Is High Serum LDL/HDL Cholesterol Ratio an Emerging Risk Factor for Sudden Cardiac Death? Findings from the KIH Study

Setor K. Kunutsor¹, Francesco Zaccardi², Jouni Karppi³, Sudhir Kurl³ and Jari A. Laukkanen^{3,4}

¹School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, UK

²Diabetes Research Centre, University of Leicester, Leicester, UK

³Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

⁴Department of Medicine, Central Finland Central Hospital, Jyväskylä, Finland

Aim: Low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), which are components of total cholesterol, have each been suggested to be linked to the risk of sudden cardiac death (SCD). However, the relationship between LDL-c/HDL-c ratio and the risk of SCD has not been previously investigated. We aimed to assess the associations of LDL-c, HDL-c, and the ratio of LDL-c/HDL-c with the risk of SCD.

Methods: Serum lipoprotein concentrations were assessed at baseline in the Finnish Kuopio Ischemic Heart Disease prospective cohort study of 2,616 men aged 42–61 years at recruitment. Hazard ratios (HRs) (95% confidence intervals [CI]) were assessed.

Results: During a median follow-up of 23.0 years, a total of 228 SCDs occurred. There was no significant evidence of an association of LDL-c or HDL-c with the risk of SCD. In analyses adjusted for age, examination year, body mass index, systolic blood pressure, smoking, alcohol consumption, physical activity, years of education, diabetes, previous myocardial infarction, family history of coronary heart disease, and serum high sensitivity C-reactive protein, there was approximately a two-fold increase in the risk of SCD (HR 1.94, 95% CI 1.21–3.11; $p=0.006$), comparing the top (>4.22) versus bottom (≤ 2.30) quintile of serum LDL-c/HDL-c ratio.

Conclusion: In this middle-aged male population, LDL-c or HDL-c was not associated with the risk of SCD. However, a high serum LDL-c/HDL-c ratio was found to be independently associated with an increased risk of SCD. Further research is warranted to understand the mechanistic pathways underlying this association.

Key words: Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol, Sudden cardiac death

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Introduction

Sudden cardiac death (SCD), generally defined as a sudden and unexpected death occurring within a short period of time after the onset of symptoms, accounts for 50% of all cardiovascular disease (CVD)-related deaths¹. Given that SCD is a global public health burden², preventive strategies which are aimed

at modulation of potential risk factors is a desirable approach to decrease the risk of SCD at the population level. Low-density lipoprotein cholesterol (LDL-c) plays a major role in the etiology of atherosclerosis³. A broad body of evidence shows LDL-c as the primary atherogenic lipoprotein⁴ and high-density lipoprotein cholesterol (HDL-c) as the predominant anti-atherosclerotic lipoprotein⁵. It is established that HDL-c is an independent protective risk factor for atherosclerotic CVD^{5,6} and serum LDL-c as a causal risk factor for atherosclerotic CVD⁷⁻⁹. Levels of these lipoproteins are now routinely measured in clinical practice for the screening of individuals with a high risk of CVD and being used as therapeutic targets for

Address for correspondence: Jari A. Laukkanen, Institute of Public Health and Clinical Nutrition, University of Eastern Finland, P.O.Box 1627, FI-70211 Kuopio, Finland
E-mail: jariantero.laukkanen@uef.fi

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the primary and secondary prevention of CVD^{10, 11}. Since approximately 80% of SCDs are attributable to underlying coronary heart disease (CHD)¹², it follows that SCD and CHD share similar risk factors, which include the traditional cardiovascular risk factors such as hypercholesterolemia, diabetes, smoking, hypertension, and obesity¹³⁻¹⁵. HDL-c and LDL-c (which are components of total cholesterol and established factors for SCD¹⁵) have each been suggested to be linked to the risk of SCD, but the reports have mostly been inconsistent^{14, 16}. It has been suggested that an LDL-c/HDL-c ratio is a better risk indicator for CVD than individual parameters¹⁷⁻²⁰. Thus, we hypothesized that the LDL-c/HDL-c ratio would relate to the risk of SCD rather than LDL-c or HDL-c alone. To the best of our knowledge, there has been no previous prospective evaluation of the association of LDL-c/HDL-c ratio with the risk of SCD. Our main objective was to evaluate the nature and magnitude of the prospective association of LDL-c/HDL-c with the risk of SCD in a population-based cohort of 2,616 apparently healthy men from eastern Finland. In subsidiary analyses, we also assessed the individual associations of serum LDL-c and HDL-c levels with the risk of SCD.

Methods

This report was conducted according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology²¹.

Study Population

The Kuopio Ischemic Heart Disease (KIHD) risk factor study, a population-based prospective cohort study, was designed to investigate traditional and emerging risk factors for atherosclerotic cardiovascular outcomes in a population-based sample of men from eastern Finland. The study population was a representative sample of men living in the city of Kuopio and its surrounding rural communities who were 42–60 years of age at baseline examinations performed from March 1984 through December 1989. A total of 2,682 eligible men participated in this study. The current analysis is based on data obtained on 2,616 participants who had complete data on serum lipoproteins, relevant covariates, and SCD outcomes. The study was approved by the Research Ethics Committee of the University of Eastern Finland, and each participant provided written informed consent.

Biochemical Measurements

Subjects provided blood specimens for lipoprotein separation between 8:00 and 10:00 a.m. after hav-

ing abstained from alcohol consumption for 3 days, from smoking for 12 h, and after an overnight fast. After the subject had rested in the supine position for 30 min, blood was drawn using Terumo Venoject VT-100PZ vacuum tubes (Terumo Corp., Tokyo, Japan). No tourniquet was used. The main serum lipoprotein fractions consisting of very-low-density lipoprotein, LDL and HDL were separated within 3 days of blood sampling by a combination of ultracentrifugation and precipitation. The cholesterol content (mmol/L) of all lipoprotein fractions and serum triglycerides (TG) were determined via enzymatic methods (cholesterol CHOD-PAP method, Boehringer Mannheim, Mannheim, Germany²²). Blood glucose was measured via glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins with trichloric acetic acid. Serum high sensitivity C-reactive protein (hs-CRP) was measured via the chemiluminescence-immunoassay method using Immulite 2000 analyzer (DPC, Los Angeles, USA).

Assessment of Risk Markers

Data on socio-demographics, physical measurements, medical history, and vascular risk factors have been previously described²³. Briefly, resting blood pressure was measured between 8:00 and 10:00 a.m. on the first examination day by a nurse using a random-zero mercury sphygmomanometer. The measuring protocol included, after a supine rest of 5 min, three measurements in the supine position: one after 1 min of standing, and two in the sitting position with 5 min intervals. Alcohol consumption was assessed via a structured quantity-frequency method on drinking behavior over the previous 12 months. Prevalent CHD and myocardial infarction (MI) were ascertained via record linkage from the national computerized hospitalization registry, which covers every hospitalization in Finland. History of diabetes was defined as having a clinical diagnosis of diabetes and regular treatment with diet, oral hypoglycemic agents or insulin therapy, fasting plasma glucose of ≥ 7.0 mmol/L, or according to self-reports. A subject was defined as a smoker if he had ever smoked on a regular basis and had smoked cigarettes, cigars, or a pipe within the past 30 days. The assessment of the use of lipid-lowering therapy over the follow-up period was based on the national social insurance institution registry.

Definition of Follow-up Events

Deaths that occurred by the end of 2010 were checked against the hospital documents, health centers, and death certificates. There were no losses to follow-up. A death was classified as SCD when it occurred within 24 h of the onset of symptoms, including non-

Table 1. Baseline participant characteristics (N=2616)

	Without SCD (N = 2388) Mean (SD) or %	With SCD (N = 228) Mean (SD) or %	P-value
Demographic characteristics			
Age at survey (years)	52.9 (5.2)	54.7 (4.0)	< 0.001
BMI (kg/m ²)	26.8 (3.5)	28.1 (4.1)	< 0.001
Years of education	8.7 (3.5)	8.0 (3.0)	0.005
Physical activity (kcal/d)	142.4 (177.1)	127.0 (146.5)	0.204
Medical history			
SBP (mmHg)	134 (17)	140 (18)	< 0.001
Alcohol consumption (g/week)	74.3 (137.3)	93.5 (134.0)	0.044
Smokers	31	45	< 0.001
Smoking (pack-years)*	7.9 (16.0)	14.5 (20.9)	< 0.001
Diabetics	5	13	< 0.001
Previous MI	6	28	< 0.001
CHD in family	48	56	0.033
Laboratory data			
Serum LDL cholesterol (mmol/L)	4.02 (1.02)	4.26 (1.01)	0.001
Serum HDL cholesterol (mmol/L)	1.30 (0.30)	1.23 (0.31)	0.001
Serum LDL-c/HDL-c ratio	3.29 (1.24)	3.67 (1.22)	< 0.001
Serum hs-CRP (mmol/L)	2.36 (3.98)	3.38 (5.59)	< 0.001

*. Pack-years denote the lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.

BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein;; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; SCD, sudden cardiac death

witnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death²⁴⁻²⁶. The sources of information were interviews, hospital documents, death certificates, autopsy reports, and medico-legal reports. The diagnostic classification of events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80%), and history of CHD, together with the clinical and electrocardiographic findings of the paramedic staff. All CVD-related and CHD deaths were coded using the 9th or 10th International Classification of Diseases Revision.

Statistical Methods

Continuous variables were presented as means (standard deviations) and categorical variables as percentages. Means of the continuous variables were compared using ANOVA, and χ^2 tests were used for categorical variables. Subjects were also classified according to fifths of the ratio of LDL-c/HDL-c. Hazard ratios (HR) and 95% confidence intervals (CIs) for SCD, calculated by quintiles defined according to the baseline distribution of lipid fractions, were estimated using Cox proportional hazards model. Covariates were selected on the basis of their previously established roles as predictive factors²⁷⁻²⁹. Two different sets

of covariates were used: Model 1) age and examination year; Model 2) age, examination year, BMI, systolic blood pressure (SBP), smoking, alcohol consumption, physical activity, years of education, diabetes, previous MI, family history of CHD, and hs-CRP. Tests for statistical significance were two-sided, and differences with $p < 0.05$ were considered statistically significant. SPSS software (version 19.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Baseline Characteristics

Table 1 describes baseline characteristics of study participants. Men who died suddenly were older, had higher BMIs and SBPs, were more frequently smokers and consumed more alcohol, and were more likely to have had previous MIs and diabetes. They also had higher serum concentrations of LDL-c, hs-CRP, and LDL-c/HDL-c ratio, but lower concentrations of serum HDL-c. Participants in the highest fifth of the ratio of LDL-c/HDL-c (> 4.22) compared with those in the lowest fifth (≤ 2.30) had higher BMIs, smoked more, but consumed less alcohol, had a higher prevalence of diabetes, and had previous MIs. Serum HDL-c level was lower and LDL-c level was higher

Table 2. Demographic characteristics of the study population by quintiles of LDL-c/HDL-c ratio

	Quintiles of LDL-c/HDL-c ratio					<i>p</i> -value [*]
	≤2.30	2.30–2.86	2.87–3.44	3.45–4.22	>4.22	
	(<i>n</i> = 523)	(<i>n</i> = 523)	(<i>n</i> = 524)	(<i>n</i> = 523)	(<i>n</i> = 523)	
	mean (SD) or %	mean (SD) or %	mean (SD) or %	mean (SD) or %	mean (SD) or %	
Demographic characteristics						
Age at survey (years)	52.7 (5.3)	52.8 (5.3)	53.2 (5.2)	53.3 (4.8)	53.3 (4.9)	0.116
BMI (kg/m ²)	26.0 (3.6)	26.9 (3.9)	26.9 (3.2)	27.5 (3.8)	27.2 (3.1)	<0.001
Years of education	8.9 (3.6)	8.9 (3.5)	8.4 (3.2)	8.4 (3.4)	8.6 (3.4)	0.015
Physical activity (kcal/d)	156.4 (170.5)	131.4 (140.2)	147.8 (200.9)	138.4 (189.1)	131.5 (165.8)	0.089
Medical history						
SBP (mmHg)	133 (18)	135 (17)	134 (16)	135 (17)	135 (17)	0.365
Alcohol consumption (g/week)	96.4 (196.0)	71.0 (123.9)	81.1 (138.2)	66.3 (107.1)	65.2 (95.2)	0.001
Smokers	30	29	28	32	41	<0.001
Smoking (pack-years) [‡]	7.5 (16.5)	8.4 (17.9)	7.2 (15.3)	8.3 (15.3)	11.1 (17.5)	0.001
Diabetes	4	6	4	9	6	0.002
Previous MI	4	5	8	11	12	<0.001
CHD in family	47	45	50	52	51	0.152
Laboratory data						
Serum LDL cholesterol (mmol/L)	1.63 (0.32)	1.39 (0.22)	1.27 (0.20)	1.17 (0.18)	1.01 (0.17)	<0.001
Serum HDL cholesterol (mmol/L)	2.98 (0.62)	3.59 (0.58)	3.99 (0.64)	4.46 (0.70)	5.18 (0.86)	<0.001
Serum hs-CRP (mmol/L)	2.23 (5.44)	2.44 (4.04)	2.36 (4.36)	2.46 (2.93)	2.74 (3.54)	0.357

BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; SD, standard deviation; SBP, systolic blood pressure; *, *p*-value for ANOVA; ‡, Pack-years denote the life-long exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked

among those in the highest ratio of LDL-c/HDL-c (**Table 2**).

Lipoproteins and the Risk of Sudden Cardiac Death

During a median (interquartile range) follow-up time of 23.0 (0.02–27.4) years, a total of 228 SCD cases occurred. In analyses adjusted for age and examination year, HRs of SCD comparing the top versus bottom fifths of LDL-c concentrations and LDL-c/HDL-c ratio were 1.59 (95% CI: 1.05–2.42; *p*=0.030) and 2.67 (95% CI: 1.68–4.23; *p*<0.001), respectively. Comparing the bottom versus top fifths of HDL-c levels, the corresponding risk was 2.08 (95% CI: 1.35–3.19; *p*=0.001). In fully adjusted analyses, only LDL-c/HDL-c ratio remained significantly associated with the risk of SCD (1.94, 95% CI: 1.21–3.11; *p*=0.006) (**Table 3**). In a subsidiary analysis which was limited to men with relevant information on serum lipoproteins, SCD outcomes, as well as information on lipid-lowering medication, the association remained consistent for LDL-c/HDL-c ratio and SCD risk in analysis that adjusted for several established risk factors and lipid-lowering medication. In separate analyses for CHD and CVD death, LDL-c/HDL-c ratio was significantly associated with each of these out-

comes, 1.95 (95% CI: 1.30–2.94; *p*=0.001) and 1.55 (95% CI: 1.14–2.12; *p*=0.006), respectively. In a sensitivity analysis, we assessed the association between LDL-c/HDL-c ratio and SCD in subjects without a prevalent history of CHD. HRs comparing the top versus bottom fifths of LDL-c/HDL-c ratio were 2.06 (95% CI: 1.21–3.48; *p*=0.007) and 1.79 (95% CI: 1.05–3.06; *p*=0.033), respectively, in analyses adjusted initially for age and examination year and further for established risk factors. To put the strength of the association of LDL-c/HDL-c ratio with SCD risk into context, direct comparisons were made to associations of serum triglycerides, non-HDL-c, TG/LDL-c ratio, and non-HDL-c/LDL-c ratio with SCD risk. There were no statistically significant associations of any of these lipid markers with the risk of SCD (**Table 4**).

Discussion

In this population-based study of middle-aged men, we observed an increased risk of SCD with a high LDL-c/HDL-c ratio. The association remained consistent when the analysis was restricted to men without a prevalent history of CHD. However, there was no significant association of SCD risk with HDL-c

Table 3. Hazard ratios for sudden cardiac death by quintiles of serum lipoproteins and LDL-c/HDL-c ratio

	Quintiles					<i>p</i> -value
	1	2	3	4	5	
LDL cholesterol (mmol/L)	< 3.18	3.18–3.72	3.73–4.18	4.19–4.85	> 4.85	
No. of cases/No. of participants	35/525	31/518	48/524	53/526	61/523	
HR (95% CI) [†]	Reference	0.87 (0.53–1.41)	1.35 (0.87–2.08)	1.42 (0.93–2.18)	1.59 (1.05–2.42)	0.030
HR (95% CI) [‡]	Reference	0.73 (0.45–1.19)	1.21 (0.78–1.88)	1.37 (0.89–2.11)	1.43 (0.93–2.19)	0.101
HDL cholesterol (mmol/L)	> 1.52	1.34–1.52	1.19–1.33	1.04–1.18	≤ 1.04	
No. of cases/No. of participants	32/532	28/517	54/525	54/525	60/517	
HR (95% CI) [†]	Reference	0.88 (0.53–1.47)	1.73 (1.11–2.67)	1.78 (1.15–2.75)	2.08 (1.35–3.19)	0.001
HR (95% CI) [‡]	Reference	0.79 (0.47–1.31)	1.27 (0.80–2.00)	1.16 (0.74–1.83)	1.45 (0.92–2.27)	0.107
LDL-c/HDL-c ratio	≤ 2.30	2.30–2.86	2.87–3.44	3.45–4.22	> 4.22	
No. of cases/No. of participants	25/523	36/523	35/524	65/523	67/523	
HR (95% CI) [†]	Reference	1.37 (0.82–2.28)	1.32 (0.79–2.21)	2.59 (1.63–4.11)	2.67 (1.68–4.23)	< 0.001
HR (95% CI) [‡]	Reference	1.08 (0.64–1.82)	1.16 (0.69–1.95)	1.96 (1.22–3.15)	1.94 (1.21–3.11)	0.006

[†] Adjusted for age and examination year.

[‡] Adjusted for Model 1 plus BMI, systolic blood pressure, smoking, alcohol consumption, physical activity, years of education, diabetes, previous MI, CHD history in family and serum hs-CRP.

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction

or LDL-c. Although total cholesterol (which has LDL-c and HDL-c as its components) is a major risk factor for SCD^{13, 14}, prospective studies on the associations of its component lipoproteins have been limited and mostly conducted in individuals with pre-existing cardiometabolic disease, and the results have been inconsistent^{14, 30}. Consistent with our results, it remains uncertain if LDL-c or HDL-c is independently associated with a future risk of SCD.

It is well established that the oxidative modification of LDL-c plays a key role in the pathogenesis of atherosclerosis³¹. Oxidized LDL has a low affinity for macrophage scavenger receptors, and, thereby, oxidized LDL enters the blood circulation stimulating adhesion molecules and chemokines. Oxidized LDL can be taken up by macrophages through the scavenger receptors, leading to the formation of foam cells³¹. This cascade leads to initiation and progression of atherosclerosis in coronary arteries, which is an underlying cause of SCD³². In a postmortem study of SCDs, elevated LDL-c levels were shown to be correlated with the severity of coronary atherosclerosis³³. It has also been shown that plasma lipid and lipoprotein levels are significantly elevated in SCD cases¹⁶. Among the LDL-c subclasses which differ in physiochemical properties and atherogenicity³⁴, small, dense LDL are regarded as more atherogenic than large LDL particles^{35, 36}. Non-HDL-c, which can easily be estimated from routine lipid panels, has been suggested to be a surrogate marker of small, dense LDL-c³⁷. In our study, however, we found no evidence of an associa-

tion when LDL-c/HDL-c ratio was substituted for non-HDL-c/LDL-c ratio. For HDL-c, there is a growing body of evidence which supports the concept that the functional properties of HDL-c rather than circulating levels, may be more important in determining CHD risk³⁸. Recent studies have shown that elevated HDL-c does not necessarily cause a decrease in the risk of CHD. In the Framingham study, 40% of CHD events occurred in individuals with normal or elevated HDL levels⁵. Very high levels of HDL-c have also been demonstrated not to be associated with the risk of vascular events³⁹. Indeed, the evidence suggests that enhancing HDL-c function rather than increasing its levels, is associated with clinical benefit¹¹.

Given that this is the first prospective study on the association of LDL-c/HDL-c ratio and the risk of SCD in a general population, it is difficult to compare our findings in the context of previous studies. Based on data from clinical trials^{40–42}, a high LDL-c/HDL-c ratio is associated with coronary plaque progression, whereas a decreased LDL-c/HDL-c ratio achieved by pharmacological interventions, may be associated with coronary plaque regression. Some studies have recommended that individuals with a high ratio of LDL-c/HDL-c should commence treatment because of abnormal cholesterol levels⁴³. A pooled analysis of data from four prospective randomized trials revealed a positive linear correlation between an index of LDL-c/HDL-c ratio and changes in coronary plaque volume⁴². In addition, an elevated LDL-c/HDL-c ratio has been suggested to be a predictor of coronary

Table 4. Hazard ratios for sudden cardiac death by quintiles of serum triglycerides, non-HDL-c, TG/LDL-c ratio, and non-HDL-c/LDL-c ratio

	Quintiles					<i>p</i> -value
	1	2	3	4	5	
Triglycerides (mmol/L)	<0.76	0.76–0.99	1.00–1.26	1.27–1.73	>1.73	
No. of cases/No. of participants	37/525	45/531	31/492	52/513	63/555	
HR (95% CI) [†]	Reference	1.24 (0.80–1.91)	0.86 (0.53–1.39)	1.54 (1.01–2.36)	2.03 (1.33–3.08)	<0.001
HR (95% CI) [‡]	Reference	1.09 (0.70–1.69)	0.73 (0.45–1.18)	1.15 (0.74–1.78)	1.15 (0.73–1.80)	0.503
non-HDL-c (mmol/L)	<1.57	1.57–1.73	1.74–1.89	1.90–2.11	>2.11	
No. of cases/No. of participants	52/527	38/541	41/510	48/516	49/522	
HR (95% CI) [†]	Reference	0.70 (0.46–1.06)	0.80 (0.53–1.20)	0.95 (0.64–1.42)	1.00 (0.67–1.48)	0.555
HR (95% CI) [‡]	Reference	0.82 (0.54–1.26)	0.90 (0.59–1.36)	0.93 (0.62–1.40)	1.01 (0.67–1.52)	0.799
TG/LDL-c ratio	<0.19	0.19–0.24	0.24–0.32	0.32–0.44	>0.44	
No. of cases/No. of participants	42/515	45/515	41/515	43/515	57/556	
HR (95% CI) [†]	Reference	1.05 (0.69–1.61)	0.99 (0.64–1.53)	1.11 (0.72–1.71)	1.61 (1.06–2.44)	0.037
HR (95% CI) [‡]	Reference	0.91 (0.59–1.40)	0.85 (0.55–1.32)	0.91 (0.58–1.41)	0.99 (0.63–1.57)	0.989
non-HDL-c/LDL-c ratio	<1.07	1.07–1.10	1.10–1.14	1.15–1.20	>1.20	
No. of cases/No. of participants	36/523	42/523	46/523	56/524	48/523	
HR (95% CI) [†]	Reference	1.21 (0.77–1.89)	1.42 (0.91–2.20)	1.70 (1.10–2.60)	1.59 (1.02–2.48)	0.011
HR (95% CI) [‡]	Reference	1.06 (0.67–1.66)	1.22 (0.78–1.91)	1.29 (0.83–1.99)	1.10 (0.69–1.76)	0.478

[†] Adjusted for age and examination year.

[‡] Adjusted for Model 1 plus BMI, systolic blood pressure, smoking, alcohol consumption, physical activity, years of education, diabetes, previous MI, CHD history in family and serum hs-CRP.

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; TG, triglycerides

lipid-rich plaques and plaque vulnerability leading to an elevated SCD risk^{44, 45}. Rupture of high-risk vulnerable plaques is considered to be the major pathway in the development of coronary thrombosis, which eventually leads to acute MI and SCD⁴⁶. Coronary heart disease is the most common pathology underlying SCD^{47, 48}. However, in our study, the observed association of LDL-c/HDL-c ratio with the risk of SCD persisted when we restricted analysis to men without a history of CHD. Though the findings may partly reflect undiagnosed CHD, other pathways such as chronic inflammation may be involved. Further research is needed to help understand the mechanistic pathways of LDL-c/HDL-c ratio in the pathogenesis of SCD. Our findings demonstrate a clear and independent link between LDL-c/HDL-c ratio and SCD risk, which may have potential clinical implications. Assays for these lipoproteins are already being used in clinical practice to predict CVD risk in patients. Estimation of the ratio may have the potential to be used in the identification of individuals at high risk for SCD. However, further studies are needed to unequivocally establish this potential preventive strategy.

The strengths and limitations of the current study merit consideration. Strengths include its prospective population-based design, complete and long

follow-up period, assessment of a comprehensive range of potential confounders, which enabled reliable assessments of the associations. Our representative sample makes it possible to generalize the observed results to male Caucasian populations, which was the primary focus of the study design; however, these results need to be replicated in female populations. The assessment of baseline clinical conditions by self-administered questionnaires is a limitation of the study. Further, we could not correct for regression dilution bias, which may have underestimated the observed associations, as we had only one-time assessment of lipid profiles, which may have changed during follow-up because of the probable changes in health habits or medication of participants over the time. Though many potential confounders were measured and carefully adjusted to ensure the validity of our key findings, there was still a potential for residual confounding owing to unmeasured risk factors.

In conclusion, the evidence suggests that a high LDL-c/HDL-c ratio, but not the individual lipoprotein components, is associated with an increased risk of SCD. Further studies are needed to replicate these associations and assess the mechanistic pathways underlying the relationships.

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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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