Circulation

ORIGINAL RESEARCH ARTICLE

Long-Term Association of Low-Density Lipoprotein Cholesterol With Cardiovascular Mortality in Individuals at Low 10-Year Risk of Atherosclerotic Cardiovascular Disease

Results From the Cooper Center Longitudinal Study

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BACKGROUND: The associations of low-density lipoprotein cholesterol (LDL-C) with cardiovascular disease (CVD) and coronary heart disease mortality in an exclusively low estimated 10-year risk group are not well delineated. We sought to determine the long-term associations of various LDL-C and non–high-density lipoprotein cholesterol (HDL-C) thresholds and CVD and coronary heart disease mortality in a large, low 10-year risk cohort.

METHODS: The study sample included participants of the CCLS (Cooper Center Longitudinal Study) without a history of CVD or diabetes mellitus and defined as low risk (<7.5%) for 10-year atherosclerotic CVD events at baseline based on Pooled Cohort Risk Assessment Equations. The associations of fasting LDL-C and non–HDL-C with CVD mortality were tested with Cox proportional hazards models.

RESULTS: In 36 375 participants (72% men, median age 42) followed for a median of 26.8 years, 1086 CVD and 598 coronary heart disease deaths occurred. Compared with LDL-C <100 mg/dL, LDL-C categories 100 to 129 mg/dL, 130 to 159 mg/dL, 160 to 189.9 mg/dL, and ≥190 mg/dL were associated with a significantly higher risk of CVD death, with hazard ratios of 1.4 (95% CI, 1.1–1.7), 1.3 (95% CI, 1.1–1.6), 1.9 (95% CI, 1.5–2.4), and 1.7 (95% CI, 1.3–2.3), and mean reductions in years free of CVD death of 1.8, 1.1, 4.3, and 3.9, respectively. After adjustment for atherosclerotic CVD risk factors, LDL-C categories 160 to 189 mg/dL and ≥190 mg/dL remained independently associated with CVD mortality, with hazard ratios of 1.7 (95% CI, 1.4–2.2) and 1.5 (95% CI, 1.2–2.1), respectively. In multivariable-adjusted models using non–HDL-C <130 mg/dL as the reference, non–HDL-C 160 to 189 mg/dL, 190 to 219 mg/dL, and ≥220 mg/dL were significantly associated with CVD death, with hazard ratios of 1.3 (95% CI, 1.1–1.6), 1.8 (95% CI, 1.4–2.2), and 1.5 (95% CI, 1.2–2.0), respectively. Restricting the cohort to those with 10-year risk <5% did not diminish the associations of LDL-C and non–HDL-C with CVD mortality.

CONCLUSIONS: In a low 10-year risk cohort with long-term follow-up, LDL-C and non–HDL-C ≥160 mg/dL were independently associated with a 50% to 80% increased relative risk of CVD mortality. These findings may have implications for future cholesterol treatment paradigms.

Key Words: low-density lipoprotein ■ long-term follow-up ■ primary prevention

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Clinical Perspective

What Is New?

- In 36 375 subjects of the CCLS (Cooper Clinic Longitudinal Study) cohort who were at low 10-year estimated risk of atherosclerotic cardiovascular disease (CVD) (ie, <7.5%) followed for >2 decades (median of 26.8 years), low-density lipoprotein cholesterol (LDL-C) and nonhigh-density lipoprotein cholesterol ≥160 mg/dL were associated with CVD and coronary heart disease mortality.
- The associations between LDL-C and CVD mortality were more robust when follow-up was extended beyond the traditional 10-year estimated risk period.
- The associations remained significant in those with an estimated 10-year atherosclerotic CVD risk of <5%.

What Are the Clinical Implications?

- These data suggest that LDL-C levels ≥160 mg/dL in individuals deemed to be at low 10-year atherosclerotic CVD risk are associated with worse long-term CVD mortality.
- These findings, along with other observational data and data extrapolated from clinical trials, support further consideration of appropriate LDL-C thresholds for lipid-lowering interventions in individuals categorized as low short-term risk.
- In addition to LDL-C, nonhigh-density lipoprotein cholesterol ≥160 mg/dL may also be considered as a risk factor for increased long-term risk of CVD and coronary heart disease mortality.

Clinical trials evaluating lipid-lowering therapy for primary prevention have mostly been limited to intermediate- and high-risk groups,[1–3] and trial data for patients at exclusively low estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk (<7.5%) are scarce. Although evidence from epidemiological studies in the general population demonstrates a strong correlation of total cholesterol levels with cardiovascular prognosis,[4–7] studies evaluating the association of cholesterol with cardiovascular disease (CVD) and coronary heart disease (CHD) death, specifically in the low 10-year risk group, are limited despite the fact that this group represents the majority of the population.[8,9] The 2013 American Heart Association (AHA)/American College of Cardiology (ACC) cholesterol guidelines do not recommend statin therapy in low 10-year risk individuals unless plasma levels of low-density lipoprotein cholesterol (LDL-C) are ≥190 mg/dL, with a class IIb recommendation to consider treatment with LDL-C ≥160 mg/dL,[10] despite uncertainty as to whether cholesterol is associated with CVD in a low-risk population and what is the optimal threshold for treatment. The present study seeks to assess the associations of LDL-C and non-high–density lipoprotein cholesterol (HDL-C) thresholds with CVD and CHD mortality in a cohort at low 10-year risk of ASCVD from the CCLS (Cooper Center Longitudinal Study), with long-term follow-up of >2.5 decades.

METHODS

Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration with the CCLS and data sharing to contact the corresponding author directly for further discussions.

The CCLS is a prospective study of participants evaluated at the Cooper Clinic, a preventive medicine practice in Dallas, TX.[11] Participants were included in the present study if they had a lipid panel measured between 1978, the first year HDL-C was routinely recorded, and 1998, to minimize the effects of lipid-lowering therapy, which became more prevalent after the early 2000s.[12] Low-risk status of participants was defined as an estimated 10-year atherosclerotic CVD (ASCVD) risk <7.5% by the Pooled Cohort Equations.[8,10] Exclusion criteria included having established CVD, diabetes mellitus, or plasma triglycerides >450 mg/dL. Also, participants who died ≤1 year of lipid measurement were not included in the present analyses. The CCLS undergoes annual review by the institutional review board at Cooper Institute, and all participants provided written informed consent for study participation.

Measurements

Plasma lipids were collected during the clinical visit after a 12-hour fast. In addition to laboratory testing, all participants underwent a complete medical evaluation, including medical history, physical examination, and anthropometric measurements. The Friedewald equation was used to calculate LDL-C from total cholesterol, triglyceride, and HDL-C measurements. Non–HDL-C was calculated as total cholesterol minus HDL-cholesterol. All assays were conducted by Cooper Clinic personnel in accordance with standard operating procedures.

Hypertension was defined as blood pressure ≥140/90 or a history of hypertension. Family history of coronary artery disease was defined as an affected first-degree relative ≤50 years of age.

Outcomes

Mortality data for participants was ascertained using the National Death Index Plus service. CVD mortality was classified using the International Classification of Diseases, 9th revision (codes 390.0–458.9) for deaths occurring before 1999 and 10th revision (codes I00–I78) for deaths during 1999 to 2014. CHD mortality was classified using 9th revision (codes 410–414) and 10th revision (codes I20–I26).

Statistical Analysis

Baseline variables are presented as medians with interquartile ranges for continuous variables and percentages for categorical variables. Tests for trends across LDL-C categories were

based on the nonparametric Jonckheere-Terpstra method. Participants were divided into the following categories of LDL-C levels: <100 mg/dL, 100 to 129.9 mg/dL, 130 to 159.9 mg/dL, 160 to 189.9 mg/dL, and ≥190 mg/dL. These categories have been demonstrated to correlate with cardiovascular outcomes similarly to linear LDL-C.[13] Participants were also divided into the following categories of non–HDL-C levels: <130 mg/dL, 130 to 159.9 mg/dL, 160 to 189.9 mg/dL, 190 to 219.9 mg/dL, and ≥220 mg/dL.

Survival curves were estimated using the Kaplan–Meier method. Curves were compared using age-stratified log-rank statistics with the following age strata: 18 to 40 years (N=14 733), 40 to 50 years (N=14 378), 50 to 60 years (N=6527), and >60 years (N=737). Empirical survival by follow-up age rather than time was estimated using the Breslow method. Crude incident rates of CVD and CHD mortality were determined per 1000 patient-years for each LDL-C category. Differences in survival time free of CVD and CHD mortality between LDL-C categories were estimated using a parametric proportional hazards model based on a Gompertz mortality rule (exponential in follow-up age) adjusted for age and sex.

Cox regression analyses were performed to estimate the risk of mortality of each LDL-C group using the <100 mg/dL group as the reference group and for each non–HDL-C group using <130 mg/dL as the reference group. Baseline hazards were stratified by age in all models as described earlier because of proportional hazards violations when age was entered as a covariable. Univariable associations between either LDL-C or non–HDL-C and CVD or CHD mortality were evaluated in separate models. Multivariable analyses were then performed adjusting for sex, HDL-C, current tobacco use, hypertension, and family history of premature coronary artery disease. Selection of variables for the multivariable models was based on risk factors that the Adult Treatment Panel-3 or 2013 AHA/ACC national cholesterol guidelines have recommended to determine risk.[10,14] Interaction testing was performed between LDL-C and non–HDL-C, and sex and the years lipids were measured (1978–1988 versus 1988–1998) for both CVD and CHD mortality. Proportional hazards assumptions were tested by calculating the correlations between Schoenfeld residuals associated with each covariate and the ranked event times. Because age was not able to be entered as a covariable, sensitivity analyses were performed using an alternative set of proportional hazards regression models using follow-up age rather than time, accounting for left truncation as well as right censoring of follow-up ages.

All analyses were programmed in SAS/STAT statistical software (version 9.4, SAS Institute Inc).

RESULTS

Baseline Characteristics

Of the 45 643 participants without ASCVD and with valid LDL-C measurements during the specified time period, 2178 were excluded because of missing Pooled Cohort Equations variables, 6856 were excluded because of estimated 10-year ASCVD ≥7.5%, and 234 were excluded because of a history of diabetes mellitus, yielding 36 375 participants (72% men, median age 42, median estimated 10-year risk 1.3%) for the current analyses. Median follow-up was 26.8 years (interquartile range, 21.2–31.3 years). Baseline characteristics stratified by LDL-C categories are presented in Table 1. Statistically significant trends were seen for all CVD risk factors with increasing LDL-C categories, including direct associations with age and estimated ASCVD risk. In contrast, the proportion of women decreased across increasing LDL-C categories. In all, 1086 CVD deaths and 598 CHD deaths occurred.

Association of LDL-C With CVD and CHD Mortality

Kaplan–Meier plots for CVD and CHD mortality for LDL-C categories are shown in Figure 1A and 1B. After adjustment for age strata, increasing LDL-C levels were significantly associated with increased risk for CVD (log rank χ^2=37.0, P<0.0001) and CHD mortality (log rank χ^2=58.0, P<0.0001). In Gompertz models assessing survival free of CVD and CHD mortality, those in the LDL-C categories 100 to 129 mg/dL, 130 to 159 mg/dL, 160 to 189 mg/dL, and ≥190 mg/dL had an approximate mean reduction of 1.8, 1.1, 4.3, and 3.9 years free of CVD death, respectively, and an approximate mean reduction of 1.7, 2.2, 7.8, and 7.2 years free of CHD death, respectively, compared with those in the LDL-C <100 mg/dL group. The crude incidence rate of CVD and CHD mortality generally increased with increasing LDL-C categories (Figure 2).

Cox proportional hazards analyses were performed to further evaluate the differences in CVD and CHD mortality among different LDL-C categories. Using LDL-C <100 mg/dL as the reference, significant associations with CVD death were seen for the LDL-C categories 100 to 129 mg/dL (hazard ratio [HR], 1.4; 95% CI, 1.1–1.7), 130 to 159 mg/dL (HR, 1.3; 95% CI, 1.1–1.6) 160 to 189 mg/dL (HR, 1.9; 95% CI, 1.5–2.4), and >190 mg/dL (HR, 1.7; 95% CI, 1.3–2.3) (Table 2). The hazard ratios for LDL-C categories 100 to 129.9 mg/dL, 160 to 189.9 mg/dL, and ≥190 mg/dL for CVD mortality remained statistically significant after multivariable adjustment, with HRs of 1.3 (95% CI, 1.01–1.6), 1.7 (95% CI, 1.4–2.2), and 1.5 (95% CI, 1.2–2.1), respectively. No significant interactions with LDL-C were seen for sex (P-interaction 0.47) or year of baseline LDL-C measurement (P-interaction 0.93).

In Cox proportional hazards models for CHD mortality using LDL-C <100 mg/dL as the reference category, significant associations were seen for LDL-C categories 130 to 159 mg/dL, 160 to 189 mg/dL, and ≥190 mg/dL, with HRs of 1.5 (95% CI, 1.1–2.1), 2.6 (95% CI, 1.9–3.6), and 2.3 (95% CI, 1.6–3.3), respectively (Table 2). In multivariable analyses, the HRs for CHD mortality of the LDL-C 160 to 189 mg/dL and ≥190 mg/dL categories remained statistically signifi-

Table 1. Baseline Characteristics

	LDL, mg/dL						
	Total	<100	100–129.9	130–159.9	160–189.9	≥190	*P*
N	36375	6949	12426	10397	4689	1914	
Age, y	42 (36–48)	39 (33–46)	41 (35–48)	43 (37–49)	43 (38–49)	44 (38–49)	<0.001
Women, %	28.0	42.9	29.4	20.9	17.6	21.0	<0.001
Current smoker, %	11.7	12.4	12.4	11.8	10.2	7.8	<0.001
Hypertension, %	21.8	16.8	20.7	23.5	25.8	27.8	<0.001
Coronary heart disease family history, %	17.6	17.0	16.8	17.7	19.2	20.4	<0.001
Body mass index, kg/m^2	24.8 (22.6–27.8)	23.3 (21.1–25.9)	24.5 (22.3–27.0)	25.3 (23.2–27.7)	25.8 (23.8–28.1)	26.1 (24.1–28.4)	<0.001
Glucose, mg/dL	96 (91–103)	95 (89–100)	96 (90–102)	97 (91–104)	98 (92–104)	98 (92–105)	<0.001
Total cholesterol	200 (176–226)	157 (145–170)	186 (176–198)	215 (204–226)	244 (234–256)	282 (268–300)	<0.001
Triglycerides, mg/dL	95 (67–140)	75 (55–112)	88 (64–129)	103 (74–147)	115 (84–159)	125 (92–172)	<0.001
HDL-C, mg/dL	48 (40–59)	53 (43–65)	49 (40–60)	46 (39–55)	46 (39–55)	46 (39–55)	<0.001
LDL-C, mg/dL	127 (105–151)	87 (77–94)	115 (108–122)	143 (136–150)	171 (165–178)	205 (196–219)	<0.001
Non–HDL-C	149 (124–177)	103 (93–112)	135 (125–145)	166 (156–176)	196 (186–206)	233 (222–250)	<0.001
Estimated ASCVD risk, %	1.3 (0.5–3.1)	0.4 (0.2–1.2)	1.0 (0.4–2.4)	1.8 (0.8–3.6)	2.5 (1.3–4.4)	3.3 (1.9–5.1)	<0.001
Estimated ASCVD <5%, %	89	96.4	92.6	86.6	80.6	73.2	<0.001
Total no. of deaths	4045	538	1365	1239	652	251	
No. of deaths from cardiovascular disease	1086	110	344	322	225	85	
No. of deaths from coronary heart disease	598	56	166	177	146	53	

Continuous variables are presented as medians (interquartile range). ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and non–HDL-C, non–high-density lipoprotein cholesterol.

cant, with HRs of 2.2 (95% CI, 1.6–3.0) and 2.0 (95% CI, 1.4–2.9), respectively. There were no significant interactions of LDL-C for sex (*P*-interaction 0.24) or year of LDL-C measurement (*P*-interaction 0.83). LDL-C categories ≥160 mg/dL remained significantly associated with CVD and CHD mortality in multivariable models further adjusted for body mass index and glucose (Supplemental Table 1).

Trend tests for LDL-C categories in log-rank and Cox regression analyses for CVD and CHD mortality were all ≤ 0.001. Since age was not entered as a covariable in the multivariable models due to proportional hazards violations, an alternative set of Kaplan Meier analyses and Cox models of follow-up age instead of follow-up time were fit as a sensitivity analysis (Figure IA and IB and Table II in the online-only Data Supplement). In these models for CHD and CVD death, similar results were seen to the models using follow-up time scales.

CVD and CHD mortality at 10 years

To assess whether the associations between LDL-C and CVD and CHD mortality were present at intermediate term follow-up, Kaplan-Meier analyses were performed truncating follow-up at 10 years (Figure 3A and 3B). After adjustment for age strata, there were no significant associations between LDL-C levels and CVD mortality (log rank χ^2= 5.7, *P*=0.22) or CHD mortality (log rank χ^2=8.2, *P*=0.08).

Non–HDL-C and CVD and CHD Mortality

Kaplan-Meier plots and Cox models were also used to analyze the associations of non–HDL-C with CVD and CHD mortality. Kaplan-Meier plots again demonstrated significant associations of increasing non–HDL-C categories with CVD (log rank χ^2= 57.4, *P*<0.0001) and CHD (log rank χ^2= 83.1, *P*<0.0001) mortality risks (Figure 4A and 4B). In univariable analysis for CVD mortality, compared with the non–HDL-C <130 mg/dL group, all categories of non-HDL ≥130 mg/dL were significantly associated with CVD mortality (Table 2). In the multivariable model for CVD mortality, non–HDL-C categories 160 to 189 mg/dL, 190 to 220 mg/dL, and ≥220 mg/dL continued to have significant associations with CVD mortality, with HR [95% CI] of 1.3 [1.1–1.6], 1.8 [1.4–2.2], and 1.5 [1.2–2.0], respectively. Compared with non–HDL-C <130 mg/dL, all non–HDL-C categories >130 mg/dL were significantly associated with CHD mortality in univariable and multivariable Cox models (Table 2). Non–HDL-C categories ≥160 mg/dL remained significantly associated with CVD and CHD mortality in multivariable models further adjusted for body mass index and glucose (Table I in the online-only Data Supplement).

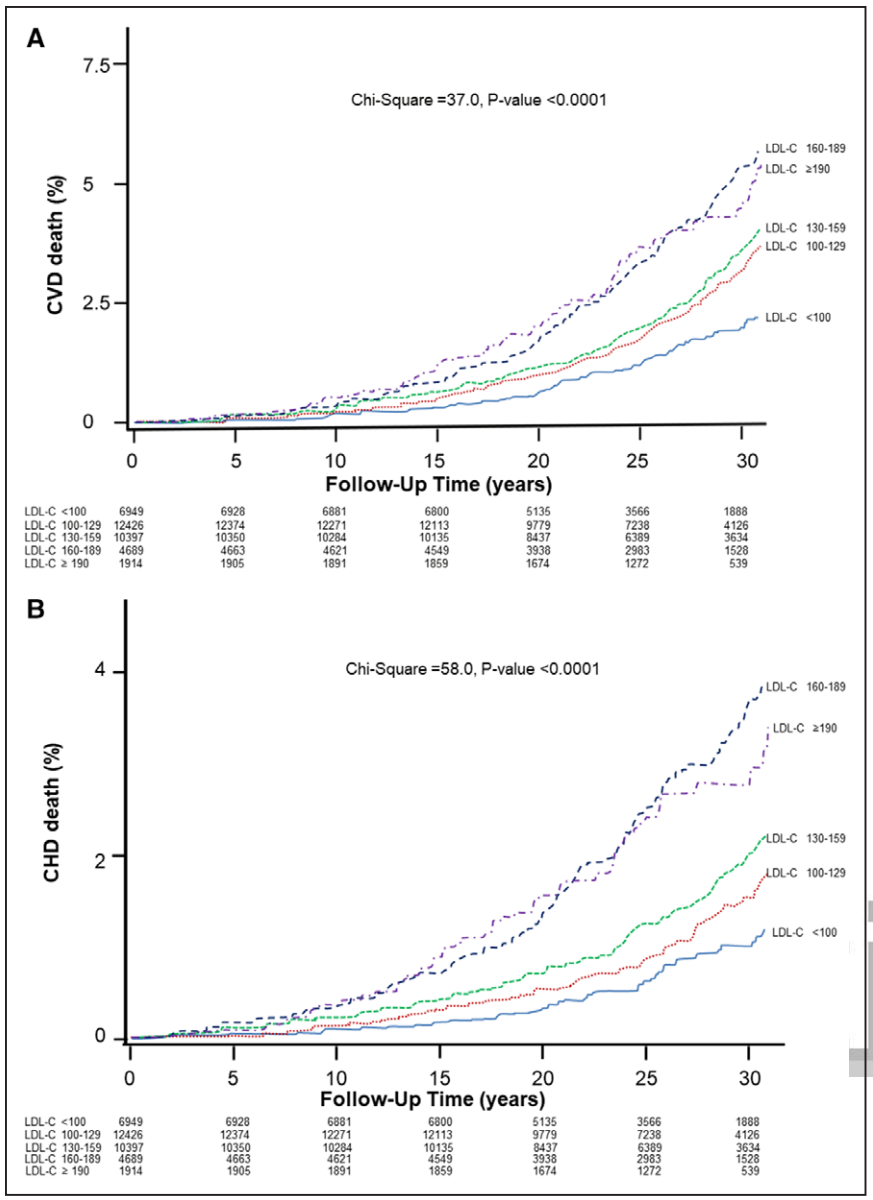

Figure 1. Kaplan–Meier curves of LDL-C and CVD and CHD mortality.
A and **B**, Kaplan–Meier plots with follow-up time scale adjusted for baseline age strata for CVD (**A**) and CHD (**B**) mortality for increasing categories of LDL-C over a median follow-up of 26.8 years. CHD indicates coronary heart disease; CVD, cardiovascular disease; and LDL-C, low-density lipoprotein cholesterol.

Trend tests for non–HDL-C categories in log-rank and Cox regression analyses for CVD and CHD mortality were all <0.001. Results for sensitivity analyses of CVD and CHD mortality based on follow-up age instead of follow-up time were not significantly different (Figure IIA and IIB and Table III in the online-only Data Supplement).

Although the number of women in the higher LDL-C and non–HDL-C categories were too low to assess for statistical differences in CVD and CHD mortality among categories, similar patterns of increased risk with higher levels of these lipoproteins were seen in both sexes (Tables IV and V and Figures III through VIII in the online-only Data Supplement).

CVD and CHD Mortality in ASCVD Risk <5%

To assess the associations of LDL-C and non–HDL-C with CVD and CHD mortality in a population at an even lower predicted risk, the cohort was further restricted to those participants who had an estimated ASCVD risk <5% (n=32 388) (Table 3). Similar to the findings of the overall cohort, LDL-C 160 to 189 mg/dL and ≥190 mg/dL were significantly associated with CVD and CHD mortality in univariable and multivariable models. In models of non–HDL-C, non–HDL-C categories ≥160 mg/dL were significantly associated with CVD mortality in both univariable and multivariable analyses. In Cox models for CHD mortality, significant associations were seen for all categories of non–HDL-C ≥130 mg/dL in univariable analysis and non–HDL-C ≥160 mg/dL in multivariable analysis. Sensitivity analyses using follow-up age scales did not significantly alter the results (Table VI in the online-only Data Supplement).

All-Cause Mortality

Compared with LDL-C <100 mg/dL, LDL-C categories 100 to 129 mg/dL, 130 to 159 mg/dL, 160 to 189 mg/

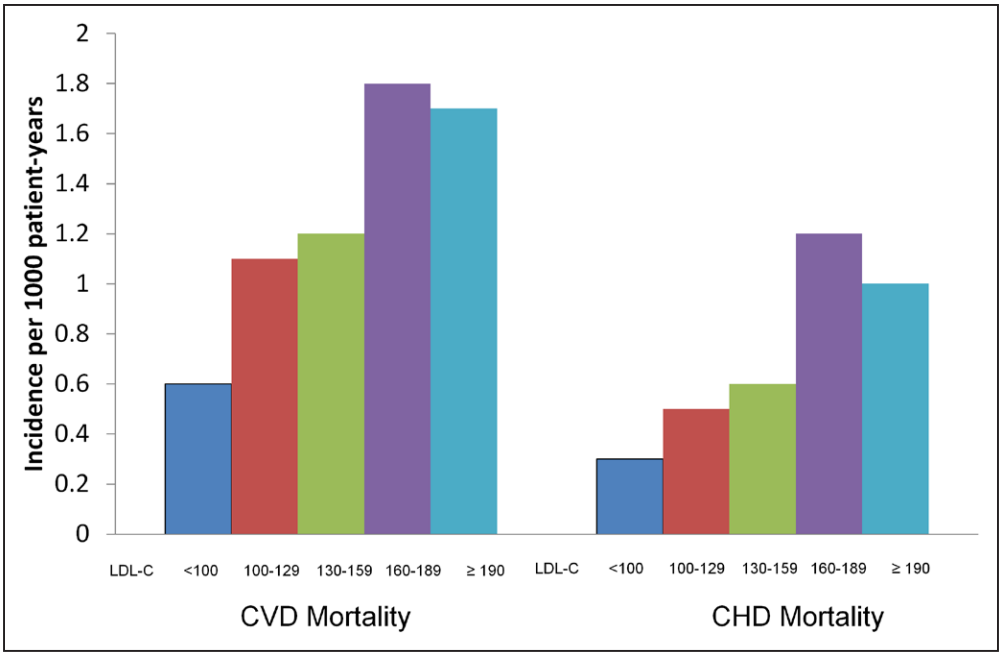

Figure 2. Increasing LDL-C levels and crudes incidence rates for CVD and CHD mortality.
Incidence of CVD (**left**) and CHD mortality (**right**) by increasing LDL-C levels. CHD indicates coronary heart disease; CVD, cardiovascular disease; and LDL-C, low-density lipoprotein cholesterol.

dL, and ≥190 mg/dL had HRs of 1.1 (95% CI, 1.02–1.2), 1.1 (95% CI, 0.97–1.2), 1.2 (95% CI, 1.04–1.3), and 1.1 (95% CI, 0.93–1.3, respectively, in univariable Cox analyses for all-cause mortality. Compared with non–HDL-C <130 mg/dL, non–HDL-C categories 130 to 159 mg/dL, 160 to 189 mg/dL, 190 to 219 mg/dL, and ≥220 mg/dL had HRs of 1.2 (95% CI, 1.1–1.3), 1.2 (95% CI, 1.05–1.3), 1.3 (95% CI, 1.2–1.5), and 1.2 (95% CI, 1.05–1.4), respectively, in univariable Cox analyses for all-cause mortality.

DISCUSSION

In the present study with a median follow-up of 27 years, significant associations of elevated LDL-C and non–HDL-C levels with CVD and CHD mortality were demonstrated in a population at exclusively low 10-year estimated ASCVD risk, with a median 10-year estimated ASCVD risk of 1.3%. In unadjusted analyses, LDL-C categories ≥100 mg/dL were associated with a ≥30% increase in the relative risk of CVD death, and LDL-C

Table 2. Hazard Ratios for LDL-C and Non–HDL-C Categories for Cardiovascular Disease and Coronary Heart Disease Mortality From Univariable and Multivariable Cox Models in a Population With Estimated 10-Year ASCVD Risk ≤7.5%

	Cardiovascular Disease Mortality		Coronary Heart Disease Mortality	
Variable	Univariable Model	Multivariable Model	Univariable Model	Multivariable Model
LDL-C, mg/dL				
100–129	1.4 (1.1–1.7)	1.3 (1.01–1.6)	1.3 (0.99–1.8)	1.2 (0.9–1.6)
130–159	1.3 (1.1–1.6)	1.2 (0.9–1.4)	1.5 (1.1–2.1)	1.2 (0.9–1.7)
160–189	1.9 (1.5–2.4)	1.7 (1.4–2.2)	2.6 (1.9–3.6)	2.2 (1.6–3.0)
≥190	1.7 (1.3–2.3)	1.5 (1.2–2.1)	2.3 (1.6–3.3)	2.0 (1.4–2.9)
Non–HDL-C, mg/dL				
130–159	1.3 (1.1–1.6)	1.2 (0.97–1.4)	1.6 (1.3–2.2)	1.4 (1.04–1.8)
160–189	1.6 (1.3–1.9)	1.3 (1.1–1.6)	2.3 (1.8–3.0)	1.8 (1.4–2.3)
190–219	2.1 (1.7–2.5)	1.8 (1.4–2.2)	3.3 (2.5–4.4)	2.6 (1.9–3.4)
≥220	1.8 (1.4–2.3)	1.5 (1.2–2.0)	2.8 (2.0–4.0)	2.2 (1.5–3.1)

Values shown are hazard ratio (95% CI). For LDL-C, LDL-C <100 mg/dL was the reference category. For non–HDL-C, non–HDL-C <130 mg/dL was the reference category. Univariable models were adjusted for age strata. Multivariable models were adjusted for age strata, sex, HDL-C, tobacco use, hypertension, and family history of premature coronary artery disease. ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and non–HDL-C, non–high-density lipoprotein cholesterol.

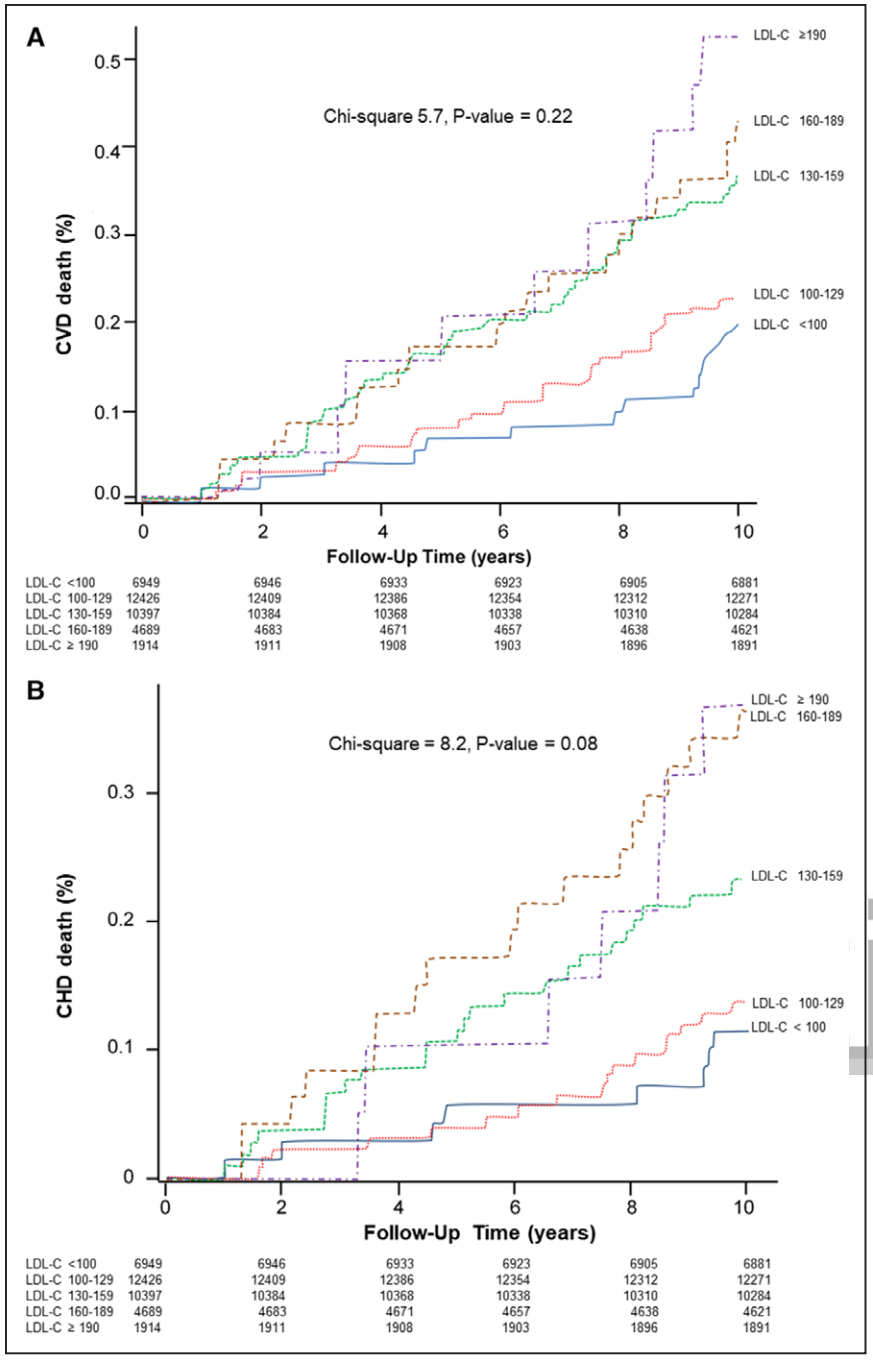

Figure 3. Kaplan–Meier curves for LDL-C categories and CVD and CHD mortality truncating follow-up at 10 years.
A and **B**, Kaplan–Meier plots adjusted for age strata for CVD (**A**) and CHD (**B**) mortality for increasing categories of LDL-C over the first 10 years of follow-up. CHD indicates coronary heart disease; CVD, cardiovascular disease; and LDL-C, low-density lipoprotein cholesterol.

categories ≥130 mg/dL were associated with a ≥50% relative risk increase in CHD death. In multivariable analyses, significant associations with CVD and CHD mortality persisted for LDL-C ≥160 mg/dL. Non–HDL-C ≥160 mg/dL was associated with CVD, and ≥130 mg/dL was associated with CHD mortality in multivariable analyses. Last, the associations between LDL-C and non–HDL-C with outcomes remained significant even in participants with estimated 10-year ASCVD risk <5%.

Several previous epidemiological studies have demonstrated a continuous, graded association of total cholesterol levels to CVD and CHD mortality.[4–7,15–19] However, few of these studies were specific to low-risk populations. In a study of 1017 young men with a mean age of 22 years and mean total cholesterol of 192 mg/dL, Klag et al[7] demonstrated that increasing total cholesterol quartiles were associated with incident CHD and cardiovascular mortality after 40 years of follow-up, although many of these individuals had comorbidities, including almost half with tobacco use. Similarly, in the 356 222 middle-age men of the MRFIT (Multiple Risk Factor Intervention Trial) cohort, a continuous, graded increase in the risk for CHD death was seen with increasing quintiles of total cholesterol.[16,17] It is important to note that a threshold cholesterol level did not exist below which the risk did not appear to

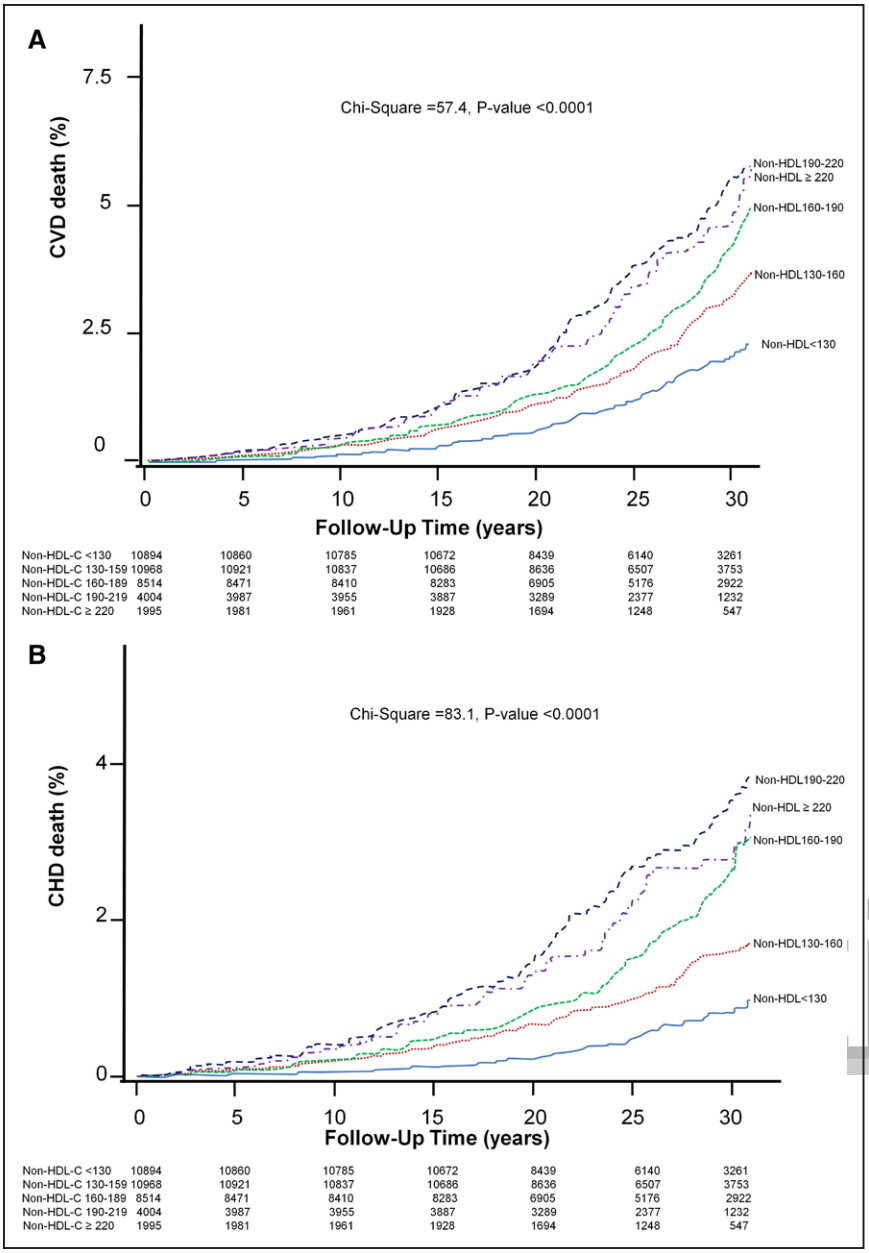

Figure 4. Kaplan–Meier curve of non–HDL-C and CVD mortality.
A and **B**, Kaplan–Meier plots with follow-up time scale adjusted for baseline age strata for CVD (**A**) and CHD (B) mortality for increasing categories of non–HDL-C over a median follow-up of 26.8 years. CVD indicates cardiovascular disease; and non–HDL-C, nonhigh-density lipoprotein cholesterol.

be present, with higher relative risks being seen in the second and third cholesterol quintiles compared with the first quintile.

The present study adds to the existing data by making it more applicable to the contemporary clinical setting by testing this association in a low-risk cohort as defined by the 2013 AHA/ACC cholesterol guidelines and by evaluating the more commonly used LDL-C and non–HDL-C subfractions. In addition, few in the present cohort were >60 years of age, underscoring the prognostic impact that elevated apolipoprotein B-containing lipoproteins in young and middle adulthood have on CVD and CHD mortality decades later. Unlike previous studies, the incidence of CVD and CHD mortality appeared to plateau at higher levels of LDL-C and non–HDL-C. One potential explanation for these findings is that lipid-lowering therapy was subsequently initiated in participants with higher LDL-C levels, therefore blunting the difference in CVD and CHD mortality seen between the highest LDL-C and non–HDL-C categories.

Recently, Navar-Boggan et al[20] demonstrated that in the Framingham Offspring Cohort, those who were at low estimated risk of ASCVD and had a continuous exposure to non-HDL ≥160 mg/dL over an 11- to 20-year period had a stronger association with a composite CHD end point (myocardial infarction, angina, coronary insufficiency, and CHD death) compared with non–HDL-C below that threshold or with exposure over a shorter time period. The present cohort with a longer follow-up demonstrates that non–HDL-C levels as low as 130 to 160 mg/dL are associated with CVD and CHD death even after accounting for other CHD risk factors.

Table 3. Hazard Ratios for LDL-C and Non–HDL-C Categories for Cardiovascular Disease and Coronary Heart Disease Mortality From Univariable and Multivariable Cox Models in a Population With Estimated 10-Year ASCVD Risk ≤5%

	Cardiovascular Disease Mortality		Coronary Heart Disease Mortality	
Variable	Univariable Model	Multivariable Model	Variable	Univariable Model
LDL-C, mg/dL				
100–129	1.4 (1.1–1.8)	1.3 (1.03–1.7)	1.4 (0.97–2.0)	1.2 (0.9–1.8)
130–159	1.4 (1.1–1.8)	1.3 (0.97–1.6)	1.5 (1.1–2.2)	1.3 (0.9–1.9)
160–189	2.1 (1.6–2.8)	1.9 (1.4–2.5)	3.2 (2.2–4.6)	2.7 (1.8–3.9)
≥190	2.1 (1.5–3.1)	2.0 (1.4–2.8)	2.4 (1.5–4.0)	2.1 (1.3–3.5)
Non–HDL-C, mg/dL				
130–159	1.2 (1.0–1.5)	1.1 (0.9–1.4)	1.5 (1.1–2.1)	1.3 (0.94–1.8)
160–189	1.6 (1.3–2.0)	1.4 (1.1–1.8)	2.4 (1.8–3.3)	1.9 (1.4–2.6)
190–219	2.2 (1.8–2.9)	2.0 (1.5–2.5)	3.6 (2.6–5.1)	2.9 (2.0–4.1)
≥220	2.1 (1.5–2.9)	1.8 (1.3–2.6)	2.9 (1.8–4.6)	2.3 (1.5–3.7)

Values shown are hazard ratio (95% CI). For LDL-C, LDL-C <100 m g/dL was the reference category. For non–HDL-C, non–HDL-C <130 mg/dL was the reference category. Univariable models were adjusted for age strata. Multivariable models were adjusted for age strata, sex, HDL-C, tobacco use, hypertension, and family history of premature coronary artery disease. ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and non–HDL-C, non–high-density lipoprotein cholesterol.

The 2013 AHA/ACC guidelines did not comment on the use of non–HDL-C, which the previous Adult Treatment Panel-3 guidelines recommended as a secondary target for treatment.[14] In the present study, associations between non–HDL-C and CHD mortality were seen at lower levels than their corresponding LDL-C levels, and the increase in risk for CVD and CHD mortality appeared in a more stepwise fashion with each increment increase in non–HDL-C, compared to LDL-C. Previous studies in patients with higher baseline ASCVD risk factors have demonstrated that non–HDL-C is superior to LDL-C in assessing CVD risk.[21,22] Because non–HDL-C includes prognostic information of the atherogenic very LDL-C subfraction, can be performed at no additional costs to LDL-C, and is a more robust prognostic marker than LDL-C, many have advocated for the continued role of non–HDL-C in clinical decision making.[23]

Although several clinical trials support statin therapy for primary prevention in higher risk individuals,[1–3] there are limited trial data for the use of statins in such an exclusively low-risk group.[24,25] The 2013 AHA/ACC cholesterol guidelines eliminated LDL-C thresholds in the majority of cases, but for patients at low estimated 10-year risk (<7.5%), they retained a LDL-C ≥190 mg/dL cutoff because of the likely association with a genetic cause, and had an optional class IIB recommendation for LDL-C ≥160 mg/dL to inform initiation of statin therapy. The present data support a paradigm that uses 10-year risk as well as absolute LDL-C or non–HDL-C in low-risk individuals when considering statin therapy and suggest a stronger consideration of using the LDL-C ≥160 mg/dL cutoff. These data complement the recent report from 20-year follow-up of the West of Scotland Coronary Prevention Study that treatment with pravastatin appears beneficial in low 10-year risk individuals with LDL-C levels between 155 and 190 mg/dL.[24,26] Until additional trial data are available in this population, data derived from observational studies and extrapolated from randomized trials of other populations will be used to guide recommendations.

LDL-C levels have declined in the US population over the last several decades, and based on data extrapolated from recent cohorts, mean LDL-C in those not taking statins is estimated to be 119 mg/dL.[27] However, it has also been reported that ≈28.5 million US citizens still have total cholesterol levels ≥240 mg/dL, which roughly corresponds to LDL-C ≥160 mg/dL. Based on the results of the current study, these individuals are at increased risk of CVD death and may benefit from interventions to lower LDL-C.[28]

Because of uncertainty as to the optimal risk assessment method in the primary prevention population, the 2013 AHA/ACC guidelines proposed alternative strategies of using an estimated 10-year risk cutoff of <5% or using lifetime risk estimates.[29] In the present study, decreasing the 10-year ASCVD risk to <5% did not markedly affect the associations of either LDL-C or non–HDL-C with CVD and CHD death. However, these associations were more robust at full follow-up compared with 10-year follow-up. It is likely that for a low-risk population, hard outcomes such as CVD mortality and myocardial infarction require risk assessment of a time frame beyond the 10-year horizon, and interventions targeting LDL-C will similarly require a longer follow-up to see benefits.

The present study has several limitations. Lipid-modifying therapies were not documented at baseline, and records of subsequent initiation of therapy are not

available. Although statin use was low in low-risk populations until the early 2000s,[12] it may be assumed that lipid-modifying therapy was more commonly started in the higher LDL-C categories in recent years, attenuating the estimates of associations of LDL-C and non–HDL-C categories with outcomes. Age was not entered as a covariable in the multivariable analyses and was accounted for by performing analyses stratified by baseline age. In addition, no significant differences were noted when the survival analysis time scale was changed from follow-up time to follow-up age. Current guidelines recommend reassessing global ASCVD risk every 4 to 6 years, and most participants do transition from low-risk status over the course of the follow-up period because of age alone. However, our objective was to determine the long-term implications of elevated LDL-C and non–HDL-C, and most study participants had a 10-year estimated risk of <7.5% for 15 to 20 years before which they exceeded this threshold by increasing age alone. As expected in a relatively young, low-risk population, absolute CVD and CHD mortality rates for the entire cohort were low, and records of other end points, including nonfatal myocardial infarction, were not available to fully assess the associations between elevated cholesterol levels and total CVD burden. The CCLS is not a population-based study, and participants in this cohort in general are from higher socioeconomic groups and at lower 10-year cardiovascular risk compared with the overall US population, which may affect the generalizability of these results. However, some studies have shown that lower socioeconomic status is associated with higher cholesterol levels and higher CVD risk,[30,31] suggesting that our findings could have even greater implications for those at lower socioeconomic status. Further, the low 10-year risk of a large proportion of individuals in this cohort with follow-up of >25 years enables us to evaluate the association of LDL-C and non–HDL-C with hard outcomes such as CVD and CHD mortality in this population. Also, although we do not have race data on the entire study sample, white subjects comprise an overwhelming majority of the CCLS. However, studies of other races, including blacks and Hispanics, have not demonstrated that the association between atherogenic lipoprotein components and CVD and CHD outcomes is modified by race or ethnicity.[32–35]Finally, the current epidemiological study does not provide direct evidence that lowering LDL-C improves outcomes in this population.

In conclusion, the present study demonstrates associations between LDL-C and non–HDL-C with CVD and CHD mortality in a low-risk cohort over a 27-year follow-up period. These associations become more robust as follow-up is extended well beyond the 10-year horizon typically used to assign risk. Further research is required to ascertain whether lipid-modifying lifestyle interventions and pharmacological therapy favorably impact CVD outcomes in low-risk individuals with elevated LDL-C and non–HDL-C.

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