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ORIGINAL RESEARCH

Serum Cholesterol and Impact of Age on Coronary Heart Disease Death in More Than 4 Million Veterans

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BACKGROUND: The lipid hypothesis postulates that lower blood cholesterol is associated with reduced coronary heart disease (CHD) risk, which has been challenged by reports of a U-shaped relation between cholesterol and death in recent studies. We sought to examine whether the U-shaped relationship is true and to assess the impact of age on this association.

METHOD AND RESULTS: We conducted a prospective cohort study of 4 467 942 veterans aged >18 years, with baseline outpatient visits from 2002 to 2007 and follow-up to December 30, 2018, in the Veterans Health Administration electronic health record system. We observed a J-shaped relation between total cholesterol (TC) and CHD mortality after a comprehensive adjustment of confounding factors: flat for TC <180 mg/dL, and greater risk was present at higher cholesterol levels. Compared with veterans with TC between 180 and 199 mg/dL, the multiadjusted hazard ratios (HRs) for CHD death were 1.03 (95% CI, 1.02–1.04), 1.07 (95% CI, 1.06–1.09), 1.15 (95% CI, 1.13–1.18), 1.25 (95% CI, 1.22–1.28), and 1.45 (95% CI, 1.42–1.49) times greater among veterans with TC (mg/dL) of 200 to 219, 220 to 239, 140 to 259, 260 to 279 and ≥280, respectively. Similar J-shaped TC-CHD mortality patterns were observed among veterans with and without statin use at or before baseline.

CONCLUSIONS: The cholesterol paradox, for example, higher CHD death in patients with a low cholesterol level, was a reflection of reverse causality, especially among older participants. Our results support the lipid hypothesis that lower blood cholesterol is associated with reduced CHD. Furthermore, the hypothesis remained true when TC was low due to use of statins or other lipid-lowering medication.

Key Words: cohort study ■ coronary heart disease death ■ low cholesterol ■ veterans

Across different populations, the association of blood cholesterol concentration with death has raised much debate, ranging from linear[1,2] to U-shaped[3–7] and L-shaped,[8] with differences observed across age groups. For example, in the 1980s and before widespread statin use, the association between serum cholesterol categories and risk of coronary heart disease (CHD) among middle-aged men screened for a large multifactor intervention trial showed a continuous, graded relationship that persisted after adjusting for age, race, ethnicity, income levels, smoking status, blood pressure level, diabetes status, and prior myocardial infarction.[9,10] Observational data have been complemented in recent years by the Cholesterol Treatment Trialists' Collaboration summary analyses demonstrating that statin therapy is associated with a reduction in risk for cardiovascular events even at low total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) levels.[11,12]

The lipid hypothesis has been challenged for decades by the U- and L-shaped relations between

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CLINICAL PERSPECTIVE

What Is New?

- In this observational cohort study of roughly 4.5 million adult veterans, we replicated the previously reported U-shaped blood cholesterol to coronary heart disease (CHD) death relation with multivariable adjustment. Risk of CHD death among those with low cholesterol was attenuated after comprehensive adjustment for baseline comorbidities and high-density lipoprotein cholesterol and applying the 2-year lag analysis strategy.
- A continuous and graded increased CHD mortality risk was observed with greater serum total cholesterol concentration. This risk profile was consistent among veterans regardless of heart disease status or statin usage at baseline.
- Reverse causality, especially among the older participants, accounted for the high risk of CHD death among those with low cholesterol levels.

What Are the Clinical Implications?

- This study supports the lipid hypothesis that lower blood cholesterol is associated with reduced CHD; clinical practice based on the lipid hypothesis should not be challenged.

Nonstandard Abbreviations and Acronyms

TC	total cholesterol
VHA	Veterans Health Administration

cholesterol and death among older individuals[2,8] and patients with catabolic conditions, such as heart failure or renal failure, wherein cholesterol catabolism is low.[6,13,14] Poor health and subclinical diseases associated with chronic inflammation may also reduce lipid levels.[15–17] The reverse epidemiology of low TC–death relation has been proposed to be attributable to the hypocholesterolemia effect of the catabolic diseases or inflammation/malnutrition.[14,18] When this reverse epidemiology interpretation has been taken into consideration, a U-shaped association of cholesterol level with death was observed in the overall study population and in the subgroup presence of inflammation/malnutrition, whereas a positive association was seen in the absence of inflammation/malnutrition. Among patients with coronary artery disease, the U-shaped spline curve between non–high-density lipoprotein cholesterol (HDL-C) and death was flattened and reversed to a linear dose–response relationship with adjustment for malnutrition and other confounding factors.[14] Lower cholesterol achieved by statins in the older populations is associated with a decreased risk of death and provides further evidence for this reverse epidemiology.[19]

Reverse epidemiology is repeatedly forgotten or neglected in some cross-sectional, short-term, or insufficiently adjusted studies. A recently reported U-shaped TC–death relationship among large nationally representative population studies extended this confusion into the general population.[4,5] The US Preventive Services Taskforce recently released recommendations for statin therapy eligibility for the primary prevention of cardiovascular disease. This stricter recommendation reduces by 15% the eligibility for statin therapy in US adults compared with the 2018 American Heart Association/American College of Cardiology/Multisociety cholesterol guidelines, including 37% fewer patients with diabetes aged 40 to 75 years.[20] A reappraisal of the evidence regarding the cholesterol paradox is important for both disease control in clinical settings and disease prevention in public health.

In this study, we sought to evaluate the association of TC and 10-year CHD death among almost 4.5 million veteran users of the Veterans Health Administration (VHA) services from 2002 to 2007. Analyses accounted for potential differences in mortality risk by age, race, geography, statin use, comprehensive records of subclinical and clinical diseases, and other potential confounders.

METHODS

Data cannot be shared publicly because of VA policies regarding data privacy and security. Data contain potentially identifying and sensitive patient information. All relevant summary-level data are included in the article. For investigators with appropriate authorizations within the Department of Veterans Affairs (VA), requests for data access can be made.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Emory University and VA Boston Institutional Review Boards and the Atlanta VA Medical Center and Boston VA Research and Development Committees and granted a Health Insurance Portability and Accountability Act waiver obviating the need for subject consent.

Cohort Selection

The VHA provides medical care for more than 21 million veterans nationwide. Participants in this study were 4 467 942 adult VHA users with ≥1 outpatient lipid profile (total and HDL-C) in the electronic health record (EHR). Data from 2002 and 2007 were extracted from

the VA Corporate Data Warehouse.[21] Follow-up extended to December 31, 2018, unless death occurred before this date. We defined a baseline index date as the date of first outpatient lipid results between 2002 and 2007. This study was approved by the Emory University and VA Boston Institutional Review Boards and the Atlanta VA Medical Center and Boston VA Research and Development Committees, and no informed consent was required to extract EHR data.

Exposure

A panel of clinicians reviewed laboratory values across all VA locations and adjudicated discrepancies to ensure consistency of laboratory measures. Only outpatient blood lipid data were analyzed. To maximize the use of lipid information and because fasting status was uncertain, we focused analyses on TC and HDL-C, as both measures are reliable predictors of CHD mortality risk in both the fasting and nonfasting state.[14,15] In a sensitivity analysis, we also analyzed triglyceride, non–HDL cholesterol, and LDL-C. With a large sample size and range for TC values, we analyzed the following 10 TC groups in our study: <120, 120 to 139, 140 to 159, 160 to 179, 180 to 199, 200 to 219, 220 to 239, 240 to 259, 260 to 279, and ≥280 mg/dL. To characterize the relation between cholesterol level and CHD mortality risk we used the terms *U-shaped* (high risk at low levels, low risk at middle-range levels, and high risk at high levels), *V-shaped* (similar to U-shaped but with tighter middle-range effects), and *L-shaped* (high risk at low levels, low risk at middle range, and low risk at higher levels).[1–8]

Outcome

The study outcome was CHD death, which was defined as having CHD listed as the primary cause of death. Outcomes were based on VHA EHR, Centers for Medicare and Medicaid Services,[22] and National Death Index[23] data.

Covariates

We extracted demographic characteristics such as age, sex, and race from the EHR. A total of 13 comorbidities diagnosed within 3 years before baseline were extracted, including hypertension, diabetes, atrial fibrillation, heart failure, anemia, coronary artery disease, cancer, stroke, dementia, depression, kidney disease, liver disease or cirrhosis, and lung disease (chronic obstructive lung disease, asthma), using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) (Table S1). Current and former smoking status were determined by analyzing data from the EHR and a modified algorithm to generate a probabilistic model to characterize smoking status.[24] A national residential zip code database that included the fraction of adults below the US poverty limits provided a geographic indicator of low-income status.

Statistical Analysis

Employing Cox proportional hazards regression, we estimated the hazard ratio (HR) and 95% CI for CHD death, with the TC category as the primary exposure and the 180 to 199 mg/dL cholesterol group serving as the reference category. We stratified analyses by statin use and race.

In the age, sex, race, and smoking-adjusted models, age was a continuous variable and derived from the date of birth in the EHR. Race and smoking variables were categorical: race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other race, race unknown or null) and smoking status (never, ever, current smoking, or missing). Covariate adjustment included initiation of statin use (no usage recorded, initiated statin therapy before or at baseline, within 2 years of follow-up, or after 2 years of follow-up), body mass index (in kg/m^2: <18.5, 18.5–22.4, 23.0–24.9, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), baseline hypertension, and baseline diabetes. In the final model, we further adjusted for HDL-C (continuous) and presence of 11 chronic diseases; in this model, we also censored deaths within the first 2 years of follow-up to reduce the potential for reverse causality.

Restricted cubic spline regression with 3 knots was applied to flexibly model the association between TC and CHD death, with an outlier at the first and 99% of each spline group.[25] Nonlinearity in the dose–response relationship was evaluated by comparing the model with the linear term to the model with the linear and cubic spline terms using the likelihood ratio test.[25]

To determine if statin therapy initiation during follow-up modified the risk of CHD death among cholesterol groups, we performed a subgroup analysis of the multivariable model to examine the relation between cholesterol and CHD death among those without record of statin usage, initiated statin therapy before or at baseline, and began statin therapy during the follow-up period, respectively. We tested the multiplicative interaction by comparing the –2 log likelihood of the multivariate adjusted models with and without the cross-product interaction term between TC and statin use. A joint effect analysis was used to examine whether the association between low cholesterol (TC <180 mg/dL) and CHD mortality risk changed if statin therapy was initiated during follow-up.

Secondary analyses examined the risk of CHD mortality by joint classification of TC and HDL-C as well as ratio of TC to HDL-C. To test the robustness of our findings, we undertook several sensitivity analyses.

First, we further adjusted for income and socioeconomic status in 1 sensitivity analysis. Second, we examined the association between TC and CHD death among veterans with and without heart diseases (atrial fibrillation, heart failure, or coronary artery disease) at baseline. Third, we evaluated the relationship between LDL-C, non–HDL cholesterol, and triglyceride with risk of CHD death. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC), and *P* values ≤0.05 were considered statistically significant.

RESULTS

Cohort

There were 4 467 942 adult veterans nationwide with a complete lipid profile at baseline. Table 1 presents the baseline characteristics of the study population by TC group. Among all participants, 9.6% had very low TC (≤140 mg/dL), 33.0% had low TC (140–179 mg/dL), 19.6% had normal TC (180–199 mg/dL), 26.2% had high TC (200–239 mg/dL), and 11.6% had very high TC (≥240 mg/dL). The lowest TC group had the lowest HDL-C, greatest age, greater likelihood of starting statin before baseline, and the highest prevalence of comorbidities, which was the opposite of what we observed in the group with the highest TC (Table 1). More than one-third of veterans with low or very low TC had initiated statin therapy before or at baseline, and >40% of veterans with very high TC initiated statin therapy within the first 2 years of follow-up (Table 1).

Association Between TC and CHD Death

After adjusting for age, sex, race, and smoking status, a V-shaped relation was observed for TC and risk of CHD mortality (Figure 1), with the lowest risk at TC of 207 mg/dL. With additional adjustment for baseline body mass index, statin use, diabetes, and hypertension, the relation between TC and CHD death became U-shaped, with the lowest risk at TC of 200 to 215 mg/dL and elevated CHD mortality risk for both the lower and higher TC groups. Applying 2-year lag analysis with further adjustment of HDL-C and common baseline comorbidities led to a J-shaped association: flat when TC<180 mg/dL; and continuous, graded, and increasing with TC>180 mg/dL (Figure 1; Model 3). Compared with veterans with normal TC (180–199 mg/dL), the risk for CHD mortality (HR [95% CI]) was 1.03 (1.02–1.04), 1.07 (1.06–1.09), 1.15 (1.13–1.18), 1.25 (1.22–1.28), and 1.45 (1.42–1.49) among veterans with TC (mg/dL) of 200 to 219, 220 to 239, 240 to 259, 260 to 279, and ≥280, respectively (Table 2). Both the associations and its transitions across different models are consistent among males and females (*P* for interaction between TC and sex=0.41) (Table S2). In a sensitivity analysis that accounted for income levels, we did not observe material differences in risk for CHD death.

The patterns for association between TC levels and CHD death with adjustment for covariates differed among age groups. TC–CHD mortality patterns were J-J-J–shaped at ages 18 to 45 years, V-U-J–shaped at 45 to 64 years, and L-U-J–shaped at ≥65 years (Figure 1, or Figure S1 in the same scale across 4 panels). Compared with veterans with normal TC (180–199 mg/dL), the risk for CHD death (HR [95% CI]) among veterans with TC (mg/dL) of 200 to 219, 220 to 239, 240 to 259, 260 to 279 and ≥280 was 1.03 (0.92–1.15), 1.17 (1.04–1.32), 1.40 (1.23–1.59), 1.32 (1.13–1.55), and 1.96 (1.71–2.24) among younger veterans; 1.02 (1.00–1.05), 1.08 (1.05–1.11), 1.17 (1.14–1.21), 1.25 (1.20–1.29), and 1.41 (1.36–1.46) among middle-aged veterans, and 1.03 (1.01–1.04), 1.06 (1.04–1.08), 1.12 (1.09–1.14), 1.21 (1.18–1.25), and 1.34 (1.29–1.99) among older veterans (*P* for interaction between TC and age group <0.001) (Table 2).

The association between TC and CHD death was consistent among veterans with or without heart disease at baseline (Figure S2). Among veterans with heart disease, the risk for CHD death (HR [95% CI]) was 1.02 (1.00–1.03), 1.06 (1.04–1.08), 1.13 (1.10–1.16), 1.23 (1.19–1.28), and 1.42 (1.37–1.47) for veterans with TC (mg/dL) of 200 to 219, 220 to 239, 240 to 259, 260 to 279, and ≥280 compared with veterans with normal TC (180–199 mg/dL). CHD mortality risk for veterans without heart disease at baseline was 1.04 (1.02–1.06), 1.10 (1.08–1.13), 1.20 (1.17–1.23), 1.30 (1.26–1.34), and 1.54 (1.49–1.60) for those with TC (mg/dL) of 200 to 219, 220 to 239, 240 to 259, 260 to 279, and ≥280, respectively, compared with veterans with normal TC (*P* for interaction <0.001).

Relationship Stratified by Status of Statin Use

In an analysis stratified by status of statin use, similar J-shaped relations were observed among veterans who did not report statin use and veterans who used statins at or before baseline. A slight U-shaped relation was seen among veterans who started statin therapy after baseline. In particular, higher CHD mortality risk was associated with high baseline TC, but the effect was attenuated among veterans who initiated statin therapy during follow-up (Figure 2). Among participants who did not use statins, the risk of CHD death (HR [95% CI]) was 1.83 (1.68–1.99) in those with TC >280 mg/dL compared with normal TC (180–199 mg/dL). Risk of CHD death was lower among the participants who began statin therapy at or before baseline: CHD mortality risk was 1.45 (1.40–1.51) in TC >280 mg/dL versus normal TC (180–199 mg/dL) and no statin use. Further reduction in CHD mortality risk was

Table 1. Baseline Characteristics by Serum Cholesterol Group of 4 467 942 Veterans With Baseline Outpatient Visits From 2002 to 2007

	Very low cholesterol		Low cholesterol		Reference	High cholesterol		Very high cholesterol			
	<120	120–139	140–159	160–179	180–199	200–219	220–239	240–259	260–279	≥280	
	N=120 138	N=306 803	N=620 719	N=855 926	N=875 825	N=707 048	N=464 456	N=262 200	N=132 898	N=121 929	*P* for trend
Percent of study population	2.7	6.9	13.9	19.2	19.6	15.8	10.4	5.9	3.0	2.7	
Cholesterol, mg/dL	107.5 (10.7)	131.1 (5.6)	150.3 (5.7)	169.8 (5.7)	189.3 (5.7)	209.0 (5.7)	228.7 (5.7)	248.5 (5.7)	268.3 (5.7)	310.6 (42.3)	<0.0001
HDL-C, mg/dL	35.3 (10.0)	39.4 (10.6)	42.1 (11.7)	44.3 (12.8)	45.9 (13.8)	47.1 (14.6)	47.9 (15.1)	48.3 (15.4)	48.5 (15.5)	48.2 (15.9)	<0.0001
Age, y	66.1 (14.6)	65.6 (15.0)	64.5 (15.0)	63.2 (14.7)	61.9 (14.4)	60.7 (13.9)	59.5 (13.5)	58.5 (13.0)	57.7 (12.6)	56.5 (12.0)	<0.0001
Men, %	98.0	97.2	96.4	95.7	95.1	94.7	94.3	93.7	93.5	92.9	<0.0001
Race, %											
White	83.2	83.5	83.0	82.4	81.7	81.2	80.8	80.4	79.8	79.4	<0.0001
Black	14.1	13.6	13.8	14.1	14.4	14.7	14.8	15.0	15.3	15.8	<0.0001
Asian	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.6	<0.0001
American Indian	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.7	0.7	<0.0001
Native Hawaiian	0.6	0.7	0.7	0.7	0.8	0.8	0.9	0.8	0.9	0.8	<0.0001
Race: other	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.005
Race: unknown or null	1.2	1.3	1.5	1.7	1.9	2.1	2.3	2.5	2.6	2.6	<0.0001
Body mass index, kg/m^2	28.2 (5.7)	28.6 (5.6)	28.7 (5.6)	28.9 (5.6)	29.0 (5.7)	29.2 (5.5)	29.2 (5.4)	29.4 (5.3)	29.5 (5.2)	29.8 (5.2)	<0.0001
Smoking status, %											
Never	16.8	16.8	16.7	16.5	16.3	15.9	15.4	14.7	14.3	13.7	<0.0001
Former	16.8	16.9	16.3	15.5	14.6	13.8	13.1	12.4	12.0	11.3	<0.0001
Current	16.7	15.8	15.9	16.7	17.3	17.9	18.9	19.6	20.5	21.7	<0.0001
Missing	49.6	50.5	51.0	51.3	51.7	52.4	52.6	53.3	53.2	53.3	<0.0001
Start using statin, %											
Not used	38.9	35.3	35.9	36.2	33.9	28.2	21.4	15.3	11.4	8.3	<0.0001
Start before baseline	42.0	44.2	40.2	33.5	27.1	23.0	22.3	24.0	26.5	31.5	<0.0001
Start first 1–2 y	11.5	11.3	11.3	12.9	16.7	23.8	32.9	40.7	46.0	47.9	<0.0001
Start after 2 y	7.5	9.3	12.7	17.5	22.4	25.0	23.5	20.1	16.1	12.4	<0.0001
Baseline comorbidities, %											
Hypertension	75.9	74.8	71.8	68.0	64.4	61.5	59.5	58.4	58.4	60.6	<0.0001
Diabetes	43.5	38.4	33.1	27.9	23.8	20.9	19.3	18.8	19.9	24.8	<0.0001
Coronary artery disease	53.5	50.0	42.5	33.8	26.5	21.5	19.0	18.1	18.1	20.1	<0.0001
Atrial fibrillation	19.5	15.7	12.5	9.8	7.7	6.3	5.3	4.7	4.4	4.3	<0.0001

(*Continued*)

Table 1. Continued

	Very low cholesterol		Low cholesterol		Reference	High cholesterol		Very high cholesterol			
	<120	120–139	140–159	160–179	180–199	200–219	220–239	240–259	260–279	≥280	
	N=120 138	N=306 803	N=620 719	N=855 926	N=875 825	N=707 048	N=464 456	N=262 200	N=132 898	N=121 929	*P* for trend
Heart failure	25.7	19.5	15.1	11.5	9.1	7.3	6.4	6.0	5.9	6.7	<0.0001
Stroke	20.8	19.4	16.9	14.2	11.9	10.1	9.0	8.5	8.2	8.7	<0.0001
Cancers	28.1	26.5	25.3	23.7	22.0	20.2	18.4	17.1	15.7	14.6	<0.0001
Anemia	32.3	24.0	19.5	16.1	13.5	11.4	10.2	9.2	8.8	9.2	<0.0001
Liver disease or cirrhosis	14.9	10.4	8.8	7.7	7.0	6.4	6.1	5.9	5.8	6.4	<0.0001
Kidney disease	15.0	10.7	8.2	6.5	5.2	4.5	4.1	3.9	4.2	5.4	<0.0001
Lung disease (COPD, asthma)	31.7	28.7	26.9	25.3	23.7	22.3	21.0	20.2	19.4	19.1	<0.0001
Depression	22.9	21.3	20.8	21.0	21.4	22.0	22.8	24.1	25.4	28.3	<0.0001
Dementia	10.0	8.2	7.1	6.3	5.7	5.2	4.8	4.6	4.5	4.6	<0.0001

Data are presented as mean (SD) or percentage. COPD indicates chronic obstructive pulmonary disease; and HDL-C, high-density lipoprotein cholesterol.

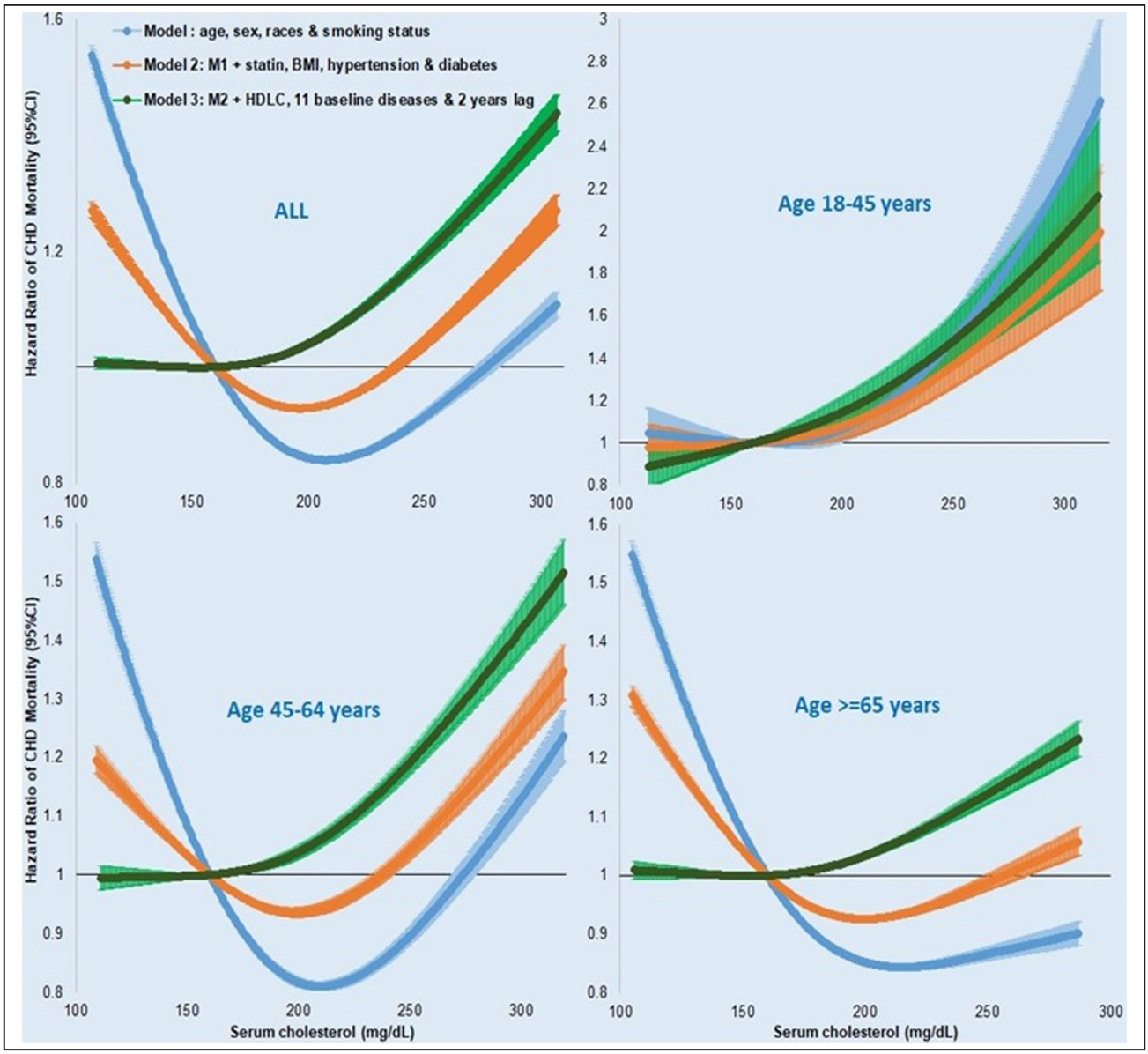

Figure 1. Dose–response relationship of serum total cholesterol (TC) with coronary heart disease (CHD) mortality.
Risk expressed as hazard ratio for CHD death according to levels of serum cholesterol (reference was set at 160 mg/dL). Model 1: adjusted age (y, continuous), sex, race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other race, race unknown or null), and smoking status (never, ever, current smoking, or missing); Model 2: further adjusted for timing of statin therapy initiation (no usage recorded, initiated statin therapy at or before baseline, within 2 y of follow-up, or after 2 y of follow-up), body mass index (kg/m^2: <18.5, 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), baseline hypertension, and diabetes; Model 3: model 2 further adjusted for high-density lipoprotein cholesterol (mg/dL, continuous), 11 baseline diseases including coronary artery disease, atrial fibrillation, heart failure, stroke, anemia, liver disease or cirrhosis, kidney disease, lung disease (chronic obstructive pulmonary disease, asthma), cancer, depression, and dementia, and excluding the mortality cases within the first 2 y of follow-up (2-y lag). BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; and HDLC, high-density lipoprotein cholesterol.

observed for veterans who initiated statin therapy after baseline (TC>280 mg/dL versus normal TC and no statin use: 1.09 [1.05–1.13]) (Table 3; *P* for interaction <0.001). In participants with low baseline cholesterol (<180 mg/dL), starting statin therapy during the follow-up period conferred an additional 20% reduction in risk for CHD death compared with those who never used statins. HR (95% CI) was 0.81 (0.79–0.83) for the 160 to 179 mg/dL group, 0.82 (0.80–0.84) for the 140 to 159 mg/dL group, 0.81 (0.78–0.83) for the 120 to 139 mg/dL group, and 0.82 (0.78, 0.85) for the <120 mg/dL cholesterol group.

Table 2. HR (95% CI) for CHD Death According to Baseline Total Cholesterol Category

	Very low cholesterol		Low cholesterol		Reference	High cholesterol		Very high cholesterol		
Age groups	<120	120–139	140–159	160–179	180–199	200–219	220–239	240–259	260–279	≥280
All										
CHD mortality, n	15126	36295	65422	78366	69536	50278	31011	17414	9079	9344
Incidence rate*	14.4	12.0	9.9	8.2	6.8	5.9	5.5	5.4	5.5	6.3
HR model 1	1.74 (1.71–1.77)	1.43 (1.41–1.45)	1.24 (1.23–1.25)	1.10 (1.09–1.11)	1.0	0.95 (0.94–0.96)	0.96 (0.95–0.97)	1.03 (1.02–1.05)	1.15 (1.12–1.17)	1.47 (1.44–1.50)
HR model 2	1.41 (1.39–1.44)	1.20 (1.18–1.22)	1.09 (1.08–1.11)	1.04 (1.03–1.05)	1.0	0.99 (0.98–1.01)	1.02 (1.01–1.03)	1.09 (1.07–1.11)	1.19 (1.16–1.21)	1.44 (1.41–1.48)
HR model 3	0.99 (0.97–1.01)	0.97 (0.96–0.99)	0.97 (0.96–0.98)	0.99 (0.97–1.00)	1.0	1.03 (1.02–1.04)	1.07 (1.06–1.09)	1.15 (1.13–1.17)	1.25 (1.22–1.28)	1.45 (1.42–1.49)
<45 y										
CHD mortality, n	55	116	339	505	668	649	562	435	241	399
Incidence rate*	0.47	0.31	0.40	0.39	0.47	0.54	0.67	0.87	0.92	1.6
HR model 1	1.23 (0.94–1.63)	0.89 (0.73–1.08)	1.05 (0.93–1.20)	0.92 (0.82–1.03)	1.0	1.04 (0.94–1.16)	1.22 (1.09–1.36)	1.50 (1.33–1.69)	1.52 (1.31–1.76)	2.51 (2.22–2.85)
HR model 2	1.13 (0.86–1.49)	0.83 (0.68–1.01)	1.03 (0.90–1.17)	0.92 (0.82–1.03)	1.0	1.03 (0.92–1.14)	1.15 (1.03–1.29)	1.35 (1.19–1.52)	1.30 (1.12–1.51)	1.89 (1.66–2.15)
HR model 3	0.93 (0.70–1.25)	0.73 (0.59–0.89)	0.95 (0.83–1.09)	0.89 (0.79–1.01)	1.0	1.03 (0.92–1.15)	1.17 (1.04–1.32)	1.40 (1.23–1.59)	1.32 (1.13–1.55)	1.96 (1.71–2.24)
45–64 y										
CHD mortality, n	2806	6417	12201	17344	17992	15223	11044	7173	4131	4974
Incidence rate*	6.7	5.6	4.7	4.2	3.7	3.5	3.5	3.8	4.1	5.1
HR model 1	1.82 (1.75–1.89)	1.49 (1.45–1.54)	1.25 (1.22–1.28)	1.12 (1.09–1.14)	1.0	0.94 (0.92–0.96)	0.96 (0.94–0.98)	1.04 (1.02–1.07)	1.15 (1.11–1.18)	1.46 (1.42–1.51)
HR model 2	1.39 (1.34–1.45)	1.18 (1.15–1.21)	1.06 (1.04–1.08)	1.03 (1.01–1.05)	1.0	0.99 (0.97–1.01)	1.02 (1.00–1.05)	1.10 (1.07–1.13)	1.17 (1.13–1.21)	1.39 (1.34–1.43)
HR model 3	1.02 (0.97–1.07)	0.98 (0.95–1.01)	0.96 (0.93–0.98)	0.99 (0.97–1.01)	1.0	1.02 (1.00–1.05)	1.08 (1.05–1.11)	1.17 (1.14–1.21)	1.25 (1.20–1.29)	1.41 (1.36–1.46)
≥65 y										
CHD mortality, n	12265	29762	52882	60517	50876	34406	19405	9806	4707	3971
Incidence rate*	23.8	19.6	16.9	14.7	13.1	12.2	11.8	12.0	13.0	15.1
HR model 1	1.72 (1.68–1.75)	1.41 (1.39–1.43)	1.24 (1.23–1.26)	1.10 (1.09–1.12)	1.0	0.95 (0.94–0.96)	0.95 (0.93–0.96)	1.00 (0.97–1.02)	1.10 (1.07–1.14)	1.35 (1.31–1.40)
HR model 2	1.42 (1.39–1.45)	1.21 (1.19–1.23)	1.11 (1.10–1.12)	1.04 (1.03–1.05)	1.0	0.99 (0.98–1.00)	1.00 (0.98–1.02)	1.05 (1.02–1.07)	1.14 (1.11–1.18)	1.34 (1.30–1.39)
HR model 3	0.99 (0.96–1.01)	0.98 (0.97–1.00)	0.98 (0.97–1.00)	0.99 (0.98–1.00)	1.0	1.03 (1.01–1.04)	1.06 (1.04–1.08)	1.12 (1.09–1.14)	1.21 (1.18–1.25)	1.34 (1.29–1.39)

Model 1: adjusted age (y, continuous), sex, race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other race, race unknown or null), and smoking status (never, ever, current smoking, or missing). Model 2: further adjusted for timing of statin therapy initiation (no usage recorded, initiated statin therapy at or before baseline, within 2 y of follow-up, or after 2 y of follow-up), body mass index (kg/m^2: <18.5, 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), baseline hypertension, and diabetes. Model 3: model 2 further adjusted for high-density lipoprotein cholesterol (mg/dL, continuous), 11 baseline diseases including coronary artery disease, atrial fibrillation, heart failure, stroke, anemia, liver disease or cirrhosis, kidney disease, lung disease (chronic obstructive pulmonary disease, asthma), cancer, depression, and dementia, and excluding the mortality cases within the first 2 y of follow-up (2-y lag). CHD indicates coronary heart disease; and HR, hazard ratio.

*Incidence rate: crude incidence rate of CHD death per 1000 person-years of follow-up (‰).

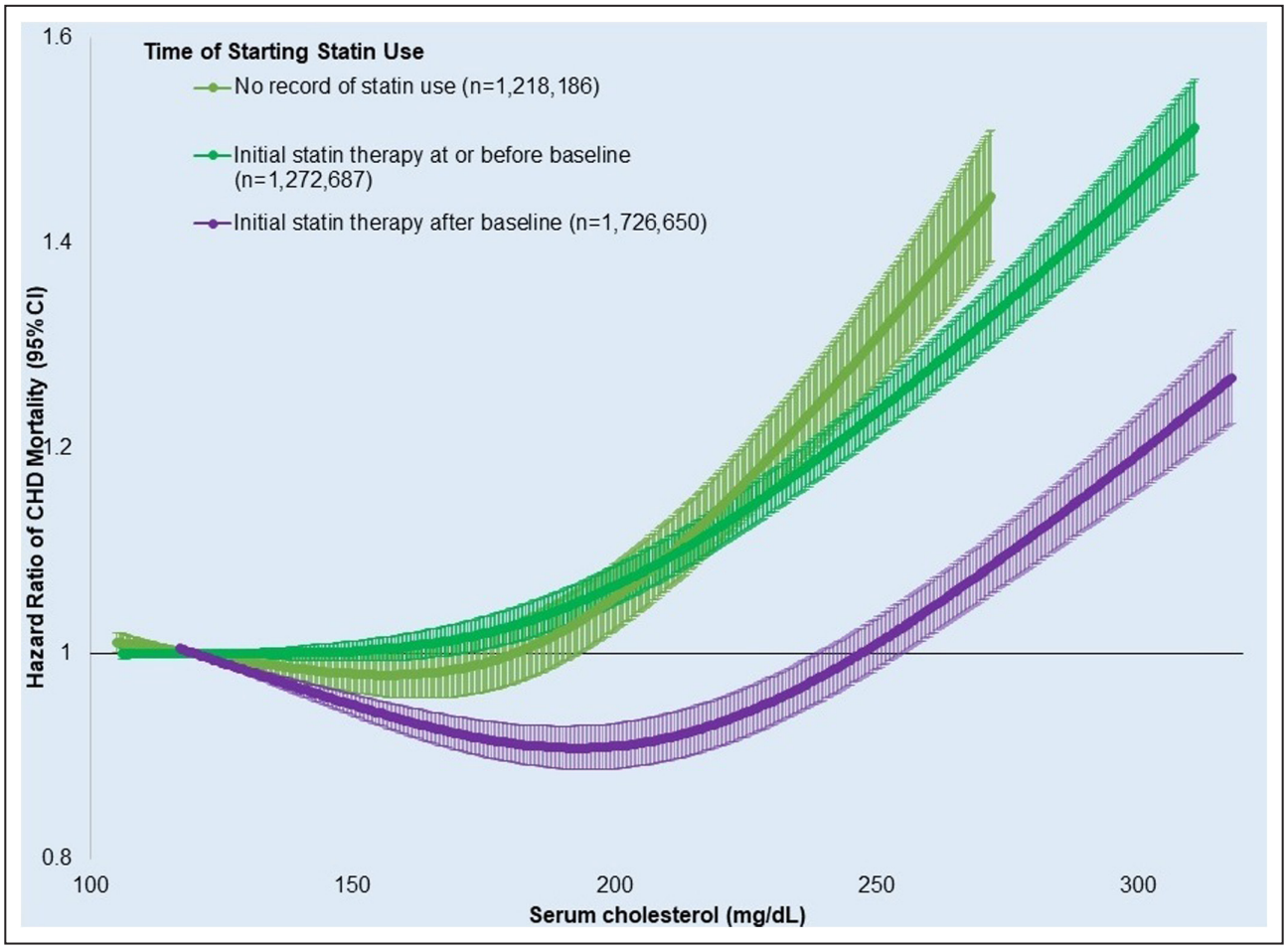

Figure 2. Dose–response relationship of serum total cholesterol (TC) with coronary heart disease (CHD) death stratified by timing of statin therapy initiation.
Comparison of CHD mortality risk among participants who never used statins, those who started statin therapy at or before baseline, and those who initiated statin therapy during follow-up. Curves includes 95% CIs of the hazard ratio estimates (reference was set at 120 mg/dL), adjusted age (y, continuous), sex, race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other race, race unknown or null), smoking status (never, ever, current smoking, or missing), body mass index (kg/m^2: <18.5, 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), hypertension, diabetes, high-density lipoprotein cholesterol (mg/dL, continuous), coronary artery disease, atrial fibrillation, heart failure, stroke, anemia, liver disease or cirrhosis, kidney disease, lung disease (chronic obstructive pulmonary disease, asthma), cancer, depression, and dementia, and excluding the mortality cases within the first 2 y of follow-up (2-y lag).

Risk of CHD Death According to Joint Classification of TC and HDL-C and Ratio of TC to HDL-C

Among veterans with low HDL-C (<40 mg/dL), risk of CHD death was continuous, graded, and increasing with increasing total TC. Veterans with high HDL-C did not have an elevated risk of CHD death unless they had a higher level of TC (Figure 3). For example, compared with veterans with TC <180 mg/dL (low) and HDL-C ≥60 mg/dL (high), veterans with TC ≥260 mg/dL (high) and HDL-C <30 mg/dL (low) had 74% higher risk of CHD death (HR, 1.77 [95% CI, 1.67–1.89]).

CHD mortality risk increased with increasing TC and decreasing HDL-C. We examined the ratio of TC to HDL-C in our models and observed a nonlinear association between TC : HDL-C ratio and risk of CHD death (Figure 4), which was consistent in White and Black veterans (all *P* values for nonlinear relationship <0.01).

Risk of CHD Death According to LDL-C, non–HDL Cholesterol, and Triglyceride

In the sensitivity analysis, we examined the effects of LDL-C, non–HDL cholesterol, and triglyceride on risk of CHD death. We observed an L-U-J risk pattern for LDL-C and CHD death across younger, middle, and older age groups, similar to the association pattern observed between TC and CHD death (Figure S3); similar pattern

Table 3. HR (95%CI) for CHD Death According to Baseline TC* Stratified by Status of Statin Use†

	Timing of statin therapy initiation		
	No statin usage	At or before baseline	During follow-up period
No.	1 218 186	1 272 687	1 726 650
CHD mortality, n	59 192	156 160	112 618
TC, mg/dL			
<120	0.96 (0.92–1.01)	0.97 (0.94–0.99)	0.82 (0.78–0.85)
120–139	0.97 (0.94–1.00)	0.94 (0.92–0.96)	0.81 (0.78–0.83)
140–159	0.98 (0.95–1.00)	0.93 (0.91–0.95)	0.82 (0.80–0.84)
160–179	0.97 (0.95–1.00)	0.95 (0.93–0.97)	0.81 (0.79–0.83)
180–199	1.0 (ref.)	0.97 (0.95–0.99)	0.80 (0.78–0.82)
200–219	1.06 (1.03–1.09)	1.04 (1.01–1.06)	0.79 (0.77–0.81)
220–239	1.14 (1.10–1.18)	1.08 (1.05–1.11)	0.82 (0.80–0.84)
240–259	1.29 (1.22–1.35)	1.16 (1.12–1.20)	0.88 (0.85–0.90)
260–279	1.44 (1.34–1.56)	1.25 (1.20–1.30)	0.95 (0.92–0.99)
≥280	1.83 (1.68–1.99)	1.45 (1.40–1.51)	1.09 (1.05–1.13)

*Adjusted age (y) and sex, race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other race, race unknown or null), smoking status (never, ever, current smoking, or missing), body mass (kg/m^2: <18.5, 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), high-density lipoprotein cholesterol and the presence of coronary artery disease, diabetes, atrial fibrillation, hypertension, anemia, heart failure, kidney disease, stroke, liver disease or cirrhosis, lung disease (chronic obstructive pulmonary disease, asthma), cancer, depression, and dementia, and excluding the mortality cases within the first 2 y of follow-up (2-y lag). CHD indicates coronary heart disease; HR, hazard ratio; and TC, total cholesterol.

†*P* for interaction between TC and statin <0.001, −2log likelihood method with a degree of freedom=18.

transitions were also observed for non–HDL cholesterol (Figure S4). The relation between LDL-C or non–HDL cholesterol and CHD death for different age groups was also similar to the patterns observed between TC and CHD.

The pattern transition of the relationship between triglyceride and CHD death was different from LDL-C or TC; CHD death was positively associated with triglyceride levels but was attenuated with covariate adjustment (Figure S5).

DISCUSSION

In this observational cohort study of roughly 4.5 million adult veterans with up to 18 years of follow-up, we observed a U-shaped cholesterol-to-CHD mortality relation with multivariable adjustment, which became J-shaped after comprehensive adjustment for baseline comorbidities, HDL-C, and applying the 2-year lag analysis strategy. A continuous and graded increased CHD mortality risk was observed with greater TC concentration. This risk profile was consistent among veterans regardless of heart disease status or statin usage at baseline. A linear trend in CHD mortality risk was observed for greater TC-to-HDL-C ratio for both Whites and Black veterans.

Several hypotheses have been proposed to explain the higher mortality rate among those with low serum cholesterol, including unhealthy lifestyle behaviors such as smoking, cancers, and noncardiovascular health conditions.[8,26–30] In the Cardiovascular Health Study, older adults with low cholesterol levels often had indications of being in worse health than those with normal levels.[31] Our results show that individuals in the lower-cholesterol groups shoulder the burden of multimorbidity, mental health disorders, nutritional deficits, and other risk factors for CHD as well as lower HDL-C. When we comprehensively adjusted for these comorbidities and HDL-C level in our multivariable model, the observed higher risk between low serum cholesterol and risk for CHD death was fully attenuated, and the risk for CHD death was increased at higher TC levels. Our findings support the lipid hypothesis that lower blood cholesterol is associated with reduced CHD and suggest that statin therapy among low blood cholesterol groups (TC<180 mg/dL) may confer additional CHD risk-reducing benefits as reported for other cohorts.[32]

Previous studies in older populations have reported inverse linear or L-shaped associations between cholesterol and all-cause death.[26,33,34] A recent large prospective cohort study of 12.8 million Korean adults similarly observed a U-shaped relationship between cholesterol level and all-cause death. The Korean investigators reported a doubling of mortality risk in the lowest-cholesterol group (<120 mg/dL) compared with a reference group with total cholesterol 220 to 229 mg/dL for adults aged ≥55 years.[4] They adjusted for age, smoking status, alcohol use, physical activity, history of heart disease, stroke, cancer, body mass index, systolic blood pressure, and fasting glucose levels at baseline. While we observed similar trends in our multivariable adjusted models, further step-by-step adjustment of confounding factors in our study suggests that

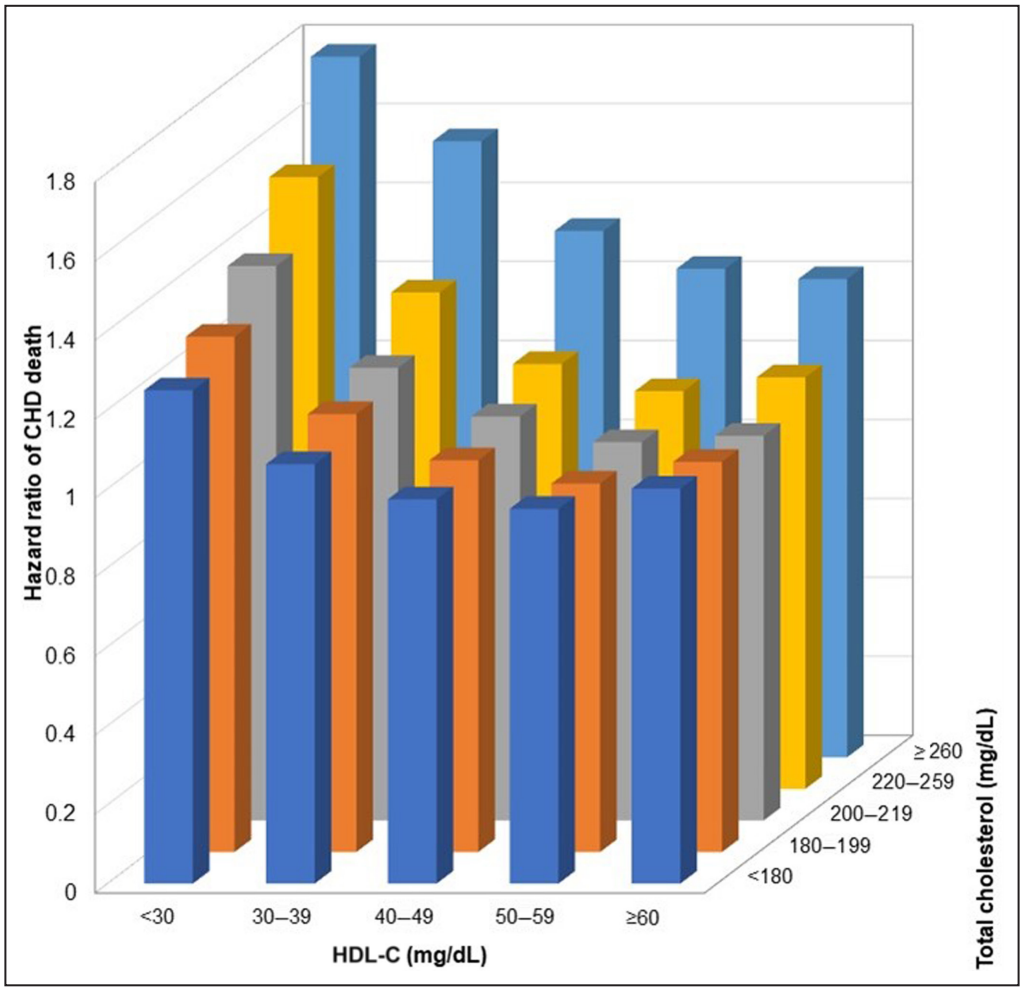

Figure 3. Hazard ratio (95% CI) for coronary heart disease (CHD) mortality according to joint classification of serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C). Risk of CHD death according to categories of HDL-C proportional to cholesterol. Estimates are adjusted for age (y, continuous), sex, race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other race, race unknown or null), smoking status (never, ever, current smoking, or missing), timing of statin therapy initiation (no usage recorded, initiated statin therapy at or before baseline, within 2 y of follow-up, or after 2 y of follow-up), body mass index (kg/m^2: <18.5, 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), hypertension, diabetes, coronary artery disease, atrial fibrillation, heart failure, stroke, anemia, liver disease or cirrhosis, kidney disease, lung disease (chronic obstructive pulmonary disease, asthma), cancer, depression, and dementia, and excluding the mortality cases within the first 2 y of follow-up (2-y lag).

previous reports of an association between high CHD mortality risk and low TC may not have fully adjusted for comorbidities associated with both TC and CHD mortality risk.

Pharmacological lowering of blood cholesterol levels generally reduces risk for CHD, but it is less clear if achieving low TC with or without statin medication affects CHD risk. We observed a similar reduction in CHD risk among veterans not prescribed statins with lower blood cholesterol versus veterans who initiated statin use at or before baseline. This result suggests that lower cholesterol levels in users and nonusers of statins can provide a similar degree of CHD mortality benefit. Additionally, we observed that veterans with higher cholesterol levels who subsequently started statins during follow-up appeared to benefit from the therapy, as favorable effects on CHD mortality risk were observed, supporting findings from the Cholesterol Treatment Trialists' Collaboration[11] and studies in older adults.[35,36]

Our study has important limitations to be considered when interpreting our results. It is retrospective and observational in nature, and the population consists entirely of veterans, of which the majority are men, limiting causal inference and generalizability to other populations. Other limitations of our study include the possibility of inadequate identification of comorbidities

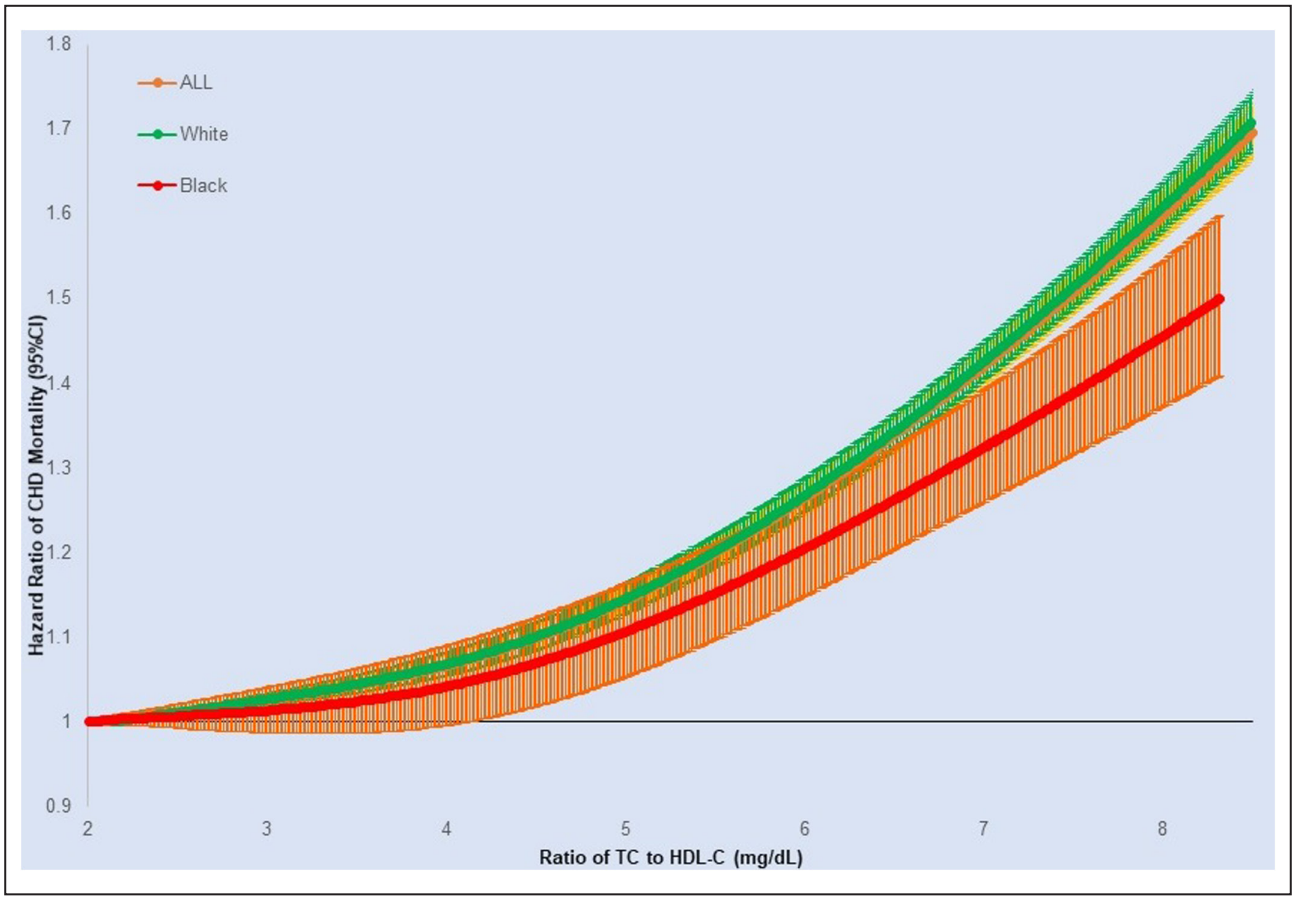

Figure 4. Dose–response relationship between ratio of serum total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) and coronary heart disease (CHD) mortality.
Plot of the total cholesterol/HDL-C ratio and risk of death (reference was set at total cholesterol/HDL-C ratio of 2). Separate analyses are shown for all, White, and Black participants. Estimates are adjusted for age (y, continuous), sex, smoking status (never, ever, current smoking, or missing), timing of statin therapy initiation (no usage recorded, initiated statin therapy at or before baseline, within 2 y of follow-up, or after 2 y of follow-up), body mass index (kg/m^2: <18.5, 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, ≥35, or missing), hypertension, diabetes, coronary artery disease, atrial fibrillation, heart failure, stroke, anemia, liver disease or cirrhosis, kidney disease, lung disease (chronic obstructive pulmonary disease, asthma), cancer, depression, and dementia, and excluding the mortality cases within the first 2 y of follow-up (2-y lag). *P* for interaction between race and ratio of TC to HDL-C=0.09.

due to *ICD-9* categorization or incomplete data on patterns of health care use for the veterans, as they may have received health care outside the VA, and that information may not be available in the VHA EHR. We used the National Death Index to assign cause of death, and we may have misclassified CHD as the primary cause of death since many veterans had chronic diseases, and noncancerous illnesses may have increased their mortality risk. Additionally, veterans in this study were older and Veterans tend to be sicker compared with the general population, limiting the generalizability of the study results. In our poverty analysis, we did not have self-reported income or prevalence of homelessness among veterans and were limited to residential zip codes as a proxy for socioeconomic status, which may not accurately reflect the socioeconomic status for individuals. Unfortunately, no information on physical activities is provided in the EHR. Lack of data on lipoprotein(a) and apolipoprotein B concentrations are also limitations to our study, as previous reports have shown significant association with CHD morbidity and death.[37–39] The implications of statin therapy for reducing high-TC–related CHD death warrants further clinical trials among older adults. Strengths of this study include a large sample size, relatively contemporary 10-year mortality experience from 2002 onward, and the ability to examine many strata of total cholesterol with more precision than previously reported. Additionally, having comprehensive data for subclinical and clinical diseases allowed for the control of confounding effects specific to older adults.

In this population of ≈4.5 million veterans with up to 17 years of follow-up data, we replicated previous findings that lower blood cholesterol is associated with reduced coronary heart disease mortality risk regardless of whether cholesterol reduction was achieved

with or without statin therapy. The changes in risk for CHD death by TC groups observed in our study (L- to U- to J-shaped) highlights the importance of fully adjusting for the presence of multimorbidity and HDL-C to avoid misleading conclusions. Initiation of statin therapy during the follow-up period among participants with low baseline cholesterol (TC<180 mg/dL) was associated with further reduction in CHD mortality risk. Future clinical studies to examine the effect of statin use in individuals with low cholesterol would help identify possible cardiovascular mortality benefits and risks in the aging veteran population.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
Figures S1–S5

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