Original Research

High-Density Lipoprotein Cholesterol and Mortality
Too Much of a Good Thing?

Mark Hamer, Gary O'Donovan, Emmanuel Stamatakis

Objective—The objective of this study was to examine the shape of the association between high-density lipoprotein cholesterol (HDL-C) and mortality in a large general population sample.

Approach and Results—Adult participants (n=37 059; age=57.7±11.9 years; 46.8% men) were recruited from general population household-based surveys (Health Survey for England and Scottish Health Survey). Individual participant data were linked with the British National Health Service Central Registry to record mortality. There were 2250 deaths from all causes during 326 016 person-years of follow-up. When compared with the reference category (HDL-C=1.5–1.99 mmol/L), a U-shaped association was apparent for all-cause mortality, with elevated risk in participants with the lowest (hazard ratio=1.23; 95% confidence interval, 1.06, 1.44) and highest (1.25; 0.97, 1.62) HDL-C concentration. Associations for cardiovascular disease were linear, and elevated risk was observed in those with the lowest HDL-C concentration (1.49; 1.15, 1.94).

Conclusions—A U-shaped association was observed between HDL-C and mortality in a large general population sample. **(*Arterioscler Thromb Vasc Biol*. 2018;38:00-00. DOI: 10.1161/ATVBAHA.117.310587.)**

Key Words: cardiovascular diseases ■ cholesterol, HDL ■ health surveys ■ lipoproteins, HDL ■ mortality

Data from early prospective cohort studies suggest that there is an inverse and linear association between high-density lipoprotein cholesterol (HDL-C) and mortality.[1] Indeed, data from 15 252 white men and women in the Framingham Heart Study, the Lipid Research Clinics Prevalence Mortality Follow-up Study, the Lipid Research Clinics Coronary Primary Prevention Trial, and the Multiple Risk Factor Intervention Trial suggest that every 0.026-mmol/L increase in HDL-C concentration reduces coronary heart disease risk by 2% to 3% and cardiovascular disease (CVD) mortality risk by 3.7% to 4.7%.[1] Data from more recent prospective cohort studies suggest that the association between HDL-C and mortality is not linear over the entire range of HDL-C concentrations.[2–4] For example, analyses from the Copenhagen City Heart Study and the Copenhagen General Population Study suggest that the association between HDL-C and mortality is U-shaped, with both extreme high and low concentrations being associated with elevated all-cause mortality risk.[4] Only 1 of the recent prospective cohort studies, however, was population based[4]; the other 2 were based on outpatients[2] and patients with kidney disease.[3] Therefore, the objective of this study was to investigate the postulated U-shaped association between HDL-C concentration and mortality in a pooled analysis of a large general population sample.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

The sample comprised 37 059 participants (57.7±11.9 years; 46.8% men). Highly elevated levels of HDL-C (≥2.5 mmol/L) were identified in 2% of the cohort, and this group contained a higher proportion of women (Table 1). There were few differences in clinical characteristics between normal and highly elevated HDL-C, except for raised systolic blood pressure in the very high HDL-C group (Table 1). Participants in the very low HDL-C group (<1 mmol/L) generally displayed more risk factors, including a greater prevalence of smoking, physical inactivity, elevated body mass index, and systolic blood pressure (Table 1).

There were 2250 deaths from all causes during 326 016 person-years of follow-up. When compared with the reference category (1.5–1.99 mmol/L), a U-shaped association was apparent (Table 2; Figure) for all-cause mortality, with elevated risk in the lowest and highest HDL-C categories. There were 649 deaths attributed to CVD although there was no evidence of a curvilinear trend. Compared with the reference category, there was an increased risk of CVD only in the lowest HDL-C category (Table 2).

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Nonstandard Abbreviations and Acronyms	
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol

We conducted a series of sensitivity analyses. The pattern of results remained largely similar when men and women were analyzed separately albeit effect estimates were more robust in women (Table I in the online-only Data Supplement). We removed participants with existing CVD at baseline (3.6% of the sample reported a physician diagnosis of heart attack, stroke, or angina) although results were not changed (Table II in the online-only Data Supplement). In a subsample from the Scottish surveys (n=10 047), we retrieved hospital admissions records and examined fatal and nonfatal CVD events (Table III in the online-only Data Supplement). There were 545 coronary heart disease events and 231 stroke events; compared with the reference category, there was an increased risk only in the lower HDL-C categories (Table III in the online-only Data Supplement) that mirrored the results for CVD mortality presented in the main analyses. We explored if the U-shaped association with all-cause mortality was being driven by cancer although no clear associations emerged (Table IV in the online-only Data Supplement).

Discussion

The aim of this study was to re-examine recent paradoxical findings from a regional cohort of Danish adults that suggested a U-shaped association between HDL-C and mortality.[4] In our pooled (nationwide) British cohort, we partially replicated the curvilinear association for all-cause mortality but not for CVD.

It was thought that there was an inverse and linear relationship between HDL-C concentration and CVD mortality.[1] Indeed, an HDL-C concentration of ≥1.55 mmol/L was regarded as a negative risk factor, and its presence removed 1 risk factor from the total count used for setting treatment goals for low-density lipoprotein cholesterol concentration.[5] However, recent prospective cohort studies suggest that the association between HDL-C concentration and mortality is U-shaped.[2–4] It has been suggested that the contradictory findings of early and recent prospective cohorts studies may be explained by the fact that few individuals have extremely high HDL-C concentrations and are often grouped together with individuals with only modestly high concentrations.[4] This would seem to be the case. In early studies, low HDL-C was defined as <1.04 mmol/L, medium as 1.04 to 1.30 mmol/L, and high as ≥1.30 mmol/L; And, a linear relationship between HDL-C concentration and CVD mortality was observed.[1] In recent studies, reference groups were defined as 1.06 to 1.29 mmol/L in men and 1.32 to 1.55 mmol/L in women (based on previous studies),[2] 1.06 mmol/L in men and women (the median value in the cohort),[3] and 1.55 to 1.99 mmol/L in men and 2.0 to 2.49 mmol/L in women (the HDL-C concentrations associated with lowest mortality);[4] And, U-shaped relationships between HDL-C concentration and CVD mortality[2] and all-cause mortality[2–4] were observed. There was relatively low statistical power in the early prospective cohort studies (only 584 deaths).[1] There were 17 952 deaths,[2] 541 682 deaths,[3] and 10 678 deaths[4] and relatively high statistical power in recent prospective cohort studies.

The mechanisms remain unclear although it is possible that in participants with highly elevated HDL-C, there may be disparity between concentration and function because HDLs have several well-documented cardioprotective properties.[6] That we found no evidence of a U-shaped association for CVD mortality is in contrast with some recent data.[4] Nevertheless, when examining secondary end points, including ischemic heart disease, myocardial infarction, and ischemic stroke events, they found no significant increase in risk with highly elevated HDL-C concentrations.[4] In our sensitivity analyses, we explored if the U-shaped association with all-cause mortality was being driven by cancer deaths although no clear patterns emerged (Table IV in the online-only Data Supplement). Nevertheless, there were insufficient events to undertake detailed analyses of cancer subtypes nor were we adequately powered to explore other death causes, for example, related to infection.

Clinicians should be aware that adults with extremely high HDL-C concentrations may be a high-risk group for all-cause mortality. Drugs that are currently prescribed to clinically manage lipid levels do not directly target HDL-C. The inhibition of cholesteryl ester transfer protein or addition of niacin

Table 1. Baseline Characteristics of the Sample

Variable	High-Density Lipoprotein Cholesterol Category, mmol/L <1.0	1.0–1.49	1.5–1.99	2.0–2.49	≥2.5
Age, mean±SD	45.7±15.8	45.5±16.3	46.9±16.1	49.6±15.8	52.7±14.7
Men (%)	73.4	56.8	33.1	19.2	17.3
Smokers (%)	31.9	25.9	20.6	17.6	19.0
Regular alcohol (at least 5/wk) (%)	9.6	13.9	19.3	25.9	39.8
Meets physical activity guideline (%)	23.5	28.1	31.3	33.1	29.7
Longstanding illness (%)	47.9	42.4	39.2	39.6	45.4
Total cholesterol, mmol/L	5.4±1.2	5.5±1.2	5.6±1.1	5.9±1.1	6.3±1.1
Systolic blood pressure, mm Hg	133.1±17.6	129.9±17.8	128.7±18.9	129.2±19.6	132.2±20.3
Body mass index, kg/m^2	28.7±4.7	27.4±4.8	25.9±4.4	24.9±3.9	24.2±3.8

Table 2. Association Between High-Density Lipoprotein Cholesterol and Mortality (n=37 059)

HDL-C Category, mmol/L	n	All Deaths	Hazard Ratio (95% CI) All-Cause Mortality	CVD Deaths	Hazard Ratio (95% CI) CVD Mortality
<1.0	2723	254	1.23 (1.06, 1.44)	95	1.49 (1.15, 1.94)
1.0–1.49	16 885	1035	1.09 (0.98, 1.20)	297	1.03 (0.85, 1.24)
1.5–1.99	13 070	664	1.00 (Ref)	195	1.00 (Ref)
2.0–2.49	3637	233	1.18 (1.02, 1.38)	51	0.89 (0.65, 1.21)
≥2.5	744	64	1.25 (0.97, 1.62)	11	0.76 (0.41, 1.40)
P curvilinear trend			0.003		0.18

Models adjusted for age, sex, smoking (never; ex-smoker; <10/d cigarettes, 10–19/d, ≥20/d), frequency of alcohol intake (≥5 per week; 1–4 per week; 1– 2 per month; once every few months; ex-drinker; never), moderate to vigorous physical activity (none, 1–149 min/wk; ≥150 min/wk), longstanding illness, total cholesterol, systolic blood pressure, and body mass index. CI indicates confidence interval; CVD, cardiovascular disease; and HDL-C, high-density lipoprotein cholesterol.

to statin therapy can produce substantial increases in HDL-C levels in addition to reductions in low-density lipoprotein cholesterol. However, some clinical trials using cholesteryl ester transfer protein inhibitors have been controversial,[7–9] and other trials testing different types of cholesteryl ester transfer protein inhibitor[10] or niacin[11,12] either did not reduce CVD risk or the effects were attributed to reduction in low-density lipoprotein cholesterol. In addition, recent observational data using cholesteryl ester transfer protein gene variants as an instrumental variable has also questioned the causal role of HDL-C in the pathogenesis of CVD.[13] It is, however, plausible that there is a disparity between concentration and function in those with extremely high HDL-C concentrations.[6]

These data are observational, thus we cannot infer causality. We cannot discount the possibility of reverse causation; however, in keeping with previous analyses in the same cohort,[14,15] we excluded deaths in the first 24 months of follow-up, we adjusted for longstanding illness, and showed that removal of participants with existing CVD did not influence the results. The covariates were selected a priori based on lifestyle and clinical factors known to influence HDL-C although we cannot discount residual confounding. For example, in the absence of data on triglyceride and low-density lipoprotein cholesterol levels, we were only able to adjust for total cholesterol.

In conclusion, the present population-based study is important because it confirms the results of the only other such study.[4] The available evidence suggests that there is a U-shaped association between HDL-C concentration and all-cause mortality in white men and women. More research is required to determine the association between HDL-C concentration and mortality in other groups.

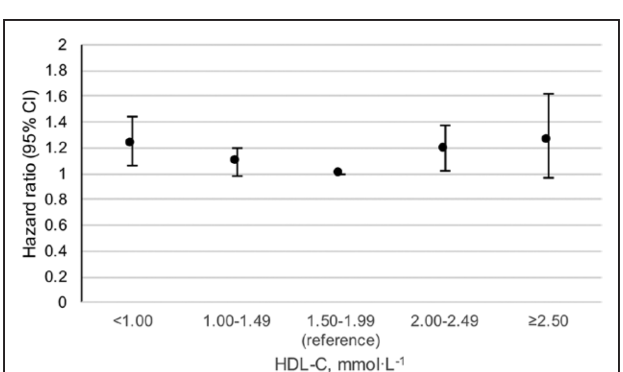

Figure. The association between high-density lipoprotein cholesterol (HDL-C) and all-cause mortality. CI indicates confidence interval.

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M. Hamer performed the analysis with full access to the data and takes responsibility for the integrity and accuracy of the results. M. Hamer drafted the manuscript. All authors contributed to the concept and design of study and critical revision of the manuscript. All authors have approved the submission of the manuscript.

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Disclosures

None.

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Highlights

- High-density lipoprotein cholesterol is generally believed to be inversely associated with risk of disease.
- We observed a U-shaped association between high-density lipoprotein cholesterol and mortality in a large population sample.
- There was a linear inverse association between high-density lipoprotein cholesterol and cardiovascular disease.

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SUPPLEMENTAL MATERIAL

Table I. Association between high density lipoprotein-cholesterol and all-cause mortality stratified by sex.

	Men (N=16,758)		**Women** (N=20,301)	
HDL-C category (mmol·L^{-1})	**Deaths/ N**	**Hazard Ratio (95% CI)**	**Deaths/ N**	**Hazard Ratio (95% CI)**
<1.0	191/ 2000	1.04 (0.86, 1.26)	63 / 723	1.53 (1.17, 2.01)
1.0 - 1.49	617/ 9597	0.91 (0.73, 1.05)	418 / 7288	1.27 (1.10, 1.46)
1.5 – 1.99	293/ 4332	1.00 *(Ref)*	371/ 8738	1.00 *(Ref)*
2.0 – 2.49	58/ 700	0.97 (0.73, 1.30)	175/ 2937	1.32 (1.10, 1.58)
≥2.5	20/ 129	1.36 (0.86, 2.15)	44/ 615	1.26 (0.92, 1.74)

Models adjusted for: age, smoking (never; ex-smoker; <10/d cigarettes, 10-19/d, ≥20/d), frequency of alcohol intake (5 or more per week; 1 – 4 per week; 1 – 2 per month; once every few months; ex-drinker; never), moderate to vigorous physical activity (none, 1 – 149 min/week; ≥150 min/wk), longstanding illness, total cholesterol, systolic blood pressure, body mass index.

Table II. Association between high density lipoprotein-cholesterol and mortality after the removal of participants with existing CVD† at baseline (N=35,562).

HDL-C category (mmol·L^{-1})	**N**	**All deaths**	**Hazard Ratio (95% CI) All cause mortality**	**CVD deaths**	**Hazard Ratio (95% CI) CVD mortality**
<1.0	2513	188	1.19 (1.00, 1.42)	61	1.48 (1.08, 2.03)
1.0 - 1.49	16,141	820	1.05 (0.94, 1.17)	212	1.04 (0.84, 1.29)
1.5 – 1.99	12,649	580	1.00 *(Ref)*	150	1.00 *(Ref)*
2.0 – 2.49	3,536	202	1.15 (0.98, 1.35)	44	0.96 (0.68, 1.35)
≥2.5	723	54	1.19 (0.90, 1.58)	9	0.80 (0.41, 1.57)

†3.6% of the sample reported a physician diagnosis of CVD (heart attack, stroke, angina).

Models adjusted for: age, sex, smoking (never; ex-smoker; <10/d cigarettes, 10-19/d, ≥20/d), frequency of alcohol intake (5 or more per week; 1 – 4 per week; 1 – 2 per month; once every few months; ex-drinker; never), moderate to vigorous physical activity (none, 1 – 149 min/week; ≥150 min/wk), longstanding illness, total cholesterol, systolic blood pressure, body mass index.

Table III. Association between high density lipoprotein-cholesterol and fatal /non fatal CVD events (N=10,047)

HDL-C category (mmol·L^{-1})	**N**	**CHD events**	**Hazard Ratio (95% CI) CHD**	**Stroke events**	**Hazard Ratio (95% CI) Stroke**
<1.0	859	133	1.89 (1.42, 2.51)	33	1.38 (0.88, 2.17)
1.0 - 1.49	4646	408	1.32 (1.06, 1.63)	125	1.12 (0.82, 1.53)
1.5 – 1.99	3395	185	1.00 *(Ref)*	68	1.00 *(Ref)*
2.0 – 2.49	938	37	0.77 (0.51, 1.17)	15	0.78 (0.43, 1.41)
≥2.5	209	10	0.77 (0.38, 1.58)	4	0.85 (0.31, 2.33)

Models adjusted for: age, sex, smoking (never; ex-smoker; <10/d cigarettes, 10-19/d, ≥20/d), frequency of alcohol intake (5 or more per week; 1 – 4 per week; 1 – 2 per month; once every few months; ex-drinker; never), moderate to vigorous physical activity (none, 1 – 149 min/week; ≥150 min/wk), longstanding illness, total cholesterol, systolic blood pressure, body mass index.

Table IV. Association between high density lipoprotein-cholesterol and cancer mortality.

HDL-C category (mmol·L^{-1})	**Deaths/ N**	**Hazard Ratio (95% CI)**
<1.0	75/ 2723	1.13 (0.86, 1.49)
1.0 - 1.49	384/ 16885	1.24 (1.04, 1.47)
1.5 – 1.99	219/ 13070	1.00 *(Ref)*
2.0 – 2.49	70/ 3637	1.08 (0.83, 1.42)
≥2.5	14/ 744	0.86 (0.50, 1.48)

Models adjusted for: age, sex, smoking (never; ex-smoker; <10/d cigarettes, 10-19/d, ≥20/d), frequency of alcohol intake (5 or more per week; 1 – 4 per week; 1 – 2 per month; once every few months; ex-drinker; never), moderate to vigorous physical activity (none, 1 – 149 min/week; ≥150 min/wk), longstanding illness, total cholesterol, systolic blood pressure, body mass index.

Methods

Participants were recruited from 10 survey years of the Health Survey for England and the Scottish Health Survey.[1] Local research ethics committees approved each survey and all participants gave written informed consent. Nurses measured blood pressure and obtained a non-fasting venous blood sample. Blood samples were analysed for total cholesterol and HDL-C (640 analyser, Olympus Corporation, Tokyo, Japan); the coefficient of variation of the assays was <4%.[2] Individual participant data were linked with the British National Health Service Central Registry to record mortality. Diagnoses for the primary cause of death were based on the International Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) Revisions. Codes corresponding to CVD mortality were 390-459 for ICD-9 and I01-I99 for ICD-10. Data for survivors were censored to the end of 2009 (SHS) or the first quarter of 2011 (HSE). Cox proportional hazards models were used to estimate associations of HDL-C (categorised using previously employed cut points)[3] with mortality. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. For the present analyses, calendar time (months) was the timescale. Models were adjusted for age, sex, smoking, alcohol, physical activity, longstanding illness, total cholesterol, systolic blood pressure, and body mass index. Curvilinear trend was estimated by adding a squared term for HDL-C. All deaths in the first two years of follow-up were removed to guard against reverse causation. All analyses were performed using SPSS version 22 (IBM Inc.).

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