 mg/dL, respectively. Compared with HDL-C level of 56 mg/dL, the pooled hazard ratios for all-cause mortality were 1.03 (95% confidence interval (CI) 1.01, 1.05) and 1.10 (95% CI 1.09, 1.12) for each 10-mg/dL increase and decrease in HDL-C levels, respectively; furthermore, compared with the reference category, the pooled hazard ratios for all-cause mortality were 1.21 (95% CI 1.09, 1.36) and 1.36 (95% CI 1.21, 1.53) for the highest and the lowest categories of HDL-C levels, respectively. Similar results were obtained for cardiovascular and cancer mortality.

Conclusions: In the general population, HDL-C level is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose–response manner; both extremely high and low HDL-C levels are associated with an increased risk of mortality.

Keywords

HDL-C, cancer, cardiovascular disease, mortality, dose–response

Received 5 October 2019; accepted 3 March 2020

Introduction

High-density lipoprotein, the smallest and densest lipoprotein particle, can transport cellular cholesterol to the liver or steroidogenic organs for excretion and reutilization. Early observational studies consistently revealed inverse linear associations between high-density

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lipoprotein cholesterol (HDL-C) levels and risks of cardiovascular disease (CVD)[1–3] and death.[1,4,5] These observational data lead the public and many physicians to consider HDL-C as the good cholesterol and to believe that raising HDL-C levels will result in a reduced cardiovascular risk ('the HDL-C hypothesis'). However, all clinical trials[6–10] except one[11] failed to detect a lower incidence of cardiovascular events among patients receiving HDL-C-raising agents than those receiving placebo. Moreover, several studies found that higher HDL-C levels were not a predictor of decreased risks of CVD and cardiovascular death in specific populations.[12–14] Notably, it was found that carriers of a variant in scavenger receptor BI, a primary HDL-C receptor, had increased HDL-C levels but a higher risk of coronary heart disease than non-carriers.[15] These facts indicate that the conventional HDL-C hypothesis appears to be questionable, and the associations of HDL-C levels with risks of CVD and death are more complicated than initially thought.

Over the past decade, extensive studies have investigated the association between HDL-C levels and mortality. However, their results were inconclusive, and most presented results different from early studies.[1,4,5] For example, some studies found that both low and high HDL-C levels were associated with an increased risk of all-cause mortality,[16–20] whereas others found no association between HDL-C levels and all-cause mortality.[21–24] These controversial data further add to the uncertainty surrounding the association between HDL-C levels and mortality.

As an easily accessible biomarker in clinical practice, HDL-C still plays a critical role in the assessment of cardiovascular risk, as evidenced by its continued use in cardiovascular risk estimators.[25,26] Thus, clarifying the association between HDL-C and mortality will have important clinical and public health implications. However, to our knowledge, a dose–response meta-analysis on this association is not available. Therefore, we conducted this study to investigate the potential dose–response associations between HDL-C levels and mortality from all causes, CVD and cancer in the general population, and to clarify the shape and the nadir of the dose–response curve.

Methods

The results of the present study were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[27]

Search strategy

We performed an electronic search of PubMed and Embase databases from the inception dates to 20 April 2019, with language restriction of English and Chinese. Detailed search strategies developed by a trained librarian (RO) and two reviewers (JJH and FBH) are described in Supplemental Material Table 1 online. We manually checked the bibliographies of pertinent articles for identifying additional studies. We did not contact the corresponding authors to obtain extra information.

Study selection

Prospective cohort studies investigating the association of HDL-C levels with mortality from all causes, CVD, cancer, coronary heart disease (CHD), or stroke in the general population were included if they reported corresponding risk estimates and 95% confidence intervals (CIs) or relevant data to calculate these required values[28–31] for at least three categories of HDL-C levels. Studies conducted in high-risk populations (e.g. patients with type 2 diabetes) were excluded. When multiple reports were derived from the same study cohort, we considered the one with the longest follow-up duration.[32–34] On the basis of the above-mentioned eligibility criteria, two reviewers (JJH and FBH) independently scrutinized titles and abstracts at first to exclude apparently ineligible studies, and then carefully checked the full text to further exclude unrelated studies. Any discrepancies were settled by discussion.

Data extraction

The following data parameters were extracted from each eligible study: first author's last name, publication year, study period, study location, mean age, the number of deaths, sample size, follow-up duration, outcome assessment, study setting, the most fully adjusted risk estimates and 95% CIs, adjustment factors and the above-mentioned required data for the dose–response analysis. One reviewer (LW) extracted these data through an electronic spreadsheet, and then another reviewer (JJH) checked the data for accuracy. Any discrepancies were settled by discussion.

Quality assessment

Based on the Newcastle–Ottawa quality assessment scale,[35] two reviewers (FBH and JJH) independently assessed the quality of included studies. This scale consists of eight items, but only seven items can be applicable to the present study. An individual study could earn a maximum of eight stars after evaluating its three aspects (i.e. selection, comparability and outcome). In our study, high-quality studies refers to those earning $\geq$7 stars. Any discrepancies were handled by discussion.

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Table 1. Characteristics of included studies on high-density lipoprotein cholesterol and mortality.

Study	Study period	Study location	Mean age (years)	Deaths	Sample size	Follow-up[a] (years)	Outcome assessment	Adjustment factors
Penson et al., 2019[45]	2003–2013	USA	64.6	All-cause: 3510 Cancer: 1156	T: 21,751 M: 9769 W: 11982	7.2	Physician review of medical history, medical records, interview with next-of-kin or proxies, autopsy reports, death certificates, and National Death Index	Age, sex, race, education, income, alcohol consumption, physical activity, current smoking, BMI, diabetes, albumin-to-creatine ratio, eGFR, use of statins and other lipid-lowering medications, high sensitivity C-reactive protein, steroid use, LDL-C, triglycerides
Oh et al., 2019[17]	2009–2015	South Korea	55.6	All-cause: 9350 CVD: 1585 Cancer: 3750	T: 365,457 M: 172,347 W: 193,110	3.5[b]	Statistics Korea	Age, SBP, BMI, fasting blood glucose, triglyceride, LDL-C, frequency of alcohol intake, smoking history, physical activity
Mazidi et al., 2019[32]	1999–2011	USA	48.8	NA	T: 25,541 M: 12,260 W: 13,281	NA	National Death Index	Age, sex, race, poverty to income ratio, education, alcohol consumption, physical activity, smoking, BMI, diabetes, eGFR, statin use, LDL-C, triglycerides
Li et al., 2019[16]	2006–2014	USA	74.4	All-cause: 1921 CVD: 665	T: 7766 M: 3324 W: 4442	5.9[b]	National Death Index and interview with a family member	Age, sex, race, education, current smoking, alcohol consumption, regular exercise, BMI, household income, TC, C-reactive protein, HbA1c, hypertension, heart disease, stroke, cancer, diabetes, lung disease, psychiatric problems, activities of daily living
Hirata et al., 2018[54]	NA	Japan	57.1	All-cause: 4995 CVD: 1280 CHD: 289 Stroke: 522	T: 43,407 M: 21,108 W: 22,299	12.1	Death certificate	Age, sex, BMI, non-high-density lipoprotein cholesterol, diabetes, hypertension, smoking, alcohol drinking, study location
Hamer et al., 2018[18]	1991–2011	UK	57.7	All-cause: 2250 CVD: 649 Cancer: 762	T: 37,059 M: 17,344 W: 19,715	8.8	Death registry	Age, sex, smoking, frequency of alcohol intake, physical activity, longstanding illness, TC, SBP, BMI
Onat et al., 2017[39]	2001–2016	Turkey	58.9	All-cause: 543	T: 2121 M: 1035 W: 1086	8.9	Interview with first-degree relatives and/or data from a local health office	Age, smoking, lipid and antihypertensive drug use, diabetes, coronary heart disease

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Table 1. Continued.

Study	Study period	Study location	Mean age (years)	Deaths	Sample size	Follow-up[a] (years)	Outcome assessment	Adjustment factors
Madsen et al., 2017[19]	1991–2014	Denmark	Men: 58.0[b] and women: 57.0[b]	All-cause: 10,678 CVD: 2777 Cancer: 2968	T: 11,6508 M: 52,268 W: 64,240	6.4	Death registry	Age, study location, BMI, current smoking, cumulative tobacco smoking, alcohol consumption, physical activity, SBP, diabetes, lipid-lowering therapy, LDL-C, triglycerides, birth year, menopausal status, hormone replacement therapy for women
Katzke et al., 2017[58]	1994–2009	Europe	51.0[b]	CVD: 381 Cancer: 761	T: 6583 M: NA W: NA	NA	Death registry	Age, sex, height, waist, BMI, alcohol consumption, red meat intake, fibre intake, smoking, socioeconomic status, physical activity, diabetes, hypertension, use of lipid-lowering drugs
Harari et al., 2017[21]	1985–2007	Israel	42.1	All-cause: 576 CVD: 172	T: 4832 M: 4832	22.1	Death registry	Age, socioeconomic status, education, father's country of origin, BMI, hypertension, diabetes, current smoking, coffee consumption, alcohol consumption, maintaining a special diet, doing sport, a family history of myocardial infarction
Lazo-Porras et al., 2016[57]	2007–2013	Peru	48.0	All-cause: 26	T: 988 M: 467 W: 521	5.0	Death certificate and interview with participant's relatives	Age, sex, deprivation index, migration status
Ko et al., 2016[36]	2008–2012	Canada	57.2	All-cause: 17,952 CVD: 4658 Cancer: 6850	T: 631,762 M: 281,766 W: 349,996	4.9	Vital Statistics Database	Age, alcohol consumption, neighbourhood income, hypertension, diabetes, smoking, cholesterol, previous comorbidities, the Johns Hopkins' Aggregated Diagnosis Groups
Hirata et al., 2016[22]	1990–2010	Japan	52.2	All-cause: 1598 CVD: 450 CHD: 95 Stroke: 79	T: 7019 M: 2946 W: 4073	18.0	National Vital Statistics	Age, sex, BMI, triglyceride, non- high-density lipoprotein cholesterol, hypertension, diabetes, smoking, alcohol consumption
Ghasemzadeh et al., 2016[42]	1999–2012	Iran	54.2	All-cause: 549 CVD: 279	T: 5518 M: 2532 W: 2986	11.9[b]	Death certificate or hospital record	Sex, lipid profiles, BMI, education, physical activity, smoking, blood pressure, glucose tolerance, lipid lowering drugs, cardiovascular disease

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Table 1. Continued.

Study	Study period	Study location	Mean age (years)	Deaths	Sample size	Follow-up[a] (years)	Outcome assessment	Adjustment factors
Chandler et al., 2016[49]	1992–2013	USA	54.1	Cancer: 647	T: 15,602 W: 15,602	19.0[b]	Medical record, death certificate or National Death Index	Age, race, BMI, treatment randomization, hormone replacement therapy, smoking, exercise, alcohol consumption, post-menopausal status, family history of cancer, aspirin use, history of colon polyps, history of fibrocystic or benign breast disease, total vegetables and fruits intake, history of mammogram
Bowe et al., 2016[20]	2003–2013	USA	64.1[b]	All-cause: 541,682	T: 176,4986 M: 176,4986	9.1[b]	VA Vital Status and Beneficiary Identification Records Locator Subsystem files	Age, race, cancer, cerebrovascular accident, chronic lung disease, diabetes, dementia, hepatitis C, HIV infection, hypertension, BMI, LDL-C, triglycerides, serum albumin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, coronary artery disease, congestive heart failure, peripheral artery disease, eGFR, dialysis, kidney transplant, statin use
Sung et al., 2015[23]	2002–2009	South Korea	39.9	All-cause: 1012 CVD: 169 Cancer: 469	T: 262,328 M: 113,272 W: 149,056	4.2[b]	Death certificate	Age, BMI, smoking, alcohol intake, regular exercise, education, history of hypertension, history of diabetes, high-sensitivity C-reactive protein, homeostatic model assessment-insulin resistance, SBP, TC
Li et al., 2015[40]	1988–2006	USA	45.8	CVD: 588	T: 131,85 M: 6228 W: 6957	13.6	National Death Index	Age, race, education, physical activity, smoking, alcohol use, BMI, SBP, serum insulin, triglycerides, serum C-reactive protein, creatinine, cholesterol
Wilkins et al., 2014[28]	NA	USA	57.2	All-cause: 5746	T: 24,440 M: 11,515 W: 12,925	12.6	NA	None
Skretteberg et al., 2012[24]	1979–2007	Norway	56.7	All-cause: 707 CVD: 296 CHD: 182	T: 1357 M: 1357	20.8	National death record	Age, smoking, SBP, TC

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Table 1. Continued.

Study	Study period	Study location	Mean age (years)	Deaths	Sample size	Follow-up[a] (years)	Outcome assessment	Adjustment factors
Rahilly-Tierney et al., 2012[46]	1997–2009	USA	81.9	All-cause: 501	T: 1351 M: 1351	6.8	Medical record	Age, hypertension, diabetes, congestive heart failure, stroke, cancer, non-high-density lipoprotein cholesterol, BMI, smoking, alcohol consumption, vigorous exercise
Rahilly-Tierney et al., 2011[55]	1979–2008	USA	65.2	All-cause: 280	T: 652 M: 652	16.3	Death certificate	Age, LDL-C, diabetes, hypertension, cerebrovascular disease, coronary heart disease, BMI, alcohol consumption, smoking, aspirin use, beta-blocker use, angiotensin-converting enzyme inhibitor use, cholesterol-modifying therapy
Upmeier et al., 2009[47]	1990–2001	Finland	70.0	All-cause: 316 CVD: 150	T: 1032 M: 370 W: 662	12.0	Death certificate	Sex, BMI, smoking, any history of angina pectoris, stroke, diabetes, hypertension, history of cancer
Cooney et al., 2009[37]	NA	Europe	NA	CVD: 2198	T: 10,4961 M: 57,302 W: 47,659	8.5	Death certificate	Age, TC, SBP, BMI, diabetes, smoking
Akerblom et al., 2008[33]	1999–2002	USA	77.0	All-cause: 427	T: 2556 M: 1690 W: 866	3.5	National Death Index	Age, sex, education, study cohort, BMI, apolipoprotein E genotype, heart disease, hypertension, diabetes, stroke, dementia, smoking
Okamura et al., 2006[60]	1990–2000	Japan	52.2	Cancer: 243	T: 7175 M: 3014 W: 4161	9.6	National Vital Statistics	Age, sex, BMI, triglyceride, non-high-density lipoprotein cholesterol, hypertension, diabetes, smoking, alcohol intake
Weverling-Rijnsburger et al., 2003[53]	1997–2001	Netherlands	85.0	All-cause: 152 CVD: 67 Cancer: 25 CHD: 35 Stroke: 25	T: 599 M: 202 W: 397	2.6[b]	Interview with general practitioner or nursing home physician	None
Cui et al., 2001[38]	1972–1995	North America	50.1	CVD: 234	T: 4462 M: 2406 W: 2056	19.0	Death certificate and National Death Index	Age
Houterman et al., 2000[41]	1984–1995	Europe	71.5	CHD: 276	T: 2132 M: 2132	10.0	Medical record	Age, BMI, SBP, smoking, alcohol intake, history of CHD
Raiha et al., 1997[48]	1982–1994	Finland	(≥65)	All-cause: 199 CVD: 127	T: 347 M: 184 W: 163	11.0	Mortality statistics	Age, sex, smoking, alcohol use, BMI, coronary heart disease, hypertension, diabetes

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Table 1. Continued.

Study	Study period	Study location	Mean age (years)	Deaths	Sample size	Follow-up[a] (years)	Outcome assessment	Adjustment factors
Paunio et al., 1996[59]	1984–1993	Finland	57.6	CHD: 258	T: 7052 M: 7052	6.7	Death certificate	Age, BMI, education, physical activity, smoking, TC
Corti et al., 1995[34]	1981–1989	USA	Men: 77.9; women: 78.9	All-cause: 788 CHD: 208	T: 3904 M: 1377 W: 2527	4.4[b]	Death certificate	Age, sex, category of blood pressure, history of high blood pressure, diabetes, heart attack, stroke, alcohol consumption, smoking, BMI, serum albumin (for all-cause mortality only)
Paunio et al., 1994[56]	1984–1991	Finland	57.6	All-cause: 620	T: 7052 M: 7052	4.7	Death certificate	Age, alcohol consumption, BMI, education, physical activity, smoking, SBP, TC
Stensvold et al., 1992[29]	1977–1987	Norway	(40–54)	All-cause: 957 CVD: 357 CHD: 259	T: 47,115 M: 23,690 W: 23,425	6.8	Mortality statistics	None
Pekkanen et al., 1990[5]	1977–1987	North America	(40–69)	CHD: 67	T: 2541 M: 2541	10.1	Death certificate	Age, hypertension, smoking, BMI, physical activity, LDL-C
Jacobs et al., 1990[30]	1972–1983	North America	($\geq$ 30)	All-cause: 429	T: 7623 M: 4152 W: 3471	8.4	Death certificate	None
Cowan et al., 1990[31]	1972–1984	North America	(40–79)	Cancer: 142	T: 5217 M: 2747 W: 2470	8.4	Death certificate	None

[a]Mean value unless otherwise specified.
[b]Median value.
BMI: body mass index; CHD: coronary heart disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; M: men; NA: not available; SBP: systolic blood pressure; T: total; TC: total cholesterol; W; women.

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Statistical analysis

Hazard ratio was used as a common measure to assess the association between HDL-C levels and mortality. The Hedges Q statistic (a $p < 0.10$ indicating statistically significance) and the I^2 statistic (an I^2 of <50%, 50.0–75.0% and >75.0% indicating low, moderate and substantial heterogeneity, respectively) were used to qualitatively and quantitatively assess the statistical heterogeneity, respectively. For studies whose authors reported risk estimates by sex,[17,19,28,36–40] by race[33] or by study location,[41] we used a fixed-effects model to pool these stratum data for the main analysis if the reference category was identical in subgroups,[17,28,39–41] otherwise they were regarded as independent cohorts.[19,33,36–38] For one study,[42] whose authors provided risk estimates for cardiovascular and non-cardiovascular mortality separately, we used a fixed-effects model to pool these stratum data to approximate risk estimates for all-cause mortality. For one study,[23] whose authors reported risk estimates by quartile of HDL-C levels for the whole study population, as HDL-C ranges in each quartile were different for men and women, we re-estimated these ranges (i.e. quartile 1, <49 mg/dL; quartile 2, 49–55 mg/dL; quartile 3, 56–62 mg/dL; quartile 4, >62 mg/dL) according to the distribution of HDL-C levels in the study population.

As the shape and the nadir of the dose–response curve for the association between HDL-C levels and mortality were unknown, we first explored the potential non-linear dose–response pattern through a restricted cubic spline model[43] with three knots at the 10th, 50th and 90th percentiles to fill this gap. A $p_{\text{non-linearity}}$ was obtained by testing the null hypothesis that the estimated value of the second spline equals zero.[43] When the exposure level was reported as range, the midpoint of lower and upper bounds was designated as the assigned dose. When the lowest range was open-ended, the assigned dose was obtained by subtracting half of the width of the adjacent range from the lowest value specified. When the highest range was open-ended, it was assumed to share the same width as the adjacent range. The method proposed by Hamling and colleagues[44] was employed to achieve risk estimates conversion when the reference category reported was not the lowest category. For studies whose authors did not report person-years by HDL-C level, we estimated these data by multiplying the number of subjects in each HDL-C level with the mean[18,19,21,24,28,33,36,37,39,41,45–48] or median[16,17,20,49] follow-up duration. We next designated the HDL-C nadir level, which was determined by the above-mentioned non-linear dose–response analysis, as the reference, and then employed a random-effects dose–response meta-regression model proposed by Orsini and colleagues[50] to calculate hazard ratios and 95% CIs for each 10-mg/dL increase and decrease in HDL-C levels. Finally, we employed a traditional meta-analytic approach to calculate hazard ratios and 95% CIs for the highest and the lowest versus reference categories of HDL-C levels. A random-effects model was employed to combine hazard ratios and 95% CIs. For each eligible study, the highest and the lowest HDL-C categories corresponded to the highest and the lowest groups, respectively; the category whose midpoint was closest to the HDL-C nadir level was chosen as the reference category. The highest and the lowest versus reference meta-analyses did not consider studies where the highest or the lowest category was found to be identical to the selected reference category.

We conducted pre-specified subgroup analyses to determine whether the observed association between HDL-C levels and mortality was modified by age, sex, study location, follow-up duration, publication year, study quality, sample size, study setting and adjustment for confounders, including low-density lipoprotein cholesterol, total cholesterol, triglycerides, the use of lipid-lowering therapy, alcohol, body mass index and physical activity. A $p_{\text{interaction}}$ for the difference between subgroups was calculated through meta-regression. To explain the observed heterogeneity and to assess the stability of combined results, we conducted the following sensitivity analyses: repeating meta-analysis through a fixed-effects model, applying diverse exclusion criteria, and omitting a single study in turn. Note that subgroup and sensitivity analyses were conducted only for all-cause and cardiovascular mortality owing to remaining outcomes of interest involving limited studies, and were based on hazard ratios for the highest and lowest versus reference categories of HDL-C levels.

We employed Begg's test[51] and Egger's test[52] to evaluate publication bias. We conducted all data analyses through STATA software (version 12.0, StataCorp, College Station, Texas, USA), and adopted a statistical significance level of $p < 0.05$ under two-sided test unless otherwise specified.

Results

Literature search

The literature search identified 4961 and 7191 records from PubMed and Embase, respectively. After removing duplicates, a total of 8954 records remained. After carefully reviewing their titles and abstracts, a total of 8880 records were excluded. The remaining 74 records were assessed for eligibility through scrutinizing the full text. Of them, 37 records were further excluded. Finally, a total of 37 records were included (Figure 1).

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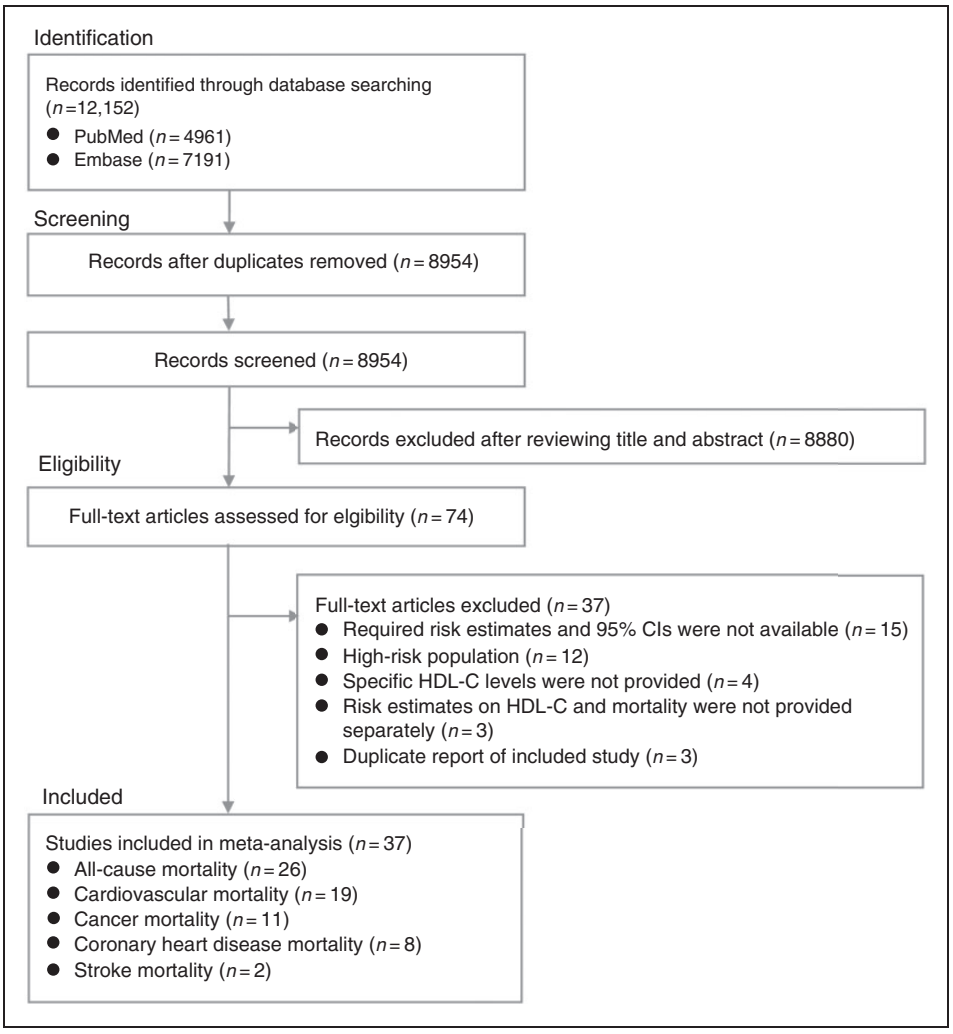

Figure 1. The flowchart of identifying relevant studies.
CI: confidence interval; HDL-C: high-density lipoprotein cholesterol.

Study characteristics and quality assessment

The main characteristics of included studies are shown in Table 1.[5,16–24,28–34,36–42,45–49,53–60] These studies were published between 1990[5,30,31] and 2019.[16,17,32,45] The mean age of study population ranged from 39.9 years[23] to 85.0 years.[53] The sample size of included studies varied from 347[48] to 1,764,986,[20] resulting in a total of 3,524,505 participants. During the follow-up period, ranging from 2.6 years[53] to 22.1 years,[21] more than 612,027 deaths occurred, with more than 607,764 all-cause deaths, 17,082 cardiovascular deaths, 17,773 cancer deaths, 1634 CHD deaths and 626 stroke deaths. The methods of outcome assessment were somewhat heterogeneous across studies, mainly including death certificate, death registry and National Death Index. As for quality assessment, 10 studies were awarded $\geq$7 stars and 17 studies were awarded six stars, suggesting that the quality of included studies was generally good (Supplemental Table 2).

HDL-C and all-cause mortality

Dose–response analysis

Twenty-four individual studies,[16–24,28–30,33,34,36,39,42,45–48,54–56] involving 3,367,943 subjects and 607,586 deaths, were included in the dose–response analysis of HDL-C levels and all-cause mortality. Overall, a J-shaped association was observed ($p_{\text{non-linearity}} < 0.01$), with the lowest risk observed at HDL-C levels of 54–58 mg/dL (Figure 2). When we conducted the analysis for men and women separately, similar dose–response patterns were found (all $p_{\text{non-linearity}} < 0.01$), with the lowest risk observed at HDL-C levels of 52–56 mg/dL for men and

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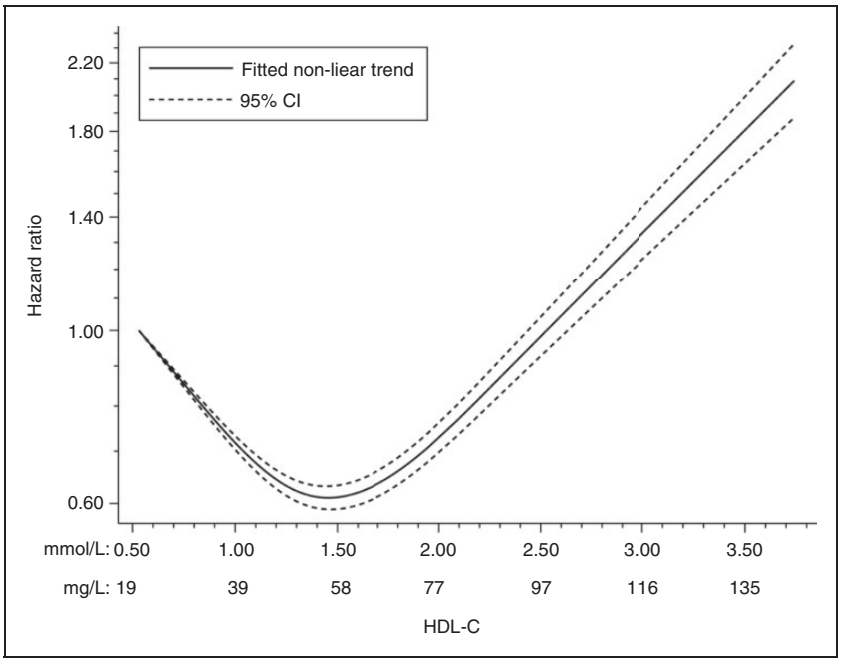

Figure 2. Non-linear dose–response analysis on high-density lipoprotein cholesterol levels and all-cause mortality, involving 3,367,943 subjects and 607,586 all-cause deaths from 24 studies.
CI: confidence interval; HDL-C: high-density lipoprotein cholesterol.

58–62 mg/dL for women (Supplemental Figure 1). When we conducted the analysis by publication year (≥2000 *vs.* <2000), both the shape and the nadir of dose–response curve did not alter substantially (all $p_{\text{non-linearity}} < 0.01$) (Supplemental Figure 2). Compared with HDL-C level of 56 mg/dL (i.e. the mid-point of the range 54–58 mg/dL), the pooled hazard ratios for all-cause mortality were 1.03 (95% CI 1.01, 1.05) and 1.10 (95% CI 1.09, 1.12) for each 10-mg/dL increase and decrease in HDL-C levels, respectively.

Highest and lowest versus reference meta-analysis

Twenty individual studies[16–19,21–24,28–30,32–34,36,39,47,48,54,56] were included in the highest versus reference meta-analysis on HDL-C and all-cause mortality. Individuals with the highest HDL-C level were found to be at an increased risk of all-cause mortality (hazard ratio 1.21, 95% CI 1.09, 1.36), with substantial heterogeneity ($p < 0.01$; $I^2 = 78.3\%$) (Supplemental Figure 3(a)), which was more pronounced in studies with follow-up duration <10 years ($p_{\text{interaction}} = 0.04$), those with sample size ≥10,000 ($p_{\text{interaction}} < 0.01$) and those with adjustment for the use of lipid-lowering therapy ($p_{\text{interaction}} = 0.03$) (Supplemental Table 3). The above-mentioned association remained in sensitivity analyses (Supplemental Figure 4(a) and Supplemental Table 4). Of note, excluding three studies[28–30] without adjustment for confounders resulted in a similar risk estimate (hazard ratio 1.17, 95% CI 1.08, 1.26) but low heterogeneity ($I^2 = 41.1\%$).

Twenty individual studies[16–19,21–24,28–30,33,34,36,39,47,48,54,56,57] were included in the lowest versus reference meta-analysis on HDL-C and all-cause mortality. Individuals with the lowest HDL-C levels were found to have an elevated risk of all-cause mortality (hazard ratio 1.36, 95% CI 1.21, 1.53), with substantial heterogeneity ($p < 0.01$; $I^2 = 88.1\%$) (Supplemental Figure 3(b)). Subgroup analyses found that this association was more evident in studies with follow-up duration <10 years, those with sample size ≥10,000 and those without adjustment for body mass index (all $p_{\text{interaction}} < 0.05$) (Supplemental Table 3). The initial association persisted in sensitivity analyses (Supplemental Figure 4(b) and Supplemental Table 4).

HDL-C and cardiovascular, CHD and stroke mortality

Dose–response analysis

Seventeen individual studies[16–19,21–24,29,36–38,40,42,48,54,58] were included in the dose–response analysis of HDL-C levels and cardiovascular mortality, with 16,865 cardiovascular deaths among 1,659,666 participants. A J-shaped association was found ($p_{\text{non-linearity}} < 0.01$), with the lowest risk observed at HDL-C levels of 68–71 mg/dL (Figure 3). Similar dose–response patterns

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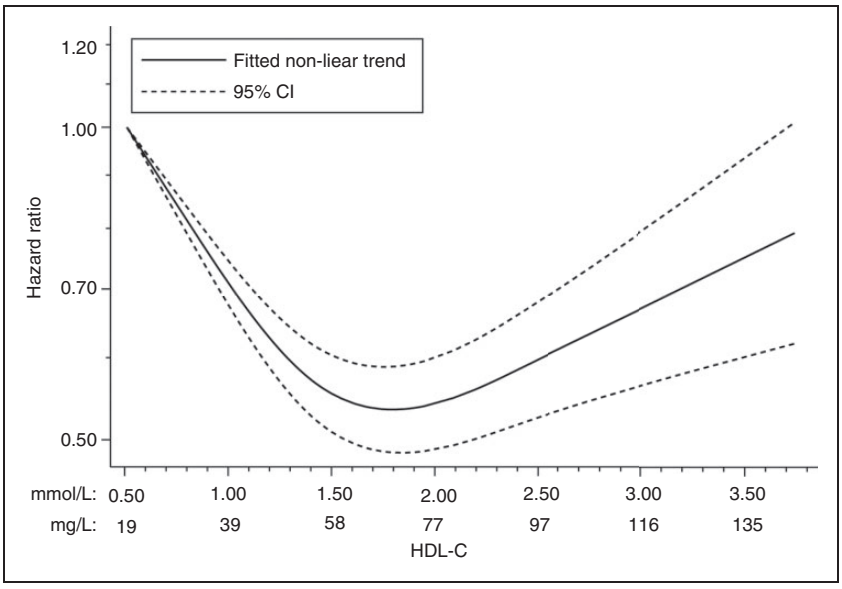

Figure 3. Non-linear dose–response analysis on high-density lipoprotein cholesterol levels and cardiovascular mortality, involving 1,659,666 subjects and 16,865 cardiovascular deaths from 17 studies.
CI: confidence interval; HDL-C: high-density lipoprotein cholesterol.

were observed for men and women (all $p_{\text{non-linearity}} < 0.01$), with the lowest risk observed at HDL-C levels of 64–68 mg/dL for men and 73–85 mg/dL for women (Supplemental Figure 5). Likewise, the dose–response analysis in studies published after the year 2000 identified a similar dose–response pattern ($p_{\text{non-linearity}} < 0.01$) (Supplemental Figure 6(a)) while, based on only two individual studies,[29,48] a non-linear inverse relationship was found for HDL-C levels and cardiovascular mortality ($p_{\text{non-linearity}} < 0.01$) (Supplemental Figure 6(b)). Compared with HDL-C level of 69 mg/dL (i.e. the midpoint of the range 68–71 mg/dL), the pooled hazard ratios for cardiovascular mortality were 1.06 (95% CI 1.01, 1.10) and 1.12 (95% CI 1.10, 1.15) for each 10-mg/dL increase and decrease in HDL-C levels, respectively.

In addition, we examined the dose–response relationship between HDL-C levels and mortality from CHD and stroke. Based on eight individual studies,[5,22,24,29,34,41,54,59] a non-linear inverse association between HDL-C levels and CHD mortality was observed ($p_{\text{non-linearity}} = 0.01$) (Figure 4). Based on two individual studies,[22,54] a J-shaped dose–response pattern was found for the association between HDL-C levels and stroke mortality ($p_{\text{non-linearity}} = 0.01$) (Supplemental Figure 7).

Highest and lowest versus reference meta-analysis

Nine individual studies[16–19,22,24,36,37,54] were included in the highest versus reference meta-analysis on HDL-C and cardiovascular mortality. Compared with the reference category, the highest category of HDL-C levels was associated with an increased risk of cardiovascular mortality (hazard ratio 1.21, 95% CI 0.98 to 1.49), with moderate heterogeneity ($p = 0.01$; $I^2 = 54.8\%$) (Supplemental Figure 8(a)), which was even more evident in studies with adjustment for the use of lipid-lowering agents ($p_{\text{interaction}} = 0.02$) (Supplemental Table 5). The above-mentioned association did not alter substantially in sensitivity analyses (Supplemental Figure 9(a) and Supplemental Table 6).

Eleven individual studies[16–19,22,24,36,37,53,54,58] were included in the lowest versus reference meta-analysis on HDL-C and cardiovascular mortality. Subjects with the lowest HDL-C level were found to be at an elevated risk of cardiovascular mortality (hazard ratio 1.62, 95% CI 1.43, 1.85), with moderate heterogeneity ($p < 0.01$; $I^2 = 61.4\%$) (Supplemental Figure 8(b)), which was more pronounced in studies conducted in North America ($p_{\text{interaction}} = 0.03$) and those with follow-up duration <10 years ($p_{\text{interaction}} = 0.02$) (Supplemental Table 5). The initial association between the lowest HDL-C level and cardiovascular mortality remained in sensitivity analyses (Supplemental Figure 9 (b) and Supplemental Table 6).

HDL-C and cancer mortality

Dose–response analysis

Ten individual studies,[17–19,23,31,36,45,49,58,60] involving a total of 1,469,442 participants and 17,748 deaths, were included in the dose–response analysis of HDL-C levels

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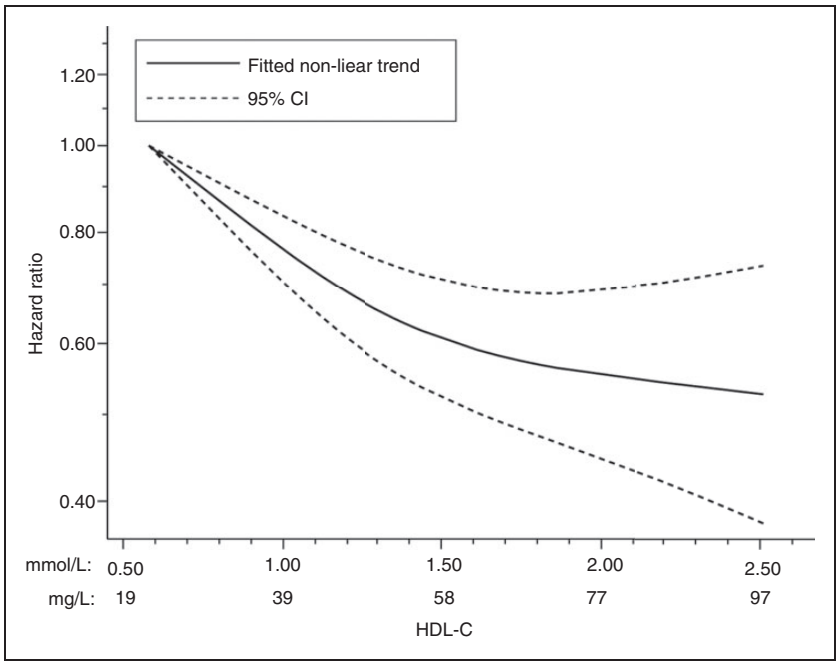

Figure 4. Non-linear dose–response analysis on high-density lipoprotein cholesterol levels and coronary heart disease mortality, involving 114,527 subjects and 1634 deaths from coronary heart disease from eight studies.
CI: confidence interval; HDL-C: high-density lipoprotein cholesterol.

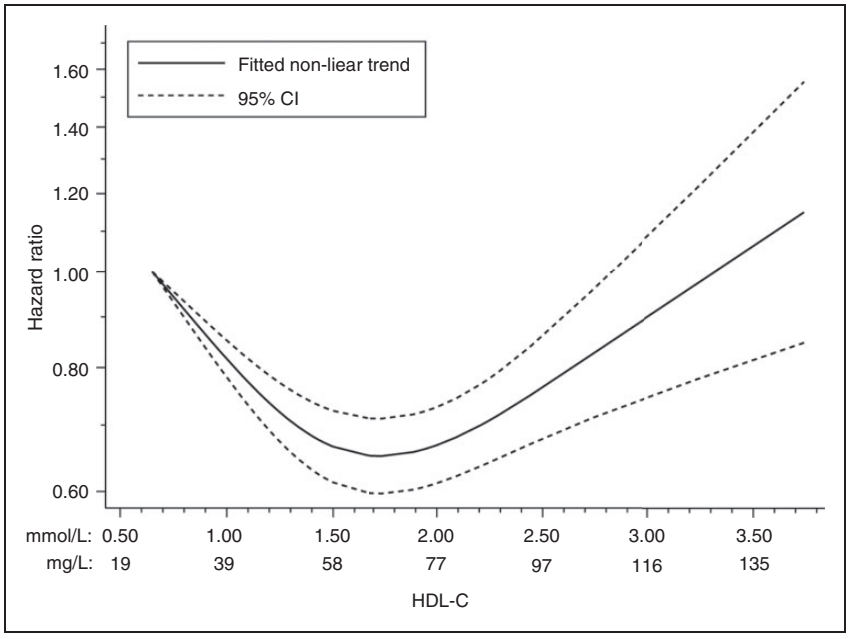

Figure 5. Non-linear dose–response analysis on high-density lipoprotein cholesterol levels and cancer mortality, involving 1,469,442 subjects and 17,748 cancer deaths from 10 studies.
CI: confidence interval; HDL-C: high-density lipoprotein cholesterol.

and cancer mortality. A J-shaped association was shown ($p_{\text{non-linearity}} < 0.01$), with the lowest risk observed at HDL-C levels of 64–68 mg/dL (Figure 5). Similar dose–response patterns were found for men and women (all $p_{\text{non-linearity}} < 0.01$), with the lowest risk observed at HDL-C levels of 56–66 mg/dL for men and 66–73 mg/dL for women (Supplemental Figure 10). Compared with HDL-C level of 66 mg/dL

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(i.e. the midpoint of the range 64–68 mg/dL), the pooled hazard ratios for cancer mortality were 1.02 (95% CI 0.98, 1.05) and 1.11 (95% CI 1.09, 1.14) for each 10-mg/dL increase and decrease in HDL-C levels, respectively.

Highest and lowest versus reference meta-analysis

Six[17–19,31,36,60] and seven[17–19,31,36,53,60] individual studies were included in the highest versus reference and the lowest versus reference meta-analyses on HDL-C and cancer mortality, respectively. Compared with the reference category, the pooled hazard ratios for cancer mortality were 1.14 (95% CI 1.01, 1.29) and 1.57 (95% CI 1.35, 1.82) for the highest and the lowest categories of HDL-C levels, respectively, with small heterogeneity (highest versus reference: $p = 0.70$, $I^2 = 0.0\%$; lowest versus reference: $p = 0.05$, $I^2 = 48.3\%$) (Supplemental Figure 11).

Publication bias

We did not find evidence of publication bias for any association of interest with Begg's test and Egger's test (all $p > 0.05$).

Discussion

Based on a total of 37 prospective cohort studies, our study found that, in the general population, the associations between HDL-C levels and mortality from all causes, CVD and cancer followed a J-shaped pattern, which was also observed in men and women; moreover, both the highest and the lowest HDL-C levels were associated with an increased risk of mortality from all causes, CVD and cancer.

Obviously, these findings do not support the conventional notion that higher HDL-C levels are better, which was mainly based on the results of early epidemiological studies.[1–5] Of note, early epidemiological studies generally involved a small number of subjects with very high HDL-C levels (defined as >100 mg/dL)[61] owing to limited sample size; therefore, those with very high HDL-C levels were often grouped with a large number of subjects with modestly high HDL-C levels. Thus, the effects of modestly high HDL-C levels on mortality would dominate in this group, and could mask the adverse effects of very high HDL-C levels on mortality, which was shown by our study. Indeed, of included studies published before 2000,[5,29–31,34,48,56,59] the number of deaths ranged from 199[48] to 957,[29] and the highest category of HDL-C levels ranged from '>46 mg/dL'[5] to '>68 mg/dL'.[59] The above-mentioned facts could explain why the results of early epidemiological studies are different from ours.

However, interestingly, our dose–response analysis found a non-linear inverse association between HDL-C levels and CHD mortality. It should be reminded that this finding is not contradictory to the observation of a J-shaped association between HDL-C levels and cardiovascular mortality, considering various subtypes of CVD. It should be acknowledged that the finding of an inverse association between HDL-C levels and CHD mortality supports 'the HDL-C hypothesis' to some extent. However, this finding should be interpreted with much caution considering the following two aspects. On the one hand, our dose–response analysis on HDL-C levels and CHD mortality included only eight individual studies and involved only 1479 CHD deaths, indicating that there were few deaths at extremely high HDL-C levels. Consequently, our analysis had limited power to detect the potential adverse effects of extremely high HDL-C levels on CHD mortality. On the other hand, the non-linear inverse association with CHD mortality was observed at HDL-C levels ranging from 22 mg/dL to 97 mg/dL. Thus, a positive association may be observed at higher HDL-C levels. Indeed, Hirata and colleagues[54] found that subjects with HDL-C levels equal to or more than 90 mg/dL had a higher risk of CHD mortality than those with HDL-C levels ranging from 40 to 60 mg/dL, which supports our speculation to some degree. Therefore, the non-linear inverse association observed in our study needs to be validated at very high HDL-C levels by studies with a large sample size.

In the highest and lowest versus reference meta-analyses on HDL-C and all-cause mortality, we observed substantial heterogeneity across studies. As suggested by our subgroup analyses, the differences in follow-up duration and sample size among eligible studies were possible sources of the observed heterogeneity (all $p_{\text{interaction}} < 0.05$). Generally, studies with larger sample size or longer follow-up duration would observe more events of interest, and are performed with more methodological rigour compared with smaller studies.[62] As suggested by our sensitivity analyses, three studies[28–30] without adjustment for confounders might also contribute to the observed heterogeneity.

The mechanisms underlying the finding that very high HDL-C levels were associated with an increased risk of mortality remain unclear. One possible explanation is that this finding is caused by the unrecognized or unmeasured confounders that can result in both high HDL-C levels and high mortality (e.g. alcohol consumption[63]). Indeed, residual confounding is an important concern when we interpret this finding, despite the fact that we had extracted the most fully adjusted risk estimates. Therefore, future studies should clarify whether the observed association of very high

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HDL-C levels with increased risk of death is causal. An alternative explanation is that very high HDL-C levels are due to the presence of some genetic variants, including ABCA1, SCARB1, LIPC and CETP, which are known to have adverse effects on health outcomes.[15,64–66] Additionally, it is possible that in subjects with very high HDL-C levels, both conformation and functionality of high-density lipoprotein are compromised, resulting in the dysfunctional high-density lipoprotein that may cause harm rather than benefit.[67] Indeed, an experimental study found that moderate to high levels of high-density lipoprotein promoted the senescence of endothelial progenitor cells and impaired their abilities of tube formation and angiogenesis, indicating that high-density lipoprotein has concentration-dependent biphasic effects.[68]

Our findings have some implications for clinical practice and public health. First, our findings suggest that the conventional notion that higher HDL-C levels are better is not the case for subjects with high HDL-C levels, as the association between HDL-C levels and mortality was J-shaped across the full range of HDL-C levels, rather than inverse linear, as traditionally thought. Current American and European guidelines on CVD prevention both recommend that HDL-C levels should be routinely measured for the assessment of cardiovascular risk and before beginning lipid-lowering therapy.[25,69] Based on our findings, the recommended optimal HDL-C range is 54–58 mg/dL; clinicians should pay attention to not only subjects with low HDL-C levels but also those with high HDL-C levels, as both subpopulations are at an increased risk of mortality. Second, our dose–response analyses identified HDL-C levels associated with the lowest risk of mortality from all causes, CVD and cancer. These findings may be useful in determining whether interventions increasing HDL-C levels can improve clinical outcomes, and which population will benefit the most from these interventions.

Our study has several limitations. First, around half of included studies employed the death certificate to determine the causes of death. However, data provided by the death certificate are inaccurate in some conditions.[70] Therefore, our findings on HDL-C levels and cause-specific mortality might be influenced by misclassification bias. Additionally, our findings were derived from the study-level data, which does not allow for an analysis of competing risk for cause-specific mortality to determine its potential impact on the corresponding results, and individual level adjustment or stratification of results. Second, we extracted the most fully adjusted risk estimates for our analyses, but we cannot exclude the possibility that our pooled results were biased by residual confounding. For example, statin use is a potential confounder of the association of HDL-C with mortality; however, limited studies included in our analysis were adjusted for this confounder, resulting in our results possibly being subject to residual confounding. Third, substantial heterogeneity was observed in the highest and lowest versus reference meta-analyses on HDL-C levels and all-cause mortality, which raises some concerns about the necessity of performing a meta-analysis and the reliability of pooled results. Nevertheless, we had identified sources of the observed heterogeneity through subgroup and sensitivity analyses. Moreover, clinical and methodological heterogeneity exists for all meta-analyses, particularly for meta-analysis of observational studies. Fourth, several earlier prospective studies,[71–74] including the Framingham Heart Study,[73] that showed an inverse association between HDL-C and mortality were excluded from our analysis, as they did not report the required data for the dose–response analysis. Therefore, it is a fact that our findings might be biased by the exclusion of these studies. Nevertheless, our dose–response and subgroup analyses by publication year both suggested that the observed association on HDL-C and all-cause mortality did not differ significantly by the date of study publication. Finally, our study included limited studies on HDL-C levels and mortality from cancer, CHD and stroke. Therefore, corresponding results should be treated with caution, and need to be confirmed by future large-scale studies.

In conclusion, HDL-C level is associated with mortality from all causes, CVD and cancer in a J-shaped dose–response pattern, with the lowest risk observed at HDL-C levels of 54–58 mg/dL, 68-71 mg/dL and 64–68 mg/dL, respectively; both higher and lower HDL-C levels are associated with an elevated risk of mortality from all causes, CVD and cancer. These findings highlight the importance of appropriate HDL-C levels in reducing the risk of death, and challenge the conventional notion that higher HDL-C levels are better. More studies are warranted to clarify whether the associations observed in our study are causal, and to elucidate the potential mechanisms.

Author contribution

GCZ and SQH conceived the study idea. FBH and JJH. performed literature search, study selection and quality assessment. LW and JJH performed data extraction. YQLW performed statistical analyses. GCZ, YQLW and TYH interpreted the results of statistical analyses. GCZ drafted the initial manuscript. All authors made critical comments and revisions for the initial manuscript. All authors approved the final version of the article, including the authorship list. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Acknowledgement

The authors thank Prof. Yong Zhao (School of Public Health and Management, Chongqing Medical University, China) for his assistance in the statistical analysis.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989; 79: 8–15.
2. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham study. *JAMA* 1986; 256: 2835–2838.
3. Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009; 302: 1993–2000.
4. Wilson PW, Abbott RD and Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis* 1988; 8: 737–741.
5. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 1990; 322: 1700–1707.
6. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014; 371: 203–212.
7. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med* 2017; 376: 1933–1942.
8. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; 365: 2255–2267.
9. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 367: 2089–2099.
10. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; 357: 2109–2122.
11. Bowman L, Hopewell JC, Chen F, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med* 2017; 377: 1217–1227.
12. Angeloni E, Paneni F, Landmesser U, et al. Lack of protective role of HDL-C in patients with coronary artery disease undergoing elective coronary artery bypass grafting. *Eur Heart J* 2013; 34: 3557–3562.
13. Silbernagel G, Schottker B, Appelbaum S, et al. High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality. *Eur Heart J* 2013; 34: 3563–3571.
14. Ridker PM, Genest J, Boekholdt SM, et al. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: An analysis from the JUPITER trial. *Lancet* 2010; 376: 333–339.
15. Zanoni P, Khetarpal SA, Larach DB, et al. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science* 2016; 351: 1166–1171.
16. Li ZH, Lv YB, Zhong WF, et al. High-density lipoprotein cholesterol and all-cause and cause-specific mortality among the elderly. *J Clin Endocrinol Metab* 2019 104: 3370–3378.
17. Oh IH, Hur JK, Ryoo JH, et al. Very high high-density lipoprotein cholesterol is associated with increased all-cause mortality in South Koreans. *Atherosclerosis* 2019; 283: 43–51.
18. Hamer M, O'Donovan G and Stamatakis E. High-density lipoprotein cholesterol and mortality: Too much of a good thing? *Arterioscler Thromb Vasc Biol* 2018; 38: 669–672.
19. Madsen CM, Varbo A and Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: Two prospective cohort studies. *Eur Heart J* 2017; 38: 2478–2486.
20. Bowe B, Xie Y, Xian H, et al. High density lipoprotein cholesterol and the risk of all-cause mortality among U.S. Veterans. *Clin J Am Soc Nephrol* 2016; 11: 1784–1793.
21. Harari G, Green MS, Magid A, et al. Usefulness of non-high-density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men in 22-year follow-up. *Am J Cardiol* 2017; 119: 1193–1198.
22. Hirata A, Okamura T, Sugiyama D, et al. The relationship between very high levels of serum high-density lipoprotein cholesterol and cause-specific mortality in a 20-year follow-up study of Japanese general population. *J Atheroscler Thromb* 2016; 23: 800–809.
23. Sung KC, Ryu S, Wild SH, et al. An increased high-density lipoprotein cholesterol/apolipoprotein A-I ratio is associated with increased cardiovascular and all-cause mortality. *Heart* 2015; 101: 553–558.
24. Skretteberg PT, Grundvold I, Kjeldsen SE, et al. HDL-cholesterol and prediction of coronary heart disease: Modified by physical fitness? A 28-year follow-up of apparently healthy men. *Atherosclerosis* 2012; 220: 250–256.
25. American College of Cardiology, American Heart Association. The Pooled Cohort Equations, http://my.americanheart.org/cvriskcalculator (2014, accessed 25 December 2019).
26. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2889–2934.

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27. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* 2009; 339: b2535.
28. Wilkins JT, Ning H, Stone NJ, et al. Coronary heart disease risks associated with high levels of HDL cholesterol. *J Am Heart Assoc* 2014; 3: e000519.
29. Stensvold I, Urdal P, Thurmer H, et al. High-density lipoprotein cholesterol and coronary, cardiovascular and all cause mortality among middle-aged Norwegian men and women. *Eur Heart J* 1992; 13: 1155–1163.
30. Jacobs DR Jr, Mebane IL, Bangdiwala SI, et al. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: The follow-up study of the Lipid Research Clinics Prevalence Study. *Am J Epidemiol* 1990; 131: 32–47.
31. Cowan LD, O'Connell DL, Criqui MH, et al. Cancer mortality and lipid and lipoprotein levels. Lipid Research Clinics program mortality follow-up study. *Am J Epidemiol* 1990; 131: 468–482.
32. Mazidi M, Mikhailidis DP and Banach M. Associations between risk of overall mortality, cause-specific mortality and level of inflammatory factors with extremely low and high high-density lipoprotein cholesterol levels among American adults. *Int J Cardiol* 2019; 276: 242–247.
33. Akerblom JL, Costa R, Luchsinger JA, et al. Relation of plasma lipids to all-cause mortality in Caucasian, African-American and Hispanic elders. *Age Ageing* 2008; 37: 207–213.
34. Corti MC, Guralnik JM, Salive ME, et al. HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA* 1995; 274: 539–544.
35. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (2000, accessed 25 December 2019).
36. Ko DT, Alter DA, Guo H, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: The CANHEART study. *J Am Coll Cardiol* 2016; 68: 2073–2083.
37. Cooney MT, Dudina A, De Bacquer D, et al. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis* 2009; 206: 611–616.
38. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 2001; 161: 1413–1419.
39. Onat A, Can G, Keskin M, et al. Tenth categories of total and HDL cholesterol fail to independently predict death risk in middle-aged Turkish adults. *Turk Kardiyol Dern Ars* 2017; 45: 590–598.
40. Li Y, Li Y, Meng L, et al. Association between serum C-peptide as a risk factor for cardiovascular disease and high-density lipoprotein cholesterol levels in nondiabetic individuals. *PLoS One* 2015; 10: e112281.
41. Houterman S, Verschuren WM, Giampaoli S, et al. Total but not high-density lipoprotein cholesterol is consistently associated with coronary heart disease mortality in elderly men in Finland, Italy, and The Netherlands. *Epidemiology* 2000; 11: 327–332.
42. Ghasemzadeh Z, Abdi H, Asgari S, et al. Divergent pathway of lipid profile components for cardiovascular disease and mortality events: Results of over a decade follow-up among Iranian population. *Nutr Metab* 2016; 13: 43.
43. Desquilbet L and Mariotti F. Dose–response analyses using restricted cubic spline functions in public health research. *Stat Med* 2010; 29: 1037–1057.
44. Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008; 27: 954–970.
45. Penson P, Long DL, Howard G, et al. Associations between cardiovascular disease, cancer, and very low high-density lipoprotein cholesterol in the REasons for Geographical And Racial Differences in Stroke (REGARDS) study. *Cardiovasc Res* 2019; 115: 204–212.
46. Rahilly-Tierney C, Sesso HD, Michael Gaziano J, et al. High-density lipoprotein and mortality before age 90 in male physicians. *Circ Cardiovasc Qual Outcomes* 2012; 5: 381–386.
47. Upmeier E, Lavonius S, Lehtonen A, et al. Serum lipids and their association with mortality in the elderly: A prospective cohort study. *Aging Clin Exp Res* 2009; 21: 424–430.
48. Raiha I, Marniemi J, Puukka P, et al. Effect of serum lipids, lipoproteins, and apolipoproteins on vascular and nonvascular mortality in the elderly. *Arterioscler Thromb Vasc Biol* 1997; 17: 1224–1232.
49. Chandler PD, Song Y, Lin J, et al. Lipid biomarkers and long-term risk of cancer in the Women's Health Study. *Am J Clin Nutr* 2016; 103: 1397–1407.
50. Orsini N, Bellocco R and Greenland S. Generalized least squares for trend estimation of summarized dose–response data. *Stata J* 2006; 6: 40–57.
51. Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
52. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
53. Weverling-Rijnsburger AW, Jonkers IJ, van Exel E, et al. High-density *vs* low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Arch Intern Med* 2003; 163: 1549–1554.
54. Hirata A, Sugiyama D, Watanabe M, et al. Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: The EPOCH-JAPAN study. *J Clin Lipidol* 2018; 12: 674–684 e675.
55. Rahilly-Tierney CR, Spiro A 3rd, Vokonas P, et al. Relation between high-density lipoprotein cholesterol and survival to age 85 years in men (from the VA normative aging study). *Am J Cardiol* 2011; 107: 1173–1177.

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56. Paunio M, Heinonen OP, Virtamo J, et al. HDL cholesterol and mortality in Finnish men with special reference to alcohol intake. *Circulation* 1994; 90: 2909–2918.
57. Lazo-Porras M, Bernabe-Ortiz A, Malaga G, et al. Low HDL cholesterol as a cardiovascular risk factor in rural, urban, and rural-urban migrants: PERU MIGRANT cohort study. *Atherosclerosis* 2016; 246: 36–43.
58. Katzke VA, Sookthai D, Johnson T, et al. Blood lipids and lipoproteins in relation to incidence and mortality risks for CVD and cancer in the prospective EPIC-Heidelberg cohort. *BMC Med* 2017; 15: 218.
59. Paunio M, Virtamo J, Gref CG, et al. Serum high density lipoprotein cholesterol, alcohol, and coronary mortality in male smokers. *BMJ* 1996; 312: 1200–1203.
60. Okamura T, Hayakawa T, Kadowaki T, et al. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. *Atherosclerosis* 2006; 184: 143–150.
61. Toth PP, Barter PJ, Rosenson RS, et al. High-density lipoproteins: A consensus statement from the National Lipid Association. *J Clin Lipidol* 2013; 7: 484–525.
62. Nnoaham KE, Webster P, Kumbang J, et al. Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies. *Fertil Steril* 2012; 98: 702–712 e706.
63. O'Keefe JH, Bybee KA and Lavie CJ. Alcohol and cardiovascular health: The razor-sharp double-edged sword. *J Am Coll Cardiol* 2007; 50: 1009–1014.
64. Agerholm-Larsen B, Nordestgaard BG, Steffensen R, J et al. Elevated HDL cholesterol is a risk factor for ischemic heart disease in white women when caused by a common mutation in the cholesteryl ester transfer protein gene. *Circulation* 2000; 101: 1907–1912.
65. Andersen RV, Wittrup HH, Tybjaerg-Hansen A, et al. Hepatic lipase mutations, elevated high-density lipoprotein cholesterol, and increased risk of ischemic heart disease: The Copenhagen City Heart Study. *J Am Coll Cardiol* 2003; 41: 1972–1982.
66. Frikke-Schmidt R, Nordestgaard BG, Jensen GB, et al. Genetic variation in ABCA1 predicts ischemic heart disease in the general population. *Arterioscler Thromb Vasc Biol* 2008; 28: 180–186.
67. Barter PJ and Rye KA. HDL cholesterol concentration or HDL function: Which matters? *Eur Heart J* 2017; 38: 2487–2489.
68. Huang CY, Lin FY, Shih CM, et al. Moderate to high concentrations of high-density lipoprotein from healthy subjects paradoxically impair human endothelial progenitor cells and related angiogenesis by activating rho-associated kinase pathways. *Arterioscler Thromb Vasc Biol* 2012; 32: 2405–2417.
69. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of The European Society Of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association For Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.
70. Kircher T, Nelson J and Burdo H. The autopsy as a measure of accuracy of the death certificate. *N Engl J Med* 1985; 313: 1263–1269.
71. Perova NV, Oganov RG, Williams DH, et al. Association of high-density-lipoprotein cholesterol with mortality and other risk factors for major chronic non-communicable diseases in samples of US and Russian men. *Ann Epidemiol* 1995; 5: 179–185.
72. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989; 79: 8–15.
73. Wilson PW, Abbott RD and Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis* 1988; 8: 737–741.
74. Yaari S, Goldbourt, Even-Zohar S, et al. Associations of serum high density lipoprotein and total cholesterol with total, cardiovascular, and cancer mortality in a 7-year prospective study of 10000 men. *Lancet* 1981; 1: 1011–1015.

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