BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-077949
Article Type:	Original research
Date Submitted by the Author:	20-Jul-2023
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Keywords:	EPIDEMIOLOGY, Primary Prevention, Adult cardiology < CARDIOLOGY

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Assessment of LDL Cholesterol and Long-Term Mortality Among Primary Prevention Adults: A Cohort Study with Implications for Risk Assessment and Patient Counseling

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Abstract

Objectives. Among primary prevention-type adults not on lipid-lowering therapy, results are conflicting on the relationship between low density lipoprotein cholesterol (LDL-C) and long-term mortality. We sought to evaluate the relationship between LDL-C and all-cause long-term mortality in a real-world evidence population of adults.

Design. Retrospective cohort study of adults during the period January 4, 2000 through December 31, 2022.

Setting. Large U.S. health care system.

Participants. Non-diabetic adults aged 50 to 89 years not on statin therapy at baseline or within 1-year and classified as primary prevention-type patients (e.g., no prior history of ASCVD). To mitigate potential reverse causation, patients who died within 1-year or had baseline total cholesterol (T-C) ≤120 mg/dL or LDL-C <30 mg/dL were excluded from analysis.

Main Exposure Measure. Baseline LDL-C categories of 30-79, 80-99, 100-129, 130-159, 160-189, or ≥190 mg/dL.

Main Outcome Measure. The primary outcome was all-cause mortality with follow-up starting 365 days after baseline cholesterol measurement.

Results. Over a mean of 6.1 years of follow-up, a U-shaped relationship was observed between the 6 LDL-C categories and mortality with crude 10-year mortality rates of 19.8%, 14.7%, 11.7%, 10.7%, 10.1%, and 14.0%, respectively. Adjusted mortality hazard ratios as compared to the referent group of LDL-C 80-99 mg/dL, were: 30-79 mg/dL (1.23), 100-129 mg/dL (0.87), 130-159 mg/dL (0.88), 160-189 mg/dL (0.91), ≥190 mg/dL (1.19), respectively. Unlike LDL-C, both T-C/HDL cholesterol and triglycerides/HDL cholesterol ratios were independently associated with long-term mortality.

Conclusions. Among non-diabetic primary prevention-type patients aged 50 to 89 years and not on statin therapy, the lowest risk for long-term mortality appears to exist in the wide LDL-C range of 100-189 mg/dL which is much higher than current recommendations and does not support the prevailing premise that "lower LDL-C is better". For counseling of these patients, minimal consideration should be given to the LDL-C concentration.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The cohort consisted of a large "real-world" sample of adults across a large health system with long-term follow-up and sufficient precision for subgroup analyses.
- The study design mitigated potential for reverse causation of mortality by excluding patients who died within 1-year of baseline cholesterol measurement or had exceptionally low total or LDL cholesterol levels at baseline.
- The analysis was limited to all-cause mortality and thus was unable to assess cause-specific mortality.

INTRODUCTION

Heart disease (HD), which includes atherosclerotic cardiovascular disease (ASCVD) as its primary component, is the leading cause of death in the United States.[1-2] A near universal but not absolute belief [3] is that high total cholesterol (T-C), low density lipoprotein cholesterol (LDL-C) in particular (the so-called "bad" cholesterol), is a root cause of ASCVD,[4] and that "lower is better" with a suggested optimal LDL-C level at or below 100 mg/dL.[5-6] In this regard, the American College of Cardiology (ACC) unequivocally implicates elevated LDL-C as a *de-facto* cause of ASCVD (and hence mortality) by stating that lowering of LDL-C with moderate intensity generic statins allows for efficacious and cost-effective primary prevention for those patients with an estimated 10-year risk of ASCVD ≥7.5%.[7]

An individual's risk of ASCVD (within 10 years) is routinely estimated by health professionals using the online ACC-ASCVD Risk Estimator which incorporates not only T-C, LDL-C, and high-density lipoprotein cholesterol (HDL-C), but also age, sex, race, systolic and diastolic blood pressure, smoking and diabetes history, and current treatment (anti-hypertensive, statin, and/or aspirin therapy).[8] For primary prevention of ASCVD among adults ages 40-75 years who are classified at 10-year "intermediate risk" of ASCVD) (estimated risk 7.5% to <20.0%), the ACC/AHA guidelines recommend that moderate-intensity statin therapy be considered with the goal of reducing LDL-C by 30-49%.[9] Again, the premise of this recommendation is that elevated LDL-C is an important causal risk factor for ASCVD and mortality.

The overall belief that "lower LDL-C is better" for primary prevention of ASCVD is supported by the 25.5% estimated prevalence of use of statins in this setting for adults aged 40 to 75 years.[10] This frequent use of statins for primary prevention of ASCVD in adults may be

attributed, in part, to routine use of the ACC-ASCVD Risk Estimator in clinical practice. To illustrate, **Table 1** shows ASCVD 10-year risk calculations for primary prevention by age, race, and sex for a hypothetical non-diabetic patient with approximate guideline-driven "normal" values for all clinical variables used in the risk equation. As seen, all males aged 59 years and older will be classified as being of at least "intermediate risk" of ASCVD principally because of their age and despite "normal" risk factor values, and hence, would potentially be referred for statin therapy per the ACC/AHA guidelines.[9] Parenthetically, **Table 1** unexpectedly shows a much more restricted range for 10-year risk estimates across years of age for blacks (males in particular).

In the backdrop of the generally accepted belief that "lower LDL-C is better," multiple sources of information suggest that high LDL-C may not be a significant cause of ASCVD or premature mortality. First, in brief, in an extensive recent meta-analysis of 60 randomized controlled trials that compared either placebo, usual care or less-intensive therapy to active or more potent lipid-lowering therapy, the number needed to treat (NNT) to reduce one death with active or more potent lipid-lowering therapy was exceptionally high at 754 persons. Moreover, there was no relationship between LDL-C percent lowering and risk of cardiovascular mortality.[11] In the context of lipid-lowering therapy, these findings do not support the belief that "lower LDL-C is better."

Second, acute coronary syndromes (ACS) routinely occur in patients with "normal" LDL-C. For example, in a large cohort of 136,905 patients hospitalized with CAD (79% attributed to ACS), of whom, 21% were on lipid-lowering therapy at admission, less than one-quarter had an admission LDL-C >130 mg/dL.[12]. In addition, women are generally considered to be at overall lower risk of CHD mortality than men (e.g.,[13]), yet tend to have higher T-C and

LDL-C,[14] which is counterintuitive to higher LDL-C being associated with ASCVD and premature mortality.

Third, the field of life insurance medicine, which focuses principally on predicting mortality hazards,[15] arguably conducts the most robust actuarial analyses of life expectancy (since organizational profit is directly related to prediction accuracy). Notably, in this field, the T-C/HDL-C ratio has been shown to be the best single measure of all-cause mortality risk among various lipid tests, including LDL-C.[16] This is further supported by examination of selected life insurance underwriting guidelines (obtained publicly and summarized) from a large US insurance company.[17] As seen in **Supplement Table 1**, T-C and HDL-C are used jointly in policy underwriting, whereas LDL-C is not used, and lipid-lowering therapy is not emphasized. Moreover, notwithstanding other important patient factors (e.g., blood pressure, smoking, etc.), **Supplement Table 1** shows that a person 70 years of age or older can potentially qualify for a "preferred-plus" life insurance policy having a T-C value as high as 300 mg/dL so long as the T-C/HDL-C ratio is 5.0 or lower (i.e., HDL-C ≥60 mg/dL). This aligns with meta-analyses/systematic reviews that report HDL-C to be inversely associated with all cause and CVD mortality risks.[18-19]

The above-described examples of conflicting beliefs and findings, along with general propensity for health professionals to prescribe LDL-C lowering therapies for primary prevention based in part through routine risk assessment with ACC-ASCVD Risk Estimator, call for a critical appraisal and analysis of the relationship between LDL-C and long-term risk of mortality in adults. Therefore, within a large, "real-world" healthcare system, we sought to evaluate the relationship between LDL-C and all-cause long-term mortality among non-diabetic

primary prevention-type adults aged 50 to 89 years. The analysis did not focus on the use of statin therapy for primary prevention.

METHODS

We conducted a retrospective cohort study of adults aged 50 to 89 years with hospital and/or office visit data captured through the University of Pittsburgh Medical Center (UPMC) electronic medical record (EMR) system. The date period for analysis was January 4, 2000 through December 31, 2022. The Quality Improvement Review Committee and Institutional Review Board provided ethical review and approval of the study as an exempt protocol, and all data remained deidentified for this analysis. Conduct and dissemination of results from this observational study were performed in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology**)** statement (see **Appendix**).

Data Sources

Health-related data captured in the UPMC EMR and its ancillary clinical systems were aggregated and harmonized in a clinical data warehouse, as previously described.[20-21] For all patients, we accessed sociodemographic data, medical history, and billing charges for all outpatient and inpatient encounters with diagnoses and procedures coded based on the International Classification of Diseases, Ninth and 10th Revisions.[22-23] Deaths were identified using hospital discharge dispositions of "ceased to breathe" sourced from the inpatient medical record system; deaths after discharge were identified via the Death Master File from the Social Security Administration's National Technical Information Service.[24]

Eligibility Criteria

The index date for selection and analysis of patients aged 50 to 89 years was the first date of cholesterol measurement performed whether through hospitalization or in conjunction with an office visit. For analysis, we required non-missing laboratory values for T-C, LDL-C, and HDL-C. The patient population was restricted to "primary prevention" patients, defined as no prior history of diabetes, coronary artery disease (CAD), carotid artery disease, peripheral vascular disease, cardiac arrest, hemorrhagic or ischemic stroke, or transient ischemic attack (TIA). Other eligibility criteria included: self-reported race of either white or black (due to very low prevalence of other races), and not on statin therapy at baseline or within 1-year of follow-up. In addition, to help offset potential bias due to reverse causation (i.e., very low cholesterol being a marker for malnutrition and overall poor health), we excluded patients who died within 1-year of the baseline cholesterol measurement, as well as those with baseline T-C and/or LDL-C values of ≤120 or <30 mg/dL, respectively.

Classification of Lipids

From the baseline measurement, we classified patients into mutually exclusive lipid-level categories using common thresholds[25] including LDL-C (30-79, 80-99, 100-129, 130-159, 160-189, or 190 mg/dL or higher) and T-C (121-160, 161-200, 201-240, 241-280, or 281 mg/dL or higher). In supplemental analyses, we classified the T-C/HDL-C ratio as ≤3.0, >3.0-4.0, >4.0-5.0, >5.0-6.0, or >6.0, and triglycerides/HDL-C ratio into quintiles. Again, to potentially mitigate potential bias due to reverse causation, we selected the LDL-C category of 80-99 mg/dL as the referent group, rather than the lowest LDL-C group (30-79 mg/dL).

Primary Outcome

The primary outcome was all-cause mortality with the number of days and years of follow-up calculated starting 365 days after the baseline cholesterol measurement. For patients

who did not die, their length of follow-up was calculated starting 365 days after the baseline cholesterol measurement and until their last record in the EMR system.

Statistical Analysis

For patients within the respective study-defined baseline LDL-C categories, means and medians for continuous variables and counts and percentages for categorical variables are presented. For each LDL-C category, the Kaplan-Meier method was used to calculate cumulative mortality rates at 1-, 5-, and 10-year follow-up, with survival curves plotted at 6-month intervals out to 12 years. Patients who did not die were censored at last date of follow-up. Cox regression was used to estimate hazard ratios (and corresponding 95% confidence intervals) of mortality over the full follow-up period by LDL-C. A crude model was first fit followed by an adjusted model that included covariates selected by a forward stepwise approach using an entry *p*-value of < .01 A second adjusted model was fit that added initiation of statin use any time after 1-year of follow-up. Separate estimates for the relationship between initiation of statin use and mortality are not presented due to expected immortal time bias (i.e., requirement to be alive during follow-up to initiate statin use). Secondary analyses of lipid parameters used the same methods as for LDC-C and included categories of the T-C/HDL-C and triglycerides/HDL-C ratios.

Subgroup Analyses

Subgroup analyses for estimation of the relationship between LDL-C category and mortality included age (50-69, 70-89), sex (female, male), and baseline ASCVD risk classification (low/borderline, intermediate, high, risk not determined).

We used SAS, version 9.4 (SAS Institute) for all analyses.

RESULTS

The prevalence of patients within the six LDL-C categories was as follows: 30-79 (9.1%), 80-99 (18.3%), 100-129 (39.1%), 130-159 (24.4%), 160-189 (7.1%), or 190 mg/dL or higher (2.0%) (**Table 2)**. The mean age of patients ranged nominally across the six LDL-C categories from 60.7 to 61.7 years. There was a general indication of overall higher baseline risk in the group of patients with LDL-C from 30-79 mg/dL (**Table 2**) (consistent with the stated concern of potential reverse causation). This included a numerically higher prevalence of current smokers and those with a history of various comorbidities (e.g., atrial fibrillation, arrythmia, congestive heart failure, chronic obstructive pulmonary disease), as well as nominally higher prevalence of selected medication use (e.g., ACE inhibitors, beta-blockers, diuretics, opioids, direct oral anticoagulants). History of cancer was slightly higher in the two lowest LDL-C categories, whereas estimated 10-year ASCVD risk was highest in those with baseline LDL-C ≥190 mg/dL.

Overall Assessment of Mortality

The mean and median follow-up after excluding the study requirement to have survived at least 1-year after baseline cholesterol measurement was 6.1 and 5.9 years, respectively, and 17% of patients had 10 or more years of follow-up. In ascending order from lowest LDL-C category (30-79 mg/dL) to highest LDL-C category (≥190 mg/dL), 10-year cumulative mortality rates were U-shaped at 19.8%, 14.7%, 11.7%, 10.7%, 10.1%, and 14.0% (**Table 3, Figures 1 and 2**). Adjusted mortality hazard ratios (HR) (model 2), as compared to the referent group of LDL-C 80-99 mg/dL, were as follows: 30-79 mg/dL (1.23), 100-129 mg/dL (0.87), 130-159 mg/dL (0.88), 160-189 mg/dL (0.91), ≥190 mg/dL (1.19), respectively. Thus, the 3 LDL-C categories within the range of 100-189 mg/dL showed similar, slightly lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL.

Subgroup Analyses

For the 2 different age groups, the 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and slightly lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Table 3, Figure 2**). In a similar manner for both females and males, the 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and slightly lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Supplement Table 2**). Males with LDL-C ≥190 mg/dL did not have a significantly higher risk of mortality than those with LDL-C 80-99 mg/dL (adjusted HR = 1.06, 95% CI: 0.85-1.32). When stratified by 10-year ASCVD risk score, again, the 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and statistically lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Supplement Table 3**).

Secondary Lipid Measures

Patients with a T-C/HDL-C ratio >6.0 had a significantly higher risk of mortality than those with a T-C/HDL-C ratio ≤3.0 (adjusted HR = 1.28, 95% CI: 1.18-1.38, **Supplement Table 4**), with similar results by age (**Figure 2**). For the 3 T-C/HDL-C ratio categories ≤3.0, >3.0-4.0, and >4.0-5.0, risk of mortality was similar. The triglycerides/HDL-C ratio showed the most consistent evidence of a gradient relationship with mortality with lower values (quintiles) progressively conferring lower risk of mortality (**Supplement Table 5)** and similar results by age (**Figure 2**). Compared to patients in the highest quintile of triglycerides/HDL-C ratio (value of ≥3.44), those in the lowest quintile (value of ≤1.06) had an estimated 24% lower risk of mortality (adjusted HR = 0.76, 95% CI: 0.72-0.81). Thus, in aggregate and irrespective of age, the secondary lipid measures of T-C/HDL-C ratio and triglycerides/HDL-C ratio appeared to be

more predictive of mortality than LDL-C, and a triglycerides/HDL-C ratio about 1 or lower appears to be optimal.

DISCUSSION

In this analysis among non-diabetic primary prevention-type patients aged 50 to 89 years not on statin therapy at baseline, we found no evidence of a gradient relationship between LDL-C and long-term mortality risk. Instead, we observed that within the entire LDL-C range of 100-189 mg/dL, mortality risk was similar and slightly lower than the referent LDL-C category of 80-99 mg/dL. These data conflict with the prevailing belief that "lower LDL-C is better"[5-6] yet align closely with results from a large general population study from Denmark among adults with a mean age of 58 years.[26] In that study, a U-shaped relationship between LDL-C and long-term mortality was also observed, and the concentration of LDL-C associated with the lowest risk of all-cause mortality among individuals not receiving lipid lowering treatment was 140 mg/dL. Collectively, these results indicate that the "optimal" or "normal" range for LDL-C for primary prevention among adults is likely wide and considerably higher than the suggested optimal LDL-C level of ≤100 mg/dL.[5-6]

For multiple reasons, we chose to evaluate a population of non-diabetic primary prevention type adults aged 50 to 89 years not on statin therapy. First, both the prevalence and potential indication for initiating lipid-lowering therapy is relatively high in this population.[9,10,27] Second, prevailing guidelines and philosophy for initiating lipid-lowering therapy for secondary prevention of ASCVD and among persons with diabetes are well entrenched.[28-30] Third, consideration of initiating lipid-lowering therapy for primary prevention, particularly among older adults, should be carefully weighed based on empirical data[31-32] and potential side effects,

including but not limited to muscle pain or weakness[33] and increased risk of developing diabetes.[34-36]

Beyond our principal finding of no indication that "lower LDL-C is better," other prominent findings were that overall and independent of age, the T-C/HDL-C and triglycerides/HDL-C ratios were predictive of long-term mortality risk, the latter of which presented in a gradient manner. The importance of high HDL-C alone, or in conjunction with other lipids, has been recognized. In brief, oxidative stress and inflammation are integral in the pathophysiology of atherosclerosis and cardiovascular disease.[37] Importantly, HDL-C exerts several physiological roles, prevents oxidation of LDL, and inhibits expression of pro-inflammatory cytokines by macrophages, as well as expression of adhesion molecules by endothelial cells,[38-40] and it is inversely associated with both all cause and CVD mortality risks.[18-19] Moreover, it is likely not coincidental nor trivial that the field of life insurance medicine recognizes and prioritizes the importance of HDL-C over LDL-C in determining underwriting classifications.[16,17,41] Unfortunately, from a public health perspective, a meta-analysis of 31 randomized controlled trials on the use of HDL-C modifying treatments showed little to no effect on cardiovascular and all-cause mortality.[42]

There is an overall lack of consensus on the magnitude and statistical and clinical interpretation of the reduction in mortality risk potentially achieved with the use of LDL-C lowering therapies. Multiple reviews suggest that absolute mortality risk reductions from treatment with statins are small as compared to the more frequent reporting and emphasis of relative risk reductions.[43-46] Moreover, mortality reductions with recent use of PCSK-9 inhibitors to lower LDL-C have been unimpressive.[47] Our postulate from both this review (e.g.,[11]) and empirical analysis is that whatever small reductions in mortality risk may occur with use of

LDL-C lowering therapies, they are most likely not causally related to LDL-C lowering, but potentially to more broad pleiotropic effects. For example, statin use has been shown to reduce inflammatory markers,[48] reduce vascular endothelial growth factor (VEGF) concentrations,[49] reduce platelet activity,[50] and increase nitric oxide bioavailability and stabilize atherosclerotic plaques.[51] These potential mechanisms of statins, rather than concomitant lowering of LDL-C per se, may be expected to result in some reduction of ASCVD events.

Arguably, it is irrelevant to patients as to the exact mechanism(s) by which use of statins may result in small absolute reductions in mortality risk. However, research suggests that use of statins (and possibly other LDL-C lowering therapies) may provide some patients with a false sense of security,[52] as expressed by higher caloric and fat intake and faster increase in BMI for statin users than for nonusers.[53] This observation places a premium on health professionals promoting established (causal) mechanisms that reduce future risk of major ASCVD events, including weight, blood pressure, and blood sugar control, physical activity, avoidance of smoking, and stress reduction. Similarly, our results suggest that adult non-diabetic patients counselled for primary prevention of ASCVD be apprised of their estimated future risk of ASCVD with minimal consideration of their LDL-C concentration and more consideration of the T-C/HDL and triglyceride/HDL-C ratios along with other known causes of ASCVD (e.g., smoking, physical inactivity). Moreover, use of coronary artery calcium scoring in primary prevention is supported by a wealth of data showing that it substantially improves risk prediction including when combined with traditional risk factors and scores.[54-56] Lastly, our analysis indicates that the routinely used ACC-ASCVD Risk Estimator over-emphasizes patient risk simply on age (i.e., intermediate or high-risk classification) when in the context of having

"normal" parameters otherwise, and that the equation itself may have differential validity by race.

Limitations

Our study has limitations. First, we were unable to assess cause-specific mortality which would have provided additional insight into the relationship between LDL-C and CVD mortality. Second, we chose the index date for follow-up mortality assessment to begin 1-year after baseline cholesterol measurement to ideally minimize potential bias due to reverse causation (i.e., low LDL-C being an overall marker of malnutrition and poor health). However, low LDL-C has been frequently reported in cancer patients (e.g.,[25,57,58]) and many cancers have a viral etiologic component[59] and with potentially long latency. Theoretically, some patients with the lowest LDL-C values in our analysis may have been in the early stages of cancer development and hence elevated long-term mortality risk. This is why we chose LDL-C 80-99 mg/dL as the referent group (rather than 30-79 mg/dL), and the observation that mortality risk was similar across a wide range of LDL-C values (100–189 mg/dL) argues against appreciable bias due to reverse causation. Third, absence of statin use at baseline and within the first year of the study (inclusion criterion) was based on patient reported data in the EMR and not from prescription data – this leaves open the possibility for some misclassification. Lastly, we cannot rule out potential residual confounding despite statistical adjustment for a large set of covariates associated with mortality.

Conclusions

Our analysis indicates that among non-diabetic primary prevention-type patients aged 50 to 89 years and not on statin therapy, the lowest risk for long-term mortality exists in the wide LDL-C range of 100-189 mg/dL which is much higher than current recommendations. Our

analysis also shows that lower T-C/HDL-C and triglycerides/HDL-C ratios are independently associated with lower mortality risk, whereas LDL-C appears to be of limited to no predictive value. Lastly, our analysis indicates that the ACC-ASCVD Risk Estimator routinely used to estimate 10-year risk of ASCVD, and corresponding risk classification (with corresponding pharmacological treatment implications), overemphasizes individual patient risk by age alone and may have differential validity by race. Collectively, these observations suggest that adult non-diabetic patients counselled for primary prevention of ASCVD be apprised of their estimated future risk of ASCVD with minimal consideration of their LDL-C concentration and more consideration of the T-C/HDL and triglycerides/HDL-C ratios along with other established causes of ASCVD (e.g., high blood pressure, smoking, physical inactivity) and potentially coronary artery calcium scoring.

Figure Legends

Figure 1. Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C categories (130-159, 160-189, ≥190 mg/dL).

Figure 2. Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals (vertical lines) across categories of LDL cholesterol (top), total cholesterol to HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio (bottom). The left side of the graph is for patients aged 50-69 years; the right side is for patients aged 70-89 years. The dashed line reflects the referent group null value (1.0) for the HR. Q: quintile.

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Primary Funding Source. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests Statement. None.

Patient and Public Involvement. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

Patient Consent for Publication. Not applicable.

Ethics Approval. The Quality Improvement Review Committee and Institutional Review Board at the University of Pittsburgh Medical Center provided ethical review and approval of the study as an exempt protocol, and all data remained deidentified for this analysis.

Provenance and Peer Review. Not commissioned, externally peer reviewed.

Reproducible Research Statement. *Study protocol*: No separate study protocol was required a priori, as this retrospective analysis was deemed a quality improvement initiative with ethical review and approval granted by the UPMC Quality Improvement Review Committee and Institutional Review Board. *Statistical code*: Selected statistical code may be requested from Dr. Kevin Kip (e-mail, kipke2@upmc.edu*). Data set*: The data set contains protected health information and will not be available.

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Table 1. ASCVD 10-Year Risk Calculations for Primary Prevention* by Age, Race, and Sex

	White Male		Black (AA) Male		White Female		Black (AA) Female	
Age	10-yr risk	Risk Category	10-yr risk	Risk Category	10-yr risk	Risk Category	10-yr risk	Risk Category
50	3.5%	Low	5.2%	Borderline	1.4%	Low	2.2%	Low
51	3.8%	Low	5.4%	Borderline	1.5%	Low	2.4%	Low
52	4.2%	Low	5.7%	Borderline	1.7%	Low	2.6%	Low
53	4.6%	Low	6.0%	Borderline	1.8%	Low	2.9%	Low
54	5.1%	Borderline	6.2%	Borderline	2.0%	Low	3.1%	Low
55	5.6%	Borderline	6.5%	Borderline	2.2%	Low	3.4%	Low
56	6.1%	Borderline	6.8%	Borderline	2.4%	Low	3.7%	Low
57	6.6%	Borderline	7.1%	Borderline	2.6%	Low	4.0%	Low
58	7.2%	Borderline	7.4%	Borderline	2.9%	Low	4.4%	Low
59	7.9%	Intermediate	7.7%	Intermediate	3.1%	Low	4.7%	Low
60	8.5%	Intermediate	8.0%	Intermediate	3.5%	Low	5.1%	Borderline
61	9.2%	Intermediate	8.3%	Intermediate	3.8%	Low	5.5%	Borderline
62	10.0%	Intermediate	8.7%	Intermediate	4.2%	Low	6.0%	Borderline
63	10.8%	Intermediate	9.0%	Intermediate	4.6%	Low	6.4%	Borderline
64	11.7%	Intermediate	9.3%	Intermediate	5.1%	Borderline	6.9%	Borderline
65	12.5%	Intermediate	9.7%	Intermediate	5.6%	Borderline	7.4%	Borderline
66	13.5%	Intermediate	10.0%	Intermediate	6.2%	Borderline	8.0%	Intermediate
67	14.5%	Intermediate	10.4%	Intermediate	6.9%	Borderline	8.5%	Intermediate
68	15.5%	Intermediate	10.7%	Intermediate	7.6%	Intermediate	9.1%	Intermediate
69	16.6%	Intermediate	11.1%	Intermediate	8.4%	Intermediate	9.7%	Intermediate
70	17.8%	Intermediate	11.5%	Intermediate	9.3%	Intermediate	10.4%	Intermediate
71	19.0%	Intermediate	11.9%	Intermediate	10.3%	Intermediate	11.1%	Intermediate
72	20.2%	High	12.3%	Intermediate	11.3%	Intermediate	11.8%	Intermediate
73	21.5%	High	12.7%	Intermediate	12.5%	Intermediate	12.5%	Intermediate
74	22.9%	High	13.1%	Intermediate	13.8%	Intermediate	13.3%	Intermediate
75	24.3%	High	13.5%	Intermediate	15.3%	Intermediate	14.1%	Intermediate
76	25.7%	High	13.9%	Intermediate	16.8%	Intermediate	15.0%	Intermediate
77	27.3%	High	14.3%	Intermediate	18.5%	Intermediate	15.9%	Intermediate
78	28.8%	High	14.7%	Intermediate	20.4%	High	16.8%	Intermediate
79	30.4%	High	15.2%	Intermediate	22.5%	High	17.7%	Intermediate

*Defined as non-diabetic persons with approximate guideline-driven "normal" values for total cholesterol (190 mg/dL), LDL cholesterol (125 mg/dL), HDL cholesterol (45 mg/dL for males, 55 mg/dL for females), systolic blood pressure (125 mmHg), diastolic blood pressure (75 mmHg), no history of smoking, not on anti-hypertensive medications, not on statin therapy, not on aspirin therapy.

https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

Table 2. Baseline Characteristics of Study Population by Baseline LDL Cholesterol Value

Characteristic	Baseline LDL Cholesterol Value (mg/dL) 30 to 79 (n=16,162)	80 to 99 (n=32,517)	100 to 129 (n=69,399)	130 to 159 (n=43,333)	160 to 189 (n=12,663)	190 or higher (n=3,586)
Age, mean, median	61.7, 59	61.4, 59	61.1, 59	60.7, 59	60.7, 59	61.4, 60
Age, n, (%)						
50 to 59	8167, (50.5)	16551, (50.9)	35706, (51.5)	22811, (52.6)	6694, (52.9)	1765, (49.2)
60 to 69	4686, (29.0)	9742, (30.0)	21632, (31.2)	13797, (31.8)	4029, (31.8)	1162, (32.4)
70 to 79	2221, (13.7)	4399, (13.5)	8808, (12.7)	5103, (11.8)	1439, (11.4)	514, (13.3)
80 and older	1088, (6.7)	1825, (5.6)	3253, (4.7)	1622, (3.7)	501, (4.0)	145, (4.0)
Sex						
Female	9027, (55.9)	18965, (58.3)	42697, (61.5)	28034, (64.7)	8654, (68.3)	2562, (71.4)
Male	7135, (44.1)	13552, (41.7)	26702, (38.5)	15299, (35.3)	4009, (31.7)	1024, (28.6)
Race						
Black	1700, (10.5)	2350, (7.2)	3855, (5.6)	2076, (4.8)	607, (4.8)	208, (5.8)
White	14462, (89.5)	30167, (92.8)	65544, (94.4)	41257, (95.2)	12056, (95.2)	3378, (94.2)
Former smoker, n, (%)	4172, (27.3)	8270, (26.9)	16871, (25.7)	10354, (25.3)	2933, (24.5)	858, (25.5)
Current smoker, n, (%)	3287, (21.5)	5430, (17.6)	9822, (15.0)	6274, (15.3)	1998, (16.7)	668, (19.8)
Body mass index, mean, median	28.4, 26	28.7, 26	28.8, 27	28.8, 27	28.8, 27	28.6, 27
History of obesity, n, (%)	6011, (37.2)	12438, (38.3)	26946, (38.8)	16949, (39.1)	4899, (38.7)	1326, (37.0)
History of obstructive sleep apnea, n, (%)	932, (5.8)	1831, (5.6)	3619, (5.2)	1931, (4.5)	507, (4.0)	136, (3.8)
History of hypertension, n, (%)	5540, (34.3)	11331, (34.8)	23634, (34.1)	13435, (31.0)	3621, (28.6)	1060, (29.6)
History of atrial fibrillation, n, (%)	687, (4.3)	1181, (3.6)	1930, (2.8)	845, (2.0)	214, (1.7)	60, (1.7)
History of arrythmia, n, (%)	1178, (7.3)	2254, (6.9)	4143, (6.0)	2054, (4.7)	528, (4.2)	133, (3.7)
History of valvular heart disease, n, (%)	431, (2.7)	834, (2.6)	1505, (2.2)	798, (1.8)	246, (1.9)	60, (1.7)
History of congestive heart failure, n, (%)	251, (1.6)	375, (1.2)	597, (0.9)	245, (0.6)	80, (0.6)	15, (0.4)
History of deep vein thrombosis, n, (%)	184, (1.1)	323, (1.0)	667, (1.0)	356, (0.8)	93, (0.8)	25, (0.7)
History of cancer, n, (%)	1554, (9.6)	2916, (9.0)	5597, (8.0)	3348, (7.7)	912, (7.2)	281, (7.8)
History of chronic obstructive pulmonary disease, n, (%)	1147, (7.1)	1783, (5.5)	3156, (4.5)	1666, (3.8)	474, (3.7)	146, (4.1)
History of chronic kidney disease, n, (%)	329, (2.0)	424, (1.3)	695, (1.0)	356, (0.8)	126, (1.0)	42, (1.2)
History of depression, n, (%)	1985, (12.3)	3981, (12.2)	8327, (12.0)	5214, (12.0)	1606, (12.7)	440, (12.3)
Systolic BP (mmHg), mean, median	128.8, 128	128.7, 127	129.0, 128	129.3, 128	129.8, 128	131.6, 130
Diastolic BP (mmHg), mean, median	77.5, 78	77.8, 78	78.5, 80	79.0, 80	79.1, 80	79.8, 80
HDL cholesterol (mg/dL), mean, median	60.0, 57	58.1, 56	57.4, 55	56.9, 55	56.2, 54	55.4, 53
Total/HDL cholesterol, mean, median	2.8, 3	3.2, 3	3.6, 3	4.2, 4	4.8, 5	5.7, 5
Triglycerides (mg/dL), mean, median	112.8, 90	109.0, 91	115.2, 100	125.0, 111	138.4, 125	166.6, 149
Hemoglobin (g/dL), mean, median	13.6, 14	13.8, 14	14.0, 14	14.1, 14	14.2, 14	14.1, 14
Glucose (mg/dL), mean, median	99.0, 94	97.6, 94	97.2, 94	96.9, 94	98.1, 95	100.4, 96

ACE Inhibitor, n, (%)	2060, (12.7)	3992, (12.3)	8024, (11.6)	4454, (10.3)	1205, (9.5)	328, (9.1)
Angiotensin receptor blocker, n, (%)	1028, (6.4)	2017, (6.2)	3927, (5.7)	2018, (4.7)	558, (4.4)	156, (4.4)
Beta blocker, n, (%)	2747, (17.0)	4827, (14.8)	8969, (12.9)	4709, (10.9)	1352, (10.7)	430, (12.0)
Calcium blocker, n, (%)	1931, (11.9)	3501, (10.8)	6612, (9.5)	3534, (8.2)	956, (7.5)	297, (8.3)
Diuretic, n, (%)	2662, (16.5)	4763, (14.6)	8814, (12.7)	4717, (10.9)	1257, (9.9)	390, (10.9)
Anti-depressant, n, (%)	3497, (21.6)	6504, (20.0)	13784, (19.9)	8624, (19.9)	2628, (20.8)	797, (22.2)
Opioids, n, (%)	3319, (20.5)	5400, (16.6)	9688, (14.0)	5711, (13.2)	1599, (12.6)	523, (14.2)
Anti-platelet agent, n, (%)	2209, (13.7)	4319, (13.3)	9006, (13.0)	5057, (11.7)	1267, (10.0)	402, (11.2)
Aspirin, n, (%)	3082, (19.1)	6087, (18.7)	12511, (18.0)	7117, (16.4)	1922, (15.2)	586, (16.3)
Direct oral anticoagulant, n, (%)	423, (2.6)	684, (2.1)	1086, (1.6)	479, (1.1)	133, (1.1)	33, (0.9)
ASCVD 10-year risk, mean, median	10.0, 6	10.0, 6	9.6, 6	9.6, 6	10.1, 7	12.0, 9
ASCVD 10-year risk, n, (%)						
Low	6204, (58.8)	12166, (58.3)	25457, (58.6)	15048, (57.3)	4144, (54.1)	900, (43.0)
Intermediate	2887, (27.4)	5804, (27.8)	12514, (28.8)	8161, (31.1)	2596, (33.9)	839, (40.0)
High	1459, (13.8)	2888, (13.8)	5472, (12.6)	3045, (11.6)	913, (11.9)	356, (17.0)
Started statin use >1 year after baseline measurement, n, (%)	484, (3.0)	921, (2.8)	2948, (4.2)	3448, (8.0)	1600, (12.6)	644, (18.0)

595

Table 3. Risks and Hazard Ratios of Death by LDL Cholesterol Level at Baseline

LDL cholesterol (mg/dL)	n	Cumulative incidence (%) 1-year	5-year	10-year	Crude HR	Adj. HR Model 1	Adj. HR Model 2	95% C.I.
30 to 79	16162	2.7	11.3	19.8	1.41	1.23	1.23	1.17 – 1.30
80 to 99	32517	1.7	8.1	14.7	1.0	1.0	1.0	-----
100 to 129	69399	1.1	6.0	11.7	0.77	0.86	0.87	0.83 – 0.91
130 to 159	43333	1.0	5.2	10.7	0.69	0.85	0.88	0.84 – 0.93
160 to 189	12663	1.2	5.4	10.1	0.68	0.86	0.91	0.84 – 0.98
190 or higher	3586	1.8	7.9	14.0	0.96	1.09	1.19	1.06 – 1.34
Patients aged 50-69								
30 to 79	12853	1.8	8.1	14.2	1.52	1.30	1.20	1.20 – 1.39
80 to 99	26293	1.1	5.2	9.6	1.0	1.0	1.0	-----
100 to 129	57338	0.7	3.9	7.6	0.76	0.86	0.86	0.81 – 0.92
130 to 159	36608	0.7	3.4	6.9	0.69	0.82	0.85	0.79 – 0.91
160 to 189	10723	0.9	3.7	6.5	0.70	0.83	0.89	0.81 – 0.99
190 or higher	2927	1.2	5.7	9.4	1.01	1.10	1.24	1.06 – 1.44
Patients aged 70-89								
30 to 79	3309	6.3	24.3	42.7	1.25	1.15	1.15	1.06 – 1.25
80 to 99	6224	4.5	20.5	37.2	1.0	1.0	1.0	-----
100 to 129	12061	2.7	16.0	31.4	0.80	0.87	0.87	0.82 – 0.93
130 to 159	6725	2.8	15.3	30.8	0.76	0.89	0.91	0.84 – 0.98
160 to 189	1940	2.9	15.0	29.7	0.75	0.89	0.92	0.82 – 1.04
190 or higher	659	4.5	17.5	34.2	0.90	1.08	1.15	0.96 – 1.37

Model 1: Adjusted for age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids.
Model 2: Adjusted for Model 1 covariates + statin initiation >1 year after baseline cholesterol measurement.

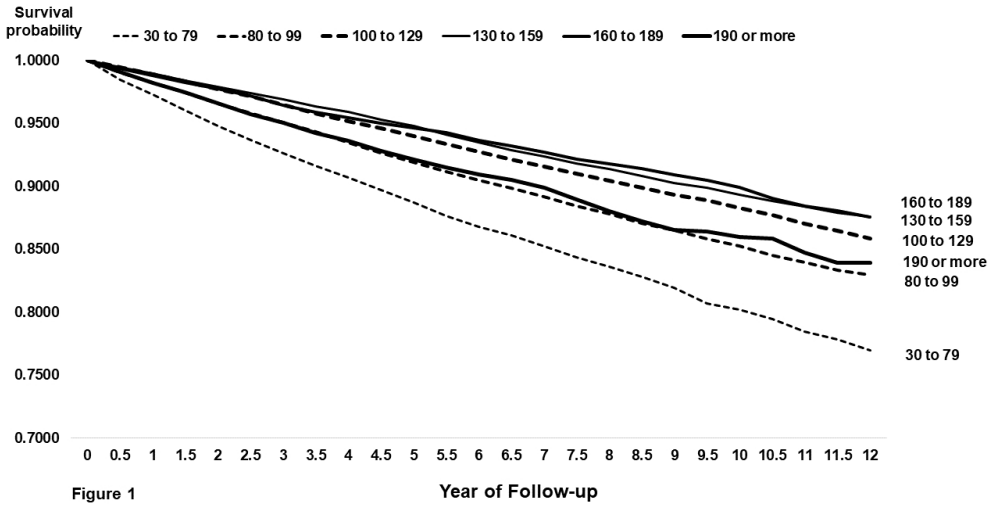

Figure 1. Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C categories (130-159, 160-189, >=190 mg/dL).

855x481mm (38 x 38 DPI)

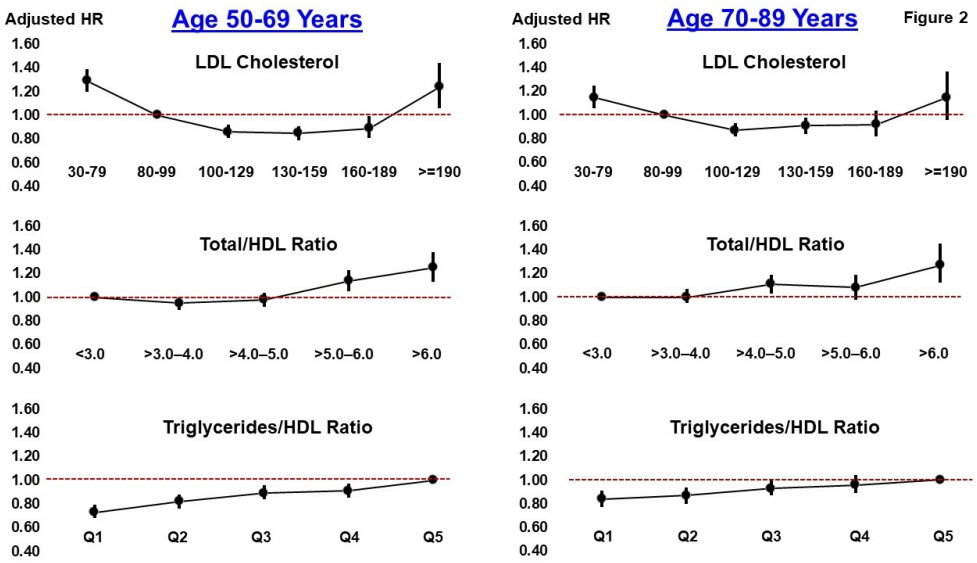

Figure 2. Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals (vertical lines) across categories of LDL cholesterol (top), total cholesterol to HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio (bottom). The left side of the graph is for patients aged 50-69 years; the right side is for patients aged 70-89 years. The dashed line reflects the referent group null value (1.0) for the HR. Q: quintile.

338x190mm (96 x 96 DPI)

Supplement Table 1. Maximum/Range of Total Cholesterol (T-C) Values Along with T-C to HDL-C Cholesterol Ratios for Different Life Insurance Underwriting Categories

Age Category	Life Insurance Underwriting Category			
	Elite Plus* **(ages 18-75)**	**Preferred Plus*** **(ages 18-75)**	**Standard Plus** **(ages 18-75)**	**Standard** **(all ages)**
54 and younger	220/4.5	240/5.0	260/6.0 or 280/5.5 280/6.5 or 300/6.0	-----
55 to 69	230/4.5	260/5.5 or 280/5.0	150 to 300/7.0 or 150 to 310/6.5	-----
70 and older	150 to 240/5.0	150 to 280/5.5 or 150 to 300/5.0	Current medication acceptable (all ages)	-----
0 to 44	-----	-----	-----	≤300/9.6 or >300/8.0
45 to 65	-----	-----	-----	≤350/9.6 or 351 to 400/8.0
66 and older	-----	-----	-----	150 to 350/10.5 or 351 to 375/9.6

*Current medication OK if acceptable level maintained for at least 12 months (all ages)

Source: http://www.cassaniinsurance.com/wp-content/uploads/2018/02/Met-Life-condensed_uw_guide.pdf

Supplement Table 2. Risks and Hazard Ratios of Death by LDL Cholesterol Levels at Baseline Stratified by Sex at Baseline

		Cumulative incidence (%)			Crude	Adj. HR	95%
LDL Cholesterol (mg/dL)	**n**	**1-year**	**5-year**	**10-year**	**HR**	**Model**	**C.I.**
Female							
30 to 79	9027	2.3	9.4	17.1	1.42	1.23	1.14 – 1.33
80 to 99	18965	1.4	6.7	12.3	1.0	1.0	-----
100 to 129	42697	0.8	5.2	10.5	0.82	0.88	0.83 – 0.94
130 to 159	28034	0.9	4.8	10.2	0.78	0.89	0.83 – 0.95
160 to 189	8654	1.1	5.2	9.7	0.80	0.91	0.82 – 1.00
190 or higher	2562	1.8	7.8	14.6	1.20	1.24	1.08 – 1.42
Male							
30 to 79	7135	3.3	13.7	23.4	1.37	1.22	1.13 – 1.32
80 to 99	13552	2.2	10.0	18.4	1.0	1.0	-----
100 to 129	26702	1.5	7.2	13.8	0.73	0.86	0.80 – 0.91
130 to 159	15299	1.3	6.0	11.5	0.61	0.85	0.79 – 0.92
160 to 189	4009	1.4	5.6	10.8	0.58	0.90	0.79 – 1.02
190 or higher	1024	1.8	8.1	12.2	0.72	1.06	0.85 – 1.32

Model: Adjusted for race, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Table 3. Risks and Hazard Ratios of Death by LDL Cholesterol Levels at Baseline Stratified by ASCVD Risk Classification

LDL cholesterol (mg/dL)	n	Cumulative incidence (%) 1-year	5-year	10-year	Crude HR	Adj. HR Model	95% C.I.
Low or Borderline Risk							
30 to 79	6204	1.5	6.7	12.2	1.66	1.51	1.34 – 1.70
80 to 99	12166	1.0	4.2	7.2	1.0	1.0	-----
100 to 129	25457	0.6	2.9	5.6	0.73	0.78	0.70 – 0.86
130 to 159	15048	0.5	2.5	5.2	0.66	0.75	0.66 – 0.84
160 to 189	4144	0.6	2.7	4.7	0.65	0.75	0.62 – 0.91
190 or higher	900	0.6	4.3	7.7	1.05	1.18	0.86 – 1.61
Intermediate Risk							
30 to 79	2887	3.5	15.6	27.1	1.38	1.25	1.11 – 1.40
80 to 99	5804	2.6	11.4	21.3	1.0	1.0	-----
100 to 129	12514	1.6	8.4	16.6	0.75	0.80	0.73 – 0.87
130 to 159	8161	1.4	7.0	13.8	0.61	0.69	0.62 – 0.77
160 to 189	2596	1.5	7.0	12.2	0.58	0.68	0.58 – 0.79
190 or higher	839	2.6	9.6	14.8	0.77	0.89	0.70 – 1.13
High Risk							
30 to 79	1459	7.9	28.0	49.9	1.25	1.17	1.04 – 1.32
80 to 99	2888	5.4	23.6	43.3	1.0	1.0	-----
100 to 129	5472	3.4	19.3	36.6	0.82	0.85	0.77 – 0.92
130 to 159	3045	3.8	17.6	33.5	0.73	0.78	0.70 – 0.87
160 to 189	913	3.9	17.9	32.3	0.75	0.82	0.70 – 0.97
190 or higher	356	4.1	15.7	34.2	0.71	0.81	0.63 – 1.04
ASCVD Risk Not Determined							
30 to 79	5612	2.3	10.1	18.0	1.45	1.34	1.22 – 1.48
80 to 99	11659	1.3	6.9	13.0	1.0	1.0	-----
100 to 129	25956	0.8	5.2	10.6	0.80	0.85	0.79 – 0.91
130 to 159	17079	0.8	4.6	10.1	0.74	0.85	0.78 – 0.92
160 to 189	5010	1.0	4.5	9.5	0.72	0.85	0.75 – 0.96
190 or higher	1491	1.5	7.3	12.6	0.98	1.17	0.97 – 1.41

Model: Adjusted for BMI, history of the following in the past year: atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, glucose, and the following medications in the past year: aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Table 4. Risks and Hazard Ratios of Death by Total Cholesterol to HDL Cholesterol Ratio at Baseline

		Cumulative incidence (%)			Crude	Adj. HR	95%
Total/HDL Cholesterol Ratio	**n**	**1-year**	**5-year**	**10-year**	**HR**	**Model**	**C.I.**
3.0 or lower	52405	1.4	6.6	12.3	1.0	1.0	-----
> 3.0 to 4.0	63482	1.2	6.3	12.3	0.98	0.98	0.94 – 1.02
> 4.0 to 5.0	37907	1.4	6.7	12.8	1.04	1.04	0.99 – 1.09
> 5.0 to 6.0	16053	1.5	7.2	14.1	1.15	1.12	1.06 – 1.19
> 6.0	7813	2.1	9.2	15.2	1.32	1.28	1.18 – 1.38
Patients aged 50-69							
3.0 or lower	42650	0.9	4.3	7.8	1.0	1.0	-----
> 3.0 to 4.0	51918	0.8	4.0	7.8	0.99	0.95	0.89 – 1.00
> 4.0 to 5.0	31713	1.0	4.4	8.5	1.10	0.98	0.92 – 1.04
> 5.0 to 6.0	13706	1.1	5.4	10.3	1.34	1.14	1.05 – 1.23
> 6.0	6755	1.7	6.8	11.7	1.60	1.25	1.13 – 1.38
Patients aged 70-89							
3.0 or lower	9755	3.5	17.3	32.9	1.0	1.0	-----
> 3.0 to 4.0	11564	3.1	16.9	32.4	0.97	1.00	0.95 – 1.07
> 4.0 to 5.0	6194	3.7	18.5	35.2	1.08	1.11	1.03 – 1.19
> 5.0 to 6.0	2347	4.0	17.8	35.7	1.10	1.08	0.98 – 1.19
> 6.0	1058	4.8	24.4	38.4	1.30	1.27	1.12 – 1.45

Model: Adjusted for race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Table 5. Risks and Hazard Ratios of Death by Triglycerides to HDL-C Ratio at Baseline

Triglycerides/ HDL-C Ratio	n	Cumulative incidence (%) 1-year	5-year	10-year	Crude HR	Adj. HR Model	95% C.I.
Quintile 1	35533	0.9	5.1	9.7	0.63	0.76	0.72 – 0.81
Quintile 2	35403	1.2	6.2	11.9	0.77	0.84	0.80 – 0.88
Quintile 3	35523	1.4	6.9	13.1	0.86	0.89	0.85 – 0.94
Quintile 4	35479	1.5	7.2	13.9	0.91	0.92	0.88 – 0.97
Quintile 5	35513	1.7	7.9	15.1	1.0	1.0	-----
Patients aged 50-69							
Quintile 1	29314	0.6	3.1	5.9	0.53	0.73	0.68 – 0.79
Quintile 2	29313	0.8	3.9	7.3	0.66	0.82	0.76 – 0.88
Quintile 3	29213	0.9	4.4	8.5	0.76	0.89	0.84 – 0.96
Quintile 4	29425	1.0	4.7	9.3	0.83	0.91	0.85 – 0.97
Quintile 5	29302	1.3	5.8	10.8	1.0	1.0	-----
Patients aged 70-89							
Quintile 1	6169	2.8	15.9	30.7	0.80	0.84	0.77 – 0.91
Quintile 2	6180	3.2	16.4	31.9	0.83	0.87	0.80 – 0.94
Quintile 3	6176	3.7	17.9	33.6	0.91	0.93	0.87 – 1.01
Quintile 4	6180	3.7	18.5	34.6	0.93	0.96	0.89 – 1.04
Quintile 5	6179	4.1	19.4	37.0	1.0	1.0	-----

Model: Adjusted for race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

APPENDIX – STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Is LDL cholesterol associated with long-term mortality among primary prevention adults? A retrospective cohort study from a large healthcare system

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-077949.R1
Article Type:	Original research
Date Submitted by the Author:	07-Mar-2024
Complete List of Authors:	Kip, Kevin; University of Pittsburgh Medical Center Health System, Clinical Analytics Diamond, David; University of South Florida, Department of Psychology Mulukutla, Suresh; University of Pittsburgh, Heart and Vascular Institute Marroquin, Oscar; UPMC, Clinical Analytics
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	EPIDEMIOLOGY, Primary Prevention, Adult cardiology < CARDIOLOGY

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Is LDL cholesterol associated with long-term mortality among primary prevention adults? A retrospective cohort study from a large healthcare system

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Abstract

Objectives: Among primary prevention-type adults not on lipid-lowering therapy, conflicting results exist on the relationship between low density lipoprotein cholesterol (LDL-C) and long-term mortality. We evaluated this relationship in a real-world evidence population of adults.

Design: Retrospective cohort study.

Setting: Electronic medical record data for adults, from January 4, 2000, through December 31, 2022, were extracted from the University of Pittsburgh Medical Center healthcare system.

Participants: Non-diabetic adults aged 50-89 years not on statin therapy at baseline or within 1-year and classified as primary prevention-type patients. To mitigate potential reverse causation, patients who died within 1-year or had baseline total cholesterol (T-C) ≤120 mg/dL or LDL-C <30 mg/dL were excluded.

Main exposure measure: Baseline LDL-C categories of 30-79, 80-99, 100-129, 130-159, 160-189, or ≥190 mg/dL.

Main outcome measure: All-cause mortality with follow-up starting 365 days after baseline cholesterol measurement.

Results: 177,860 patients with mean (SD) age of 61.1 (8.8) years and mean (SD) LDL-C of 119 (31) mg/dL were evaluated over mean of 6.1 years of follow-up. A U-shaped relationship was observed between the six LDL-C categories and mortality with crude 10-year mortality rates of 19.8%, 14.7%, 11.7%, 10.7%, 10.1%, and 14.0%, respectively. Adjusted mortality hazard ratios (HRs) as compared with the referent group of LDL-C 80-99 mg/dL were: 30-79 mg/dL (HR 1.23, 95% CI 1.17-1.30), 100-129 mg/dL (0.87, 0.83-0.91), 130-159 mg/dL (0.88, 0.84-0.93), 160-189 mg/dL (0.91, 0.84-0.98), ≥190 mg/dL (1.19, 1.06-1.34), respectively. Unlike LDL-C,

both T-C/HDL cholesterol and triglycerides/HDL cholesterol ratios were independently associated with long-term mortality.

Conclusions. Among non-diabetic primary prevention-type patients aged 50-89 years and not on statin therapy, the lowest risk for long-term mortality appears to exist in the wide LDL-C range of 100-189 mg/dL, which is much higher than current recommendations. For counseling these patients, minimal consideration should be given to LDL-C concentration.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The cohort consisted of a large, "real-world" sample of adults across a large health system with long-term follow-up and sufficient precision for subgroup analyses.
- The study design mitigated potential for reverse causation of mortality by excluding patients who died within 1-year of baseline cholesterol measurement or had exceptionally low total or LDL-C levels at baseline.
- The analysis was limited to all-cause mortality and thus was unable to assess cause-specific mortality.

INTRODUCTION

Heart disease (HD), which includes atherosclerotic cardiovascular disease (ASCVD) as its primary component, is the leading cause of death in the United States.[1-2] A near universal but not absolute belief[3] is that high total cholesterol (T-C), low density lipoprotein cholesterol (LDL-C) in particular (the so-called "bad" cholesterol), is a root cause of ASCVD,[4] and that "lower is better" with a suggested optimal LDL-C level at or below 100 mg/dL.[5-6] In this regard, the American College of Cardiology (ACC) unequivocally implicates elevated LDL-C as a *de-facto* cause of ASCVD (and hence mortality) by stating that lowering of LDL-C with moderate intensity generic statins allows for efficacious and cost-effective primary prevention for those patients with an estimated 10-year risk of ASCVD ≥7.5%.[7] Risk of ASCVD is often estimated using the online ACC-ASCVD Risk Estimator,[8] and as seen in **Supplement Table 1**, all males ages 59 and older even in the presence of "normal" ASCVD risk factors (lipids included) may be classified at intermediate or high risk of ASCVD, and thus candidates for LDL-C lowering therapy.

The overall belief that "lower LDL-C is better" for primary prevention of ASCVD is supported by the 25.5% estimated prevalence of use of statins in this setting for adults aged 40 to 75 years.[9] Despite the generally accepted belief that "lower LDL-C is better," meta-analyses indicate that high LDL-C is associated with at most a small increased absolute risk of ASCVD or premature mortality. First, in brief, in an extensive recent meta-analysis published in 2023 of 60 randomized controlled trials that compared either placebo, usual care or less-intensive therapy to active or more potent lipid-lowering therapy, the number needed to treat (NNT) to reduce one death with active or more potent lipid-lowering therapy was exceptionally high at 754 persons. Moreover, there was no relationship between LDL-C percent lowering and risk of cardiovascular

mortality.[10] Similarly, whereas an earlier meta-analysis published in 2010 indicated that both use and dose of statin therapy reduced the relative risk of major vascular events and all-cause mortality, absolute risk reductions were very small (e.g., 0.2% absolute risk reduction in all-cause mortality per 1.0 mmol/L reduction in LDL-C).[11] In the context of lipid-lowering therapy, these findings call into question the prevailing belief that "lower LDL-C is better" at least in terms of any appreciable clinical benefit.

Second, acute coronary syndromes (ACS) routinely occur in patients with "normal" LDL-C. For example, in a large cohort of 136,905 patients hospitalized with CAD (79% attributed to ACS), of whom, 21% were on lipid-lowering therapy at admission, less than one-quarter had an admission LDL-C >130 mg/dL.[12] In addition, women are generally considered to be at overall lower risk of CHD mortality than men (e.g.,[13]), yet tend to have higher T-C and LDL-C,[14] which is counterintuitive to higher LDL-C being associated with ASCVD and premature mortality.

Third, the field of life insurance medicine, which focuses principally on predicting mortality hazards,[15] arguably conducts the most robust actuarial analyses of life expectancy. Notably, in this field, the T-C/HDL-C ratio has been shown to be the best single measure of all-cause mortality risk among various lipid tests, including LDL-C.[16] This is further supported by examination of selected life insurance underwriting guidelines (obtained publicly and summarized) from a large US insurance company.[17] As seen in **Supplement Table 2**, T-C and HDL-C are used jointly in policy underwriting, whereas LDL-C is not used, and lipid-lowering therapy is not emphasized. Moreover, notwithstanding other important patient factors (e.g., blood pressure, smoking, etc.), **Supplement Table 2** shows that a person 70 years of age or older can potentially qualify for a "preferred-plus" life insurance policy having a T-C value as high as 300

mg/dL so long as the T-C/HDL-C ratio is 5.0 or lower (i.e., HDL-C ≥60 mg/dL). This aligns with meta-analyses/systematic reviews that report HDL-C to be inversely associated with all cause and CVD mortality risks.[18-19]

The above-described examples of conflicting beliefs and findings, along with general propensity for health professionals to prescribe LDL-C lowering therapies for primary prevention based in part through routine risk assessment with the ACC-ASCVD Risk Estimator, call for a critical appraisal and analysis of the relationship between LDL-C and long-term risk of mortality in adults. Therefore, within a large, "real-world" healthcare system, we evaluated the association between LDL-C and all-cause long-term mortality among non-diabetic primary prevention-type adults aged 50 to 89 years. The analysis did not focus on the use of statin therapy for primary prevention.

METHODS

We conducted a retrospective cohort study of adults aged 50 to 89 years with hospital and/or office visit data captured through the University of Pittsburgh Medical Center (UPMC) electronic medical record (EMR) system. The date period for analysis was January 4, 2000, through December 31, 2022. The Quality Improvement Review Committee and Institutional Review Board provided ethical review and approval of the study as an exempt protocol (Project ID: 4565), and all data remained deidentified for this analysis. Conduct and dissemination of results from this observational study were performed in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement.

Data sources

Health-related data captured in the UPMC EMR and its ancillary clinical systems were aggregated and harmonized in a clinical data warehouse, as previously described.[20-21] For all patients, we accessed sociodemographic data, medical history, and billing charges for all outpatient and inpatient encounters with diagnoses and procedures coded based on the International Classification of Diseases, Ninth and 10th Revisions.[22-23] Deaths were identified using hospital discharge dispositions of "ceased to breathe" sourced from the inpatient medical record system; deaths after discharge were identified externally via the Death Master File from the Social Security Administration's National Technical Information Service.[24] Cause of death was unavailable for analysis. In secondary analyses, a composite outcome of ASCVD was ascertained from UPMC hospital admission/discharge records, defined as the occurrence of myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft surgery, or peripheral vascular disease.

Eligibility criteria

The index date for selection and analysis of patients aged 50 to 89 years was the first date of cholesterol measurement performed whether through hospitalization or in conjunction with an office visit (**Supplement Figure 1**). For analysis, we required non-missing laboratory values for T-C, LDL-C, and HDL-C. The patient population was restricted to "primary prevention" patients, defined as no prior history of diabetes, coronary artery disease (CAD), carotid artery disease, peripheral vascular disease, cardiac arrest, hemorrhagic or ischemic stroke, or transient ischemic attack (TIA). Other eligibility criteria included: self-reported race of either white or black (due to very low prevalence of other races), and not on statin therapy at baseline or within 1-year of follow-up. In addition, to help offset potential bias due to reverse causation (i.e., very low cholesterol being a marker for malnutrition and overall poor health), we excluded patients

who died within 1-year of the baseline cholesterol measurement, as well as those with baseline T-C and/or LDL-C values of ≤120 or <30 mg/dL, respectively.

Classification of lipid levels

From the baseline measurement, we classified patients into mutually exclusive lipid-level categories using common clinical thresholds[25] including LDL-C (30-79, 80-99, 100-129, 130-159, 160-189, or 190 mg/dL or higher) and T-C (121-160, 161-200, 201-240, 241-280, or 281 mg/dL or higher). In supplemental analyses, we classified the T-C/HDL-C ratio as ≤3.0, >3.0-4.0, >4.0-5.0, >5.0-6.0, or >6.0, and triglycerides/HDL-C ratio into quintiles. Again, to potentially mitigate potential bias due to reverse causation, we selected the LDL-C category of 80-99 mg/dL as the referent group, rather than the lowest LDL-C group (30-79 mg/dL).

Outcome measures

The main outcome measure was all-cause mortality with the number of days and years of follow-up calculated starting 365 days after the baseline cholesterol measurement. For patients who did not die, their length of follow-up was calculated starting 365 days after the baseline cholesterol measurement and until their last record in the EMR system. In secondary analyses, the composite outcome of occurrence of ASCVD was evaluated.

Statistical analysis

For patients within the respective study-defined baseline LDL-C categories, median and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables are presented. For each LDL-C category, the Kaplan-Meier method was used to calculate cumulative mortality rates at 1-, 5-, and 10-year follow-up, with survival curves plotted at 6-month intervals out to 12 years. Patients who did not die were censored at last date of follow-up. Cox regression was used to estimate hazard ratios (and corresponding 95%

confidence intervals) of mortality over the full follow-up period by baseline LDL-C. A crude model was first fit followed by an adjusted model that included covariates selected by a forward stepwise approach using an entry *p*-value of < .01 and initiation of statin use any time after 1-year of follow-up. Separate estimates for the relationship between initiation of statin use and mortality are not presented due to expected immortal time bias (i.e., requirement to be alive during follow-up to initiate statin use). Secondary analyses of lipid parameters used the same methods as for LDL-C and included categories of the T-C/HDL-C and triglycerides/HDL-C ratios.

In addition to the clinical categories used to define and evaluate baseline lipid levels, in secondary analyses, each lipid parameter was evaluated in relation to mortality risk by use of non-parametric generalized additive models using smoothing splines adjusting for the same covariates used in the Cox regression models. The smoothing parameters including the number of degrees of freedom were optimized by use of generalized cross validation (GCV).

We used SAS, version 9.4 (SAS Institute) for all analyses.

Subgroup analyses

Subgroup analyses for estimation of the relationship between LDL-C category and mortality included age (50-69, 70-89), sex (female, male), and baseline ASCVD risk classification (low/borderline, intermediate, high, risk not determined).

Patient and public involvement

None.

RESULTS

The mean (SD) LDL-C was 119 (31) mg/dL, and the prevalence of patients within the six LDL-C categories was as follows: 30-79 (9.1%), 80-99 (18.3%), 100-129 (39.1%), 130-159 (24.4%), 160-189 (7.1%), or 190 mg/dL or higher (2.0%) (**Table 1)**. The median age of patients was 59 years and mean age ranged nominally across the six LDL-C categories from 60.7 to 61.7 years. There was a general indication of overall higher baseline risk in the group of patients with LDL-C from 30-79 mg/dL (**Table 1**) (consistent with the stated concern of potential reverse causation). This included a numerically higher prevalence of current smokers and those with a history of various comorbidities (e.g., atrial fibrillation, arrythmia, congestive heart failure, chronic obstructive pulmonary disease), as well as nominally higher prevalence of selected medication use (e.g., ACE inhibitors, beta-blockers, diuretics, opioids, direct oral anticoagulants). History of cancer was slightly higher in the two lowest LDL-C categories, whereas estimated 10-year ASCVD risk was highest in those with baseline LDL-C ≥190 mg/dL.

Patient follow-up

The mean and median follow-up after excluding the study requirement to have survived at least 1-year after baseline cholesterol measurement was 6.1 and 5.9 years, respectively, and 17% of patients had 10 or more years of follow-up. Across the six LDL-C categories, the mean years of follow-up among patients who did not die ranged from 5.8 to 6.4 years. In total, 48.9% to 55.5% of patients had their first LDL-C measurement in calendar year 2015 or earlier, and the percentage of patients with their last follow-up extending into calendar year 2023 ranged from 57.8% to 63.4%, thereby suggesting non-informative censoring.

Overall assessment of mortality

In ascending order from lowest LDL-C category (30-79 mg/dL) to highest LDL-C category (≥190 mg/dL), 10-year cumulative mortality rates were U-shaped at 19.8%, 14.7%, 11.7%,

10.7%, 10.1%, and 14.0% (**Table 2, Figures 1 and 2**). Adjusted mortality hazard ratios (HR) and 95% confidence intervals (CI) (**Table 2**), as compared to the referent group of LDL-C 80-99 mg/dL, were as follows: 30-79 mg/dL (1.23, CI:1.17-1.30), 100-129 mg/dL (0.87, CI:0.83-0.91), 130-159 mg/dL (0.88, CI:0.84-0.93), 160-189 mg/dL (0.91, CI:0.84-0.98), ≥190 mg/dL (1.19, CI:1.06-1.34), respectively. Thus, the 3 LDL-C categories within the range of 100-189 mg/dL showed similar, slightly lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL. When evaluated as a continuous variable, the relationship between LDL-C and mortality was mostly U-shaped, with the lowest risk of mortality in the range of approximately 110 to 190 mg/dL (**Supplement Figure 2, upper left**).

Assessment of ASCVD

In ascending order from lowest LDL-C category (30-79 mg/dL) to highest LDL-C category (≥190 mg/dL), 10-year cumulative rates of ASCVD were U-shaped at 6.5%, 5.3%, 4.7%, 4.8%, 5.1%, and 7.6% (**Table 3, top half**.). Adjusted HRs of risk of ASCVD as compared to the referent group of LDL-C 80-99 mg/dL, were as follows: 30-79 mg/dL (1.10, CI:1.00-1.20), 100-129 mg/dL (0.94, CI:0.88-1.00), 130-159 mg/dL (0.96, CI:0.89-1.03), 160-189 mg/dL (0.98, CI:0.88-1.08), ≥190 mg/dL (1.23, CI:1.06-1.43), respectively. Thus, the 3 LDL-C categories within the range of 100-189 mg/dL showed similar yet nominally lower risk of ASCVD compared to the referent group of LDL-C 80-99 mg/dL. Similar results were observed for the composite outcome of ASCVD/mortality (**Table 3, bottom half**.) Baseline ASCVD risk categories of low, medium, and high risk were strongly associated with 10-year rates of ASCVD (1.9%, 4.9%, 9.8%, respectively).

Subgroup analyses

For the two different age groups, the 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and slightly lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Table 2, Figure 2**). In a similar manner for both females and males, the 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and slightly lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Supplement Table 3**). Males with LDL-C ≥190 mg/dL did not have a significantly higher risk of mortality than those with LDL-C 80-99 mg/dL (adjusted HR = 1.06, CI: 0.85-1.32). When stratified by 10-year ASCVD risk score, again, the 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and statistically lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Supplement Table 4**).

Secondary lipid measures

Patients with a T-C/HDL-C ratio >6.0 had a significantly higher risk of mortality than those with a T-C/HDL-C ratio ≤3.0 (adjusted HR = 1.28, CI: 1.18-1.38, **Supplement Table 5**), with similar results by age (**Figure 2**). For the 3 T-C/HDL-C ratio categories ≤3.0, >3.0-4.0, and >4.0-5.0, risk of mortality was similar. The triglycerides/HDL-C ratio showed the most consistent evidence of a gradient relationship with mortality with lower values (quintiles) progressively conferring lower risk of mortality (**Supplement Table 6)** and similar results by age (**Figure 2**). Compared to patients in the highest quintile of triglycerides/HDL-C ratio (value of ≥3.44), those in the lowest quintile (value of ≤1.06) had an estimated 24% lower risk of mortality (adjusted HR = 0.76, CI: 0.72-0.81). Thus, in aggregate and irrespective of age, the secondary lipid measures of T-C/HDL-C ratio and triglycerides/HDL-C ratio appeared to be more predictive of mortality than LDL-C, and a triglycerides/HDL-C ratio of about 1 or lower appears to be optimal.

When evaluated as continuous variables, the relationship between T-C and adjusted risk of mortality was mostly U-shaped (similar to LDL-C), whereas other lipid/mortality relationships presented in a mostly gradient manner (**Supplement Figure 2**)**.** Specifically**,** lower HDL-C generally indicated higher adjusted risk of mortality, whereas higher triglycerides, total to HDL-C ratio, and triglycerides to HDL-C ratio indicated higher adjusted risk of mortality.

Evaluation of potential reverse causation

By study design, the 2,494 patient deaths that occurred from baseline LDL-C measurement to 365 days were excluded from the primary analysis. Among these excluded patients, the percentage of deaths distributed by LDL-C (mg) category was: 30 to 79 (30.4%), 80 to 99 (20.1%), 100 to 129 (26.5%), 130 to 159 (14.6%), 160 to 189 (5.9%), 190 or higher (2.5%). The 30.4% of deaths in the 30 to 79 mg/dL category is much higher than the 9.1% prevalence of patients in the 30 to 79 mg/dL category (see **table 1**) observed in the primary analysis. Similarly, 14.1% of deaths excluded in the first year had a total cholesterol value of 40 to 120 mg/dL compared to 1.6% prevalence of patients in the primary analysis. These results validated the need to remove the influence of potential reverse causality and early deaths and patients with very low baseline cholesterol values from the analysis.

DISCUSSION

In this analysis among non-diabetic primary prevention-type patients aged 50 to 89 years not on statin therapy at baseline or within 1-year, we found no evidence of a gradient relationship between LDL-C and long-term mortality risk. Instead, we observed that within the entire LDL-C range of 100-189 mg/dL (about two-thirds of the total patient population), mortality risk was similar and slightly lower than the referent LDL-C category of 80-99 mg/dL. These data conflict

with the prevailing belief that "lower LDL-C is better"[5-6] yet align with results from multiple studies. A large general population study of adults from Denmark showed a U-shaped relationship between LDL-C and long-term mortality, with lowest risk of all-cause mortality (among individuals not receiving lipid lowering treatment) being an LDL-C value of 140 mg/dL.[26] Similarly, a large cohort study among Korean adults not on statin therapy showed a U-shaped relationship between LDL-C and CVD mortality, with an optimal LDL-C range of 90 to 149 mg/dL.[27] Moreover, in a 20-year prospective cohort study of adults ages 18 and older derived from the National Health and Nutrition Examination Survey III (NHANES III), the lowest relative risk for all-cause mortality was for LDL-C in the range of 130 to <190 mg/dL.[28] Collectively, these results indicate that the "optimal" or "normal" range for LDL-C for primary prevention of mortality among adults is likely wide and considerably higher than the suggested optimal LDL-C level of ≤100 mg/dL.[5-6]

For multiple reasons, we chose to evaluate a population of non-diabetic primary prevention type adults aged 50 to 89 years not on statin therapy. First, both the prevalence and potential indication for initiating lipid-lowering therapy is relatively high in this population.[9,29,30] Second, prevailing guidelines and philosophy for initiating lipid-lowering therapy for secondary prevention of ASCVD and among persons with diabetes are well entrenched.[31-33] Third, consideration of initiating lipid-lowering therapy for primary prevention, particularly among older adults, should be carefully weighed based on empirical data[34-35] and potential side effects, including but not limited to muscle pain or weakness[36] and increased risk of developing diabetes.[37-39]

Beyond our principal finding of no indication that "lower LDL-C is better," other prominent findings were that overall and independent of age, the T-C/HDL-C and

triglycerides/HDL-C ratios were predictive of long-term mortality risk, the latter of which presented in a gradient manner. A study derived from NHANES data showed a U-shaped relationship between T-C/HDL-C ratio and risk of all-cause mortality,[40] whereas results from our analysis were unidirectional with elevated risk of mortality evident among adults with a T-C/HDL-C ratio more than 5.0. Similar to our results, a large study among Korean adults showed a gradient relationship between triglycerides/HDL-C ratio and risk of ischemic heart disease.[41] Importantly, the triglyceride/HDL-C ratio has recently been reported to be a stronger predictor of 10-year development of type 2 diabetes (strongly associated with mortality risk) than LDL-C, HDL-C, or triglycerides alone.[42]

The importance of high HDL-C alone, or in conjunction with other lipids, has been extensively recognized. In brief, oxidative stress and inflammation are integral in the pathophysiology of atherosclerosis and cardiovascular disease.[43] Importantly, HDL-C exerts several physiological roles, prevents oxidation of LDL, and inhibits expression of pro-inflammatory cytokines by macrophages, as well as expression of adhesion molecules by endothelial cells,[44-46] and it is inversely associated with both all cause and CVD mortality risks.[18-19] Moreover, it is likely not coincidental nor trivial that the field of life insurance medicine recognizes and prioritizes the importance of HDL-C over LDL-C in determining underwriting classifications.[16,17,47] Unfortunately, from a public health perspective, a meta-analysis of 31 randomized controlled trials on the use of HDL-C modifying treatments showed little to no effect on cardiovascular and all-cause mortality.[48]

There is an overall lack of consensus on the magnitude and statistical and clinical interpretation of the reduction in mortality risk potentially achieved with the use of LDL-C lowering therapies. Multiple reviews suggest that absolute mortality risk reductions from

treatment with statins are small as compared to the more frequent reporting and emphasis of relative risk reductions.[49-52] Moreover, mortality reductions with recent use of PCSK-9 inhibitors to lower LDL-C have been mixed and of low absolute risk.[53,54] Our postulate from both this review (e.g.,[10]) and empirical analysis is that whatever small absolute reductions in mortality risk may occur with use of LDL-C lowering therapies, they are most likely not causally related to LDL-C lowering, but potentially to more broad pleiotropic effects. For example, statin use has been shown to reduce inflammatory markers,[55] reduce vascular endothelial growth factor (VEGF) concentrations,[56] reduce platelet activity,[57] and increase nitric oxide bioavailability and stabilize atherosclerotic plaques.[58] These potential mechanisms of statins, rather than concomitant lowering of LDL-C, per se, may be expected to result in some reduction of ASCVD events.

Arguably, it is irrelevant to patients as to the exact mechanism(s) by which use of statins and other lipid-lowering therapies may result in small absolute reductions in mortality risk. Rather than focusing on LDL-C level, per se, we submit that health professionals should promote established (causal) mechanisms that reduce future risk of major ASCVD events, including weight, blood pressure, and blood sugar control, physical activity, avoidance of smoking, and stress reduction. Similarly, our results suggest that adult non-diabetic patients counselled for primary prevention of ASCVD be apprised of their estimated future risk of ASCVD with minimal consideration of their LDL-C concentration and more consideration of the T-C/HDL and triglyceride/HDL-C ratios along with other known causes of ASCVD (e.g., smoking, physical inactivity). Moreover, use of coronary artery calcium scoring in primary prevention is supported by a wealth of data showing that it substantially improves risk prediction including when combined with traditional risk factors and scores.[59-61]

Limitations

Our study has limitations. First, we were unable to assess cause-specific mortality which would have provided additional insight into the relationship between LDL-C and CVD mortality. Similarly, our assessment of risk of ASCVD in relation to baseline LDL-C levels is based on ascertainment of events within UPMC hospitals and not external facilities – there is certainly some unknown level of ascertainment of ASCVD events. Second, we chose the index date for follow-up mortality assessment to begin 1-year after baseline cholesterol measurement to ideally minimize potential bias due to reverse causation (i.e., low LDL-C being an overall marker of malnutrition and poor health). However, low LDL-C has been frequently reported in cancer patients (e.g., [25,62,63]) and many cancers have a viral etiologic component[64] and with potentially long latency. Theoretically, some patients with the lowest LDL-C values in our analysis may have been in the early stages of cancer development and hence at elevated long-term mortality risk. This is why we chose LDL-C 80-99 mg/dL as the referent group (rather than 30-79 mg/dL), and the observation that mortality risk was similar across a wide range of LDL-C values (100–189 mg/dL) argues against appreciable bias due to reverse causation. Third, absence of statin use at baseline and within the first year of the study (inclusion criterion) was based on patient reported data in the EMR and not from prescription data – this leaves open the possibility for some misclassification. In addition, the study requirement for absence of statin at baseline or within one year may have resulted in a patient population generally less likely to initiate lipid-lowering therapy in the long-term. Lastly, we cannot rule out potential residual confounding despite statistical adjustment for a large set of covariates associated with mortality.

CONCLUSIONS

Our analysis indicates that among non-diabetic primary prevention-type patients aged 50 to 89 years and not on statin therapy, the lowest risk for long-term mortality exists in the wide LDL-C range of 100-189 mg/dL which is much higher than current recommendations. Our analysis also shows that lower T-C/HDL-C and triglycerides/HDL-C ratios are independently associated with lower mortality risk, whereas LDL-C appears to be of limited to no predictive value. Collectively, these observations suggest that adult non-diabetic patients counselled for primary prevention of ASCVD be apprised of their estimated future risk of ASCVD with minimal consideration of their LDL-C concentration and more consideration of the T-C/HDL and triglycerides/HDL-C ratios along with other established causes of ASCVD (e.g., high blood pressure, smoking, physical inactivity) and potentially coronary artery calcium scoring.

Contributors

Kevin E Kip: conception, statistical analysis, writing, and editing. David M Diamond: conception, critical review, and editing. Suresh R Mulukutla: critical review and editing. Oscar C Marroquin: conception, critical review, and editing.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

None.

Patient consent for publication

Not applicable.

Ethics approval

The Quality Improvement Review Committee and Institutional Review Board at the University of Pittsburgh Medical Center provided ethical review and approval of the study as an exempt protocol (Project ID: 4565), and all data remained deidentified for this analysis.

Provenance and peer review

Not commissioned, externally peer reviewed.

Data availability statement

Study protocol: No separate study protocol was required a priori, as this retrospective analysis was deemed a quality improvement initiative with ethical review and approval granted by the UPMC Quality Improvement Review Committee and Institutional Review Board. *Statistical code*: Selected statistical code may be requested from Dr. Kevin Kip (e-mail, kipke2@upmc.edu*). Dataset*: The dataset contains protected health information and will not be available.

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FIGURE LEGENDS

Figure 1. Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C categories (130-159, 160-189, ≥190 mg/dL).

Figure 2. Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals (vertical lines) across categories of LDL cholesterol (top), total cholesterol to HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio (bottom). The left side of the graph is for patients aged 50-69 years; the right side is for patients aged 70-89 years. The dashed line reflects the referent group null value (1.0) for the HR. Q: quintile. Each model is adjusted for: age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Figure 1. Flow diagram of selection of patients for the study cohort.

Supplement Figure 2. Continuous spline plots of the relationship between different lipid parameters and adjusted risk of long-term mortality. The spline includes 95% confidence bands, with narrower bands indicating a

higher prevalence of patients with the given lipid value. X-axis values below the horizontal line with 0.0 value indicate lower risk of mortality; X-axis values above the line indicate higher risk of mortality.

Table 1. Baseline characteristics of study population by baseline LDL cholesterol value

Characteristic	Baseline LDL cholesterol value (mg/dL) 30 to 79 (n=16,162)	80 to 99 (n=32,517)	100 to 129 (n=69,399)	130 to 159 (n=43,333)	160 to 189 (n=12,663)	190 or higher (n=3,586)
Age, median, (IQR)	59, (54,67)	59, (54,67)	59, (54,66)	59, (54,65)	59, (54,65)	60, (54,67)
Age, n, (%)						
50 to 59	8167, (50.5)	16551, (50.9)	35706, (51.5)	22811, (52.6)	6694, (52.9)	1765, (49.2)
60 to 69	4686, (29.0)	9742, (30.0)	21632, (31.2)	13797, (31.8)	4029, (31.8)	1162, (32.4)
70 to 79	2221, (13.7)	4399, (13.5)	8808, (12.7)	5103, (11.8)	1439, (11.4)	514, (13.3)
80 and older	1088, (6.7)	1825, (5.6)	3253, (4.7)	1622, (3.7)	501, (4.0)	145, (4.0)
Sex						
Female	9027, (55.9)	18965, (58.3)	42697, (61.5)	28034, (64.7)	8654, (68.3)	2562, (71.4)
Male	7135, (44.1)	13552, (41.7)	26702, (38.5)	15299, (35.3)	4009, (31.7)	1024, (28.6)
Race						
Black	1700, (10.5)	2350, (7.2)	3855, (5.6)	2076, (4.8)	607, (4.8)	208, (5.8)
White	14462, (89.5)	30167, (92.8)	65544, (94.4)	41257, (95.2)	12056, (95.2)	3378, (94.2)
Former smoker, n, (%)	4172, (27.3)	8270, (26.9)	16871, (25.7)	10354, (25.3)	2933, (24.5)	858, (25.5)
Current smoker, n, (%)	3287, (21.5)	5430, (17.6)	9822, (15.0)	6274, (15.3)	1998, (16.7)	668, (19.8)
Body mass index, median, (IQR)	25.8, (25.2,33.2)	26.3, (25.2,33.8)	26.6, (25.2,34.0)	26.9, (25.2,33.9)	26.9, (25.2,33.6)	26.7, (25.2,33.1)
History of obesity, n, (%)	6011, (37.2)	12438, (38.3)	26946, (38.8)	16949, (39.1)	4899, (38.7)	1326, (37.0)
History of obstructive sleep apnea, n, (%)	932, (5.8)	1831, (5.6)	3619, (5.2)	1931, (4.5)	507, (4.0)	136, (3.8)
History of hypertension, n, (%)	5540, (34.3)	11331, (34.8)	23634, (34.1)	13435, (31.0)	3621, (28.6)	1060, (29.6)
History of atrial fibrillation, n, (%)	687, (4.3)	1181, (3.6)	1930, (2.8)	845, (2.0)	214, (1.7)	60, (1.7)
History of arrythmia, n, (%)	1178, (7.3)	2254, (6.9)	4143, (6.0)	2054, (4.7)	528, (4.2)	133, (3.7)
History of valvular heart disease, n, (%)	431, (2.7)	834, (2.6)	1505, (2.2)	798, (1.8)	246, (1.9)	60, (1.7)
History of congestive heart failure, n, (%)	251, (1.6)	375, (1.2)	597, (0.9)	245, (0.6)	80, (0.6)	15, (0.4)
History of deep vein thrombosis, n, (%)	184, (1.1)	323, (1.0)	667, (1.0)	356, (0.8)	93, (0.8)	25, (0.7)
History of cancer, n, (%)	1554, (9.6)	2916, (9.0)	5597, (8.0)	3348, (7.7)	912, (7.2)	281, (7.8)
History of chronic obstructive pulmonary disease, n, (%)	1147, (7.1)	1783, (5.5)	3156, (4.5)	1666, (3.8)	474, (3.7)	146, (4.1)
History of chronic kidney disease, n, (%)	329, (2.0)	424, (1.3)	695, (1.0)	356, (0.8)	126, (1.0)	42, (1.2)
History of depression, n, (%)	1985, (12.3)	3981, (12.2)	8327, (12.0)	5214, (12.0)	1606, (12.7)	440, (12.3)
Systolic BP (mmHg), median, (IQR)	128, (118,140)	127, (118,138)	128, (118,139)	128, (120,140)	128, (120,140)	130, (120,140)
Diastolic BP (mmHg), median, (IQR)	78, (70,84)	78, (70,84)	80, (71,84)	80, (72,84)	80, (72,84)	80, (72,86)
HDL cholesterol (mg/dL), median, (IQR)	57 (45,73)	56 (44,70)	55 (45,68)	55 (45,66)	54 (45,65)	53 (45,64)
Total/HDL cholesterol, median, (IQR)	2.5, (2.2,3.0)	3.0, (2.5,3.6)	3.5, (3.0,4.2)	4.0, (3.4,4.8)	4.6, (4.0,5.5)	5.5, (4.6,6.5)
Triglycerides (mg/dL), median, (IQR)	90, (63,137)	91, (67,131)	100, (74,140)	111, (83,151)	125, (94.167)	149, (110,201)
Hemoglobin (g/dL), median, (IQR)	13.7, (12.6,14.7)	13.9, (12.9,14.8)	14.0, (13.1,14.9)	14.1, (13.3,15.0)	14.2, (13.4,15.0)	14.1, (13.3,15.0)
Glucose (mg/dL), median, (IQR)	94, (87,104)	94, (87,103)	94, (88,102)	94, (88,102)	95, (89,103)	96, (89,105)

ACE Inhibitor, n, (%)	2060, (12.7)	3992, (12.3)	8024, (11.6)	4454, (10.3)	1205, (9.5)	328, (9.1)
Angiotensin receptor blocker, n, (%)	1028, (6.4)	2017, (6.2)	3927, (5.7)	2018, (4.7)	558, (4.4)	156, (4.4)
Beta blocker, n, (%)	2747, (17.0)	4827, (14.8)	8969, (12.9)	4709, (10.9)	1352, (10.7)	430, (12.0)
Calcium blocker, n, (%)	1931, (11.9)	3501, (10.8)	6612, (9.5)	3534, (8.2)	956, (7.5)	297, (8.3)
Diuretic, n, (%)	2662, (16.5)	4763, (14.6)	8814, (12.7)	4717, (10.9)	1257, (9.9)	390, (10.9)
Anti-depressant, n, (%)	3497, (21.6)	6504, (20.0)	13784, (19.9)	8624, (19.9)	2628, (20.8)	797, (22.2)
Opioids, n, (%)	3319, (20.5)	5400, (16.6)	9688, (14.0)	5711, (13.2)	1599, (12.6)	523, (14.2)
Anti-platelet agent, n, (%)	2209, (13.7)	4319, (13.3)	9006, (13.0)	5057, (11.7)	1267, (10.0)	402, (11.2)
Aspirin, n, (%)	3082, (19.1)	6087, (18.7)	12511, (18.0)	7117, (16.4)	1922, (15.2)	586, (16.3)
Direct oral anticoagulant, n, (%)	423, (2.6)	684, (2.1)	1086, (1.6)	479, (1.1)	133, (1.1)	33, (0.9)
ASCVD 10-year risk, median, (IQR)	5.8, (2,3,12.6)	5.8, (2,5,12.7)	5.9, (2,8,12.3)	6.3, (3.1,12.2)	6.8, (3.6,13.0)	8.7, (4,6,15.7)
ASCVD 10-year risk, n, (%)						
Low	6204, (58.8)	12166, (58.3)	25457, (58.6)	15048, (57.3)	4144, (54.1)	900, (43.0)
Intermediate	2887, (27.4)	5804, (27.8)	12514, (28.8)	8161, (31.1)	2596, (33.9)	839, (40.0)
High	1459, (13.8)	2888, (13.8)	5472, (12.6)	3045, (11.6)	913, (11.9)	356, (17.0)
Started statin use >1 year after baseline measurement, n, (%)	484, (3.0)	921, (2.8)	2948, (4.2)	3448, (8.0)	1600, (12.6)	644, (18.0)

Table 2. Risks and hazard ratios for death by LDL cholesterol level at baseline

LDL cholesterol (mg/dL)	n	Cumulative incidence (%) 1-year	5-year	10-year	Total # deaths	Crude HR	Adjusted HR	95% C.I.
30 to 79	16162	2.7	11.3	19.8	2159	1.41	1.23	1.17 – 1.30
80 to 99	32517	1.7	8.1	14.7	3232	1.0	1.0	-----
100 to 129	69399	1.1	6.0	11.7	5415	0.77	0.87	0.83 – 0.91
130 to 159	43333	1.0	5.2	10.7	2971	0.69	0.88	0.84 – 0.93
160 to 189	12663	1.2	5.4	10.1	821	0.68	0.91	0.84 – 0.98
190 or higher	3586	1.8	7.9	14.0	317	0.96	1.19	1.06 – 1.34
Patients aged 50-69								
30 to 79	12853	1.8	8.1	14.2	1241	1.52	1.20	1.20 – 1.39
80 to 99	26293	1.1	5.2	9.6	1745	1.0	1.0	-----
100 to 129	57338	0.7	3.9	7.6	2924	0.76	0.86	0.81 – 0.92
130 to 159	36608	0.7	3.4	6.9	1653	0.69	0.85	0.79 – 0.91
160 to 189	10723	0.9	3.7	6.5	472	0.70	0.89	0.81 – 0.99
190 or higher	2927	1.2	5.7	9.4	181	1.01	1.24	1.06 – 1.44
Patients aged 70-89								
30 to 79	3309	6.3	24.3	42.7	918	1.25	1.15	1.06 – 1.25
80 to 99	6224	4.5	20.5	37.2	1487	1.0	1.0	-----
100 to 129	12061	2.7	16.0	31.4	2491	0.80	0.87	0.82 – 0.93
130 to 159	6725	2.8	15.3	30.8	1318	0.76	0.91	0.84 – 0.98
160 to 189	1940	2.9	15.0	29.7	349	0.75	0.92	0.82 – 1.04
190 or higher	659	4.5	17.5	34.2	136	0.90	1.15	0.96 – 1.37

* Model adjusted for age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Table 3. Risks and hazard ratios for ASCVD and ASCVD/mortality by LDL cholesterol levels at baseline

LDL Cholesterol (mg/dL)	n	Cumulative incidence (%) 1-year	5-year	10-year	Total # events	Crude HR	Adj. HR Model	95% C.I.
ASCVD								
30 to 79	16162	0.8	3.9	6.5	816	1.25	1.10	1.00 – 1.20
80 to 99	32517	0.5	2.8	5.3	1341	1.0	1.0	-----
100 to 129	69399	0.6	2.5	4.7	2509	0.87	0.94	0.88 – 1.00
130 to 159	43333	0.5	2.4	4.8	1586	0.89	0.96	0.89 – 1.03
160 to 189	12663	0.5	2.7	5.1	490	0.98	0.98	0.88 – 1.08
190 or higher	3586	0.9	4.7	7.6	205	1.50	1.23	1.06 – 1.43
ASCVD/Mortality								
30 to 79	16162	1.0	11.8	21.4	2590	1.36	1.19	1.14 – 1.26
80 to 99	32517	0.8	8.4	16.5	4014	1.0	1.0	-----
100 to 129	69399	0.6	6.4	13.5	6952	0.79	0.89	0.85 – 0.92
130 to 159	43333	0.5	5.8	12.8	4005	0.74	0.90	0.86 – 0.94
160 to 189	12663	0.5	6.5	12.6	1160	0.77	0.93	0.87 – 0.99
190 or higher	3586	0.9	9.9	18.5	452	1.12	1.20	1.08 – 1.32

Model: Adjusted for age, race, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

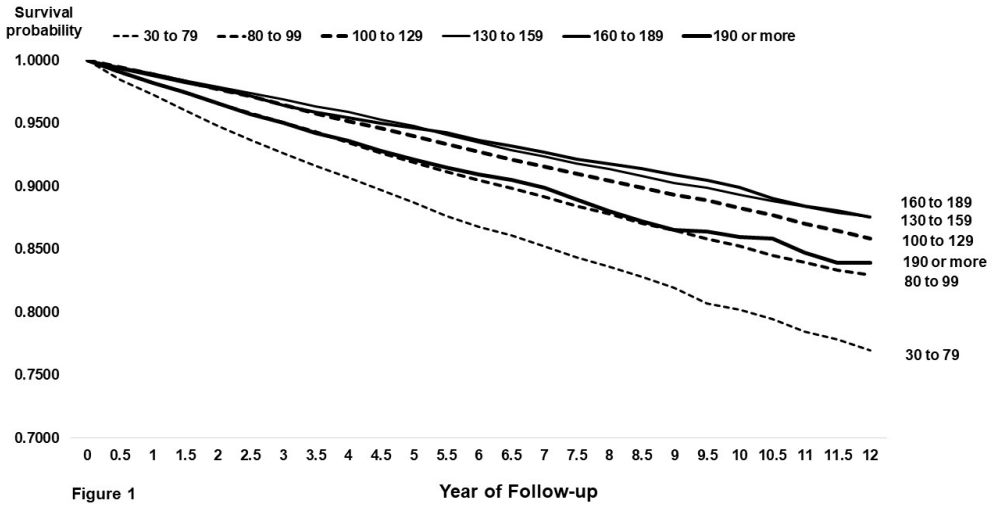

Figure 1.
Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C categories (130-159, 160-189, >190 mg/dL).

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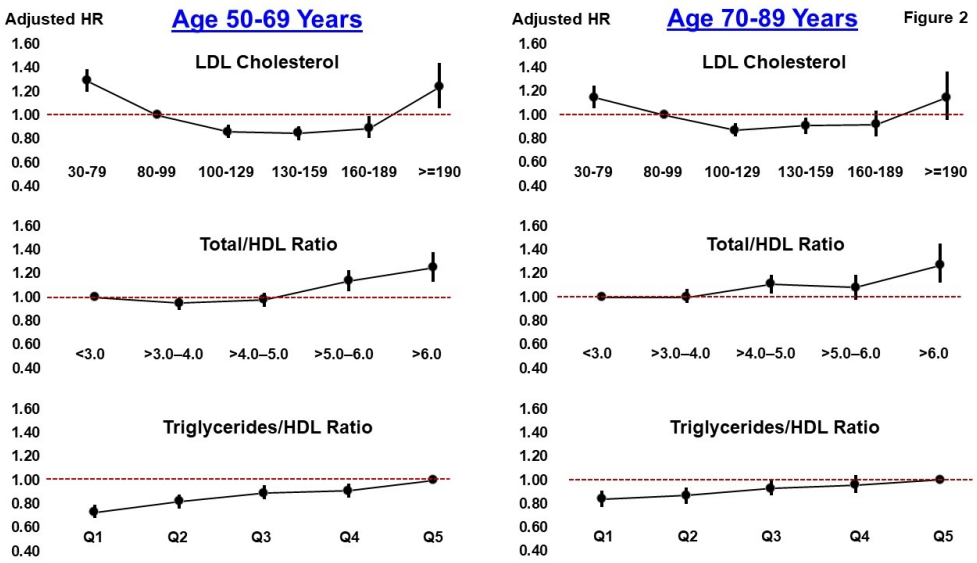

Figure 2.
Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals (vertical lines) across categories of LDL cholesterol (top), total cholesterol to HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio (bottom). The left side of the graph is for patients aged 50-69 years; the right side is for patients aged 70-89 years. The dashed line reflects the referent group null value (1.0) for the HR. Q: quintile. Each model is adjusted for: age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

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Supplement Table 1. ASCVD 10-Year Risk Calculations for Primary Prevention* by Age, Race, and Sex

	White Male		Black (AA) Male		White Female		Black (AA) Female	
Age	10-yr risk	Risk Category	10-yr risk	Risk Category	10-yr risk	Risk Category	10-yr risk	Risk Category
50	3.5%	Low	5.2%	Borderline	1.4%	Low	2.2%	Low
51	3.8%	Low	5.4%	Borderline	1.5%	Low	2.4%	Low
52	4.2%	Low	5.7%	Borderline	1.7%	Low	2.6%	Low
53	4.6%	Low	6.0%	Borderline	1.8%	Low	2.9%	Low
54	5.1%	Borderline	6.2%	Borderline	2.0%	Low	3.1%	Low
55	5.6%	Borderline	6.5%	Borderline	2.2%	Low	3.4%	Low
56	6.1%	Borderline	6.8%	Borderline	2.4%	Low	3.7%	Low
57	6.6%	Borderline	7.1%	Borderline	2.6%	Low	4.0%	Low
58	7.2%	Borderline	7.4%	Borderline	2.9%	Low	4.4%	Low
59	7.9%	Intermediate	7.7%	Intermediate	3.1%	Low	4.7%	Low
60	8.5%	Intermediate	8.0%	Intermediate	3.5%	Low	5.1%	Borderline
61	9.2%	Intermediate	8.3%	Intermediate	3.8%	Low	5.5%	Borderline
62	10.0%	Intermediate	8.7%	Intermediate	4.2%	Low	6.0%	Borderline
63	10.8%	Intermediate	9.0%	Intermediate	4.6%	Low	6.4%	Borderline
64	11.7%	Intermediate	9.3%	Intermediate	5.1%	Borderline	6.9%	Borderline
65	12.5%	Intermediate	9.7%	Intermediate	5.6%	Borderline	7.4%	Borderline
66	13.5%	Intermediate	10.0%	Intermediate	6.2%	Borderline	8.0%	Intermediate
67	14.5%	Intermediate	10.4%	Intermediate	6.9%	Borderline	8.5%	Intermediate
68	15.5%	Intermediate	10.7%	Intermediate	7.6%	Intermediate	9.1%	Intermediate
69	16.6%	Intermediate	11.1%	Intermediate	8.4%	Intermediate	9.7%	Intermediate
70	17.8%	Intermediate	11.5%	Intermediate	9.3%	Intermediate	10.4%	Intermediate
71	19.0%	Intermediate	11.9%	Intermediate	10.3%	Intermediate	11.1%	Intermediate
72	20.2%	High	12.3%	Intermediate	11.3%	Intermediate	11.8%	Intermediate
73	21.5%	High	12.7%	Intermediate	12.5%	Intermediate	12.5%	Intermediate
74	22.9%	High	13.1%	Intermediate	13.8%	Intermediate	13.3%	Intermediate
75	24.3%	High	13.5%	Intermediate	15.3%	Intermediate	14.1%	Intermediate
76	25.7%	High	13.9%	Intermediate	16.8%	Intermediate	15.0%	Intermediate
77	27.3%	High	14.3%	Intermediate	18.5%	Intermediate	15.9%	Intermediate
78	28.8%	High	14.7%	Intermediate	20.4%	High	16.8%	Intermediate
79	30.4%	High	15.2%	Intermediate	22.5%	High	17.7%	Intermediate

*Defined as non-diabetic persons with approximate guideline-driven "normal" values for total cholesterol (190 mg/dL), LDL cholesterol (125 mg/dL), HDL cholesterol (45 mg/dL for males, 55 mg/dL for females), systolic blood pressure (125 mmHg), diastolic blood pressure (75 mmHg), no history of smoking, not on anti-hypertensive medications, not on statin therapy, not on aspirin therapy.

https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

Supplement Table 2. Maximum/Range of Total Cholesterol (T-C) Values Along with T-C to HDL-C Cholesterol Ratios for Different Life Insurance Underwriting Categories

Age Category	Life Insurance Underwriting Category			
	Elite Plus* **(ages 18-75)**	**Preferred Plus*** **(ages 18-75)**	**Standard Plus** **(ages 18-75)**	**Standard** **(all ages)**
54 and younger	220/4.5	240/5.0	260/6.0 or 280/5.5 280/6.5 or 300/6.0	-----
55 to 69	230/4.5	260/5.5 or 280/5.0	150 to 300/7.0 or 150 to 310/6.5	-----
70 and older	150 to 240/5.0	150 to 280/5.5 or 150 to 300/5.0	Current medication acceptable (all ages)	-----
0 to 44	-----	-----	-----	≤300/9.6 or >300/8.0
45 to 65	-----	-----	-----	≤350/9.6 or 351 to 400/8.0
66 and older	-----	-----	-----	150 to 350/10.5 or 351 to 375/9.6

*Current medication OK if acceptable level maintained for at least 12 months (all ages)

Source: http://www.cassaniinsurance.com/wp-content/uploads/2018/02/Met-Life-condensed_uw_guide.pdf

Supplement Table 3. Risks and Hazard Ratios of Death by LDL Cholesterol Levels at Baseline Stratified by Sex at Baseline

LDL Cholesterol (mg/dL)	n	Cumulative incidence (%) 1-year	5-year	10-year	Total # deaths	Crude HR	Adj. HR Model	95% C.I.
Female								
30 to 79	9027	2.3	9.4	17.1	1043	1.42	1.23	1.14 – 1.33
80 to 99	18965	1.4	6.7	12.3	1597	1.0	1.0	-----
100 to 129	42697	0.8	5.2	10.5	2985	0.82	0.88	0.83 – 0.94
130 to 159	28034	0.9	4.8	10.2	1802	0.78	0.89	0.83 – 0.95
160 to 189	8654	1.1	5.2	9.7	542	0.80	0.91	0.82 – 1.00
190 or higher	2562	1.8	7.8	14.6	233	1.20	1.24	1.08 – 1.42
Male								
30 to 79	7135	3.3	13.7	23.4	1116	1.37	1.22	1.13 – 1.32
80 to 99	13552	2.2	10.0	18.4	1635	1.0	1.0	-----
100 to 129	26702	1.5	7.2	13.8	2430	0.73	0.86	0.80 – 0.91
130 to 159	15299	1.3	6.0	11.5	1169	0.61	0.85	0.79 – 0.92
160 to 189	4009	1.4	5.6	10.8	279	0.58	0.90	0.79 – 1.02
190 or higher	1024	1.8	8.1	12.2	84	0.72	1.06	0.85 – 1.32

Model: Adjusted for age, race, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Table 4. Risks and Hazard Ratios of Death by LDL Cholesterol Levels at Baseline Stratified by ASCVD Risk Classification

LDL cholesterol (mg/dL)	n	Cumulative incidence (%) 1-year	5-year	10-year	Total # deaths	Crude HR	Adj. HR Model	95% C.I.
Low or Borderline Risk								
30 to 79	6204	1.5	6.7	12.2	505	1.66	1.51	1.34 – 1.70
80 to 99	12166	1.0	4.2	7.2	607	1.0	1.0	-----
100 to 129	25457	0.6	2.9	5.6	927	0.73	0.78	0.70 – 0.86
130 to 159	15048	0.5	2.5	5.2	483	0.66	0.75	0.66 – 0.84
160 to 189	4144	0.6	2.7	4.7	126	0.65	0.75	0.62 – 0.91
190 or higher	900	0.6	4.3	7.7	43	1.05	1.18	0.86 – 1.61
Intermediate Risk								
30 to 79	2887	3.5	15.6	27.1	491	1.38	1.25	1.11 – 1.40
80 to 99	5804	2.6	11.4	21.3	758	1.0	1.0	-----
100 to 129	12514	1.6	8.4	16.6	1267	0.75	0.80	0.73 – 0.87
130 to 159	8161	1.4	7.0	13.8	670	0.61	0.69	0.62 – 0.77
160 to 189	2596	1.5	7.0	12.2	193	0.58	0.68	0.58 – 0.79
190 or higher	839	2.6	9.6	14.8	77	0.77	0.89	0.70 – 1.13
High Risk								
30 to 79	1459	7.9	28.0	49.9	447	1.25	1.17	1.04 – 1.32
80 to 99	2888	5.4	23.6	43.3	772	1.0	1.0	-----
100 to 129	5472	3.4	19.3	36.6	1242	0.82	0.85	0.77 – 0.92
130 to 159	3045	3.8	17.6	33.5	610	0.73	0.78	0.70 – 0.87
160 to 189	913	3.9	17.9	32.3	177	0.75	0.82	0.70 – 0.97
190 or higher	356	4.1	15.7	34.2	69	0.71	0.81	0.63 – 1.04
ASCVD Risk Not Determined								
30 to 79	5612	2.3	10.1	18.0	716	1.45	1.34	1.22 – 1.48
80 to 99	11659	1.3	6.9	13.0	1095	1.0	1.0	-----
100 to 129	25956	0.8	5.2	10.6	1979	0.80	0.85	0.79 – 0.91
130 to 159	17079	0.8	4.6	10.1	1208	0.74	0.85	0.78 – 0.92
160 to 189	5010	1.0	4.5	9.5	325	0.72	0.85	0.75 – 0.96
190 or higher	1491	1.5	7.3	12.6	128	0.98	1.17	0.97 – 1.41

Model: Adjusted for age, BMI, history of the following in the past year: atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, glucose, and the following medications in the past year: aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Table 5. Risks and Hazard Ratios of Death by Total Cholesterol to HDL Cholesterol Ratio at Baseline

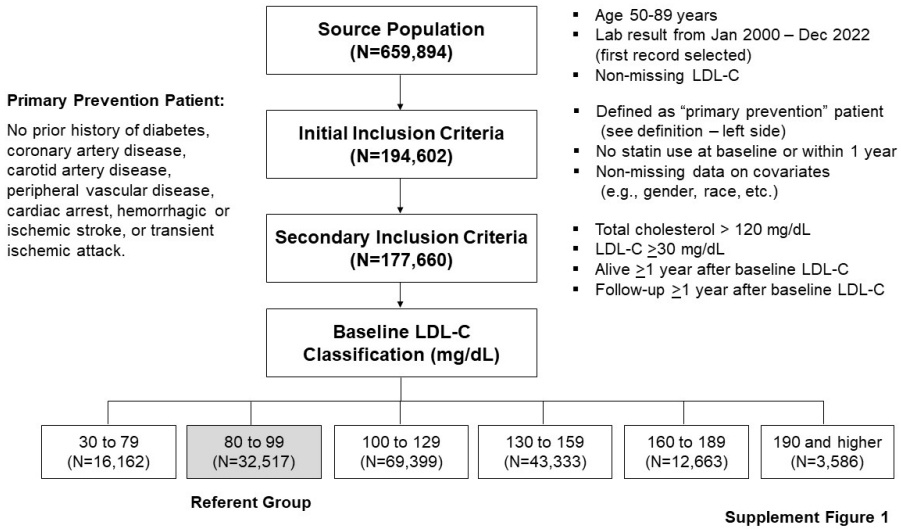
		Cumulative incidence (%)			Total	Crude	Adj. HR	95%
Total/HDL Cholesterol Ratio	**n**	**1-year**	**5-year**	**10-year**	**# deaths**	**HR**	**Model**	**C.I.**
3.0 or lower	52405	1.4	6.6	12.3	4403	1.0	1.0	-----
> 3.0 to 4.0	63482	1.2	6.3	12.3	5078	0.98	0.98	0.94 – 1.02
> 4.0 to 5.0	37907	1.4	6.7	12.8	3153	1.04	1.04	0.99 – 1.09
> 5.0 to 6.0	16053	1.5	7.2	14.1	1466	1.15	1.12	1.06 – 1.19
> 6.0	7813	2.1	9.2	15.2	815	1.32	1.28	1.18 – 1.38
Patients aged 50-69								
3.0 or lower	42650	0.9	4.3	7.8	2297	1.0	1.0	-----
> 3.0 to 4.0	51918	0.8	4.0	7.8	2673	0.99	0.95	0.89 – 1.00
> 4.0 to 5.0	31713	1.0	4.4	8.5	1771	1.10	0.98	0.92 – 1.04
> 5.0 to 6.0	13706	1.1	5.4	10.3	928	1.34	1.14	1.05 – 1.23
> 6.0	6755	1.7	6.8	11.7	547	1.60	1.25	1.13 – 1.38
Patients aged 70-89								
3.0 or lower	9755	3.5	17.3	32.9	2106	1.0	1.0	-----
> 3.0 to 4.0	11564	3.1	16.9	32.4	2405	0.97	1.00	0.95 – 1.07
> 4.0 to 5.0	6194	3.7	18.5	35.2	1382	1.08	1.11	1.03 – 1.19
> 5.0 to 6.0	2347	4.0	17.8	35.7	538	1.10	1.08	0.98 – 1.19
> 6.0	1058	4.8	24.4	38.4	268	1.30	1.27	1.12 – 1.45

Model: Adjusted for age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.

Supplement Table 6. Risks and Hazard Ratios of Death by Triglycerides to HDL-C Ratio at Baseline

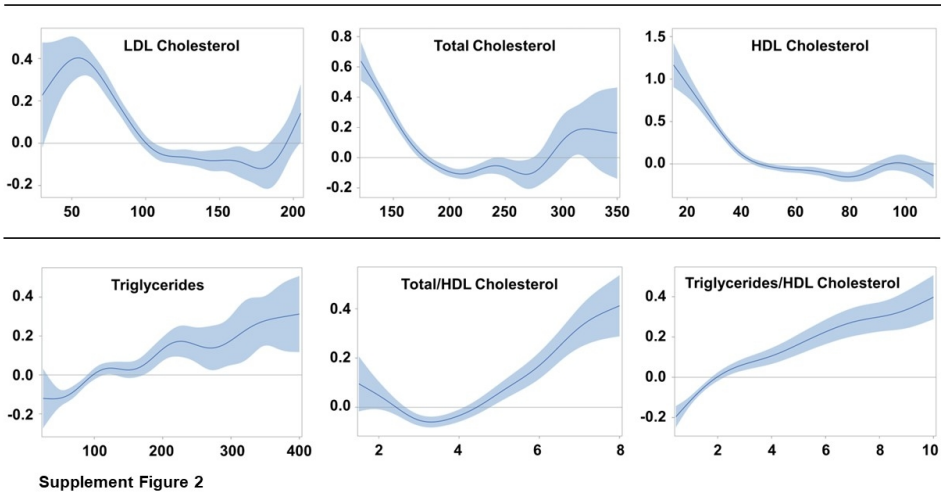
Triglycerides/ HDL-C Ratio	n	Cumulative incidence (%) 1-year	5-year	10-year	Total # deaths	Crude HR	Adj. HR Model	95% C.I.
Quintile 1	35533	0.9	5.1	9.7	2370	0.63	0.76	0.72 – 0.81
Quintile 2	35403	1.2	6.2	11.9	2771	0.77	0.84	0.80 – 0.88
Quintile 3	35523	1.4	6.9	13.1	3056	0.86	0.89	0.85 – 0.94
Quintile 4	35479	1.5	7.2	13.9	3183	0.91	0.92	0.88 – 0.97
Quintile 5	35513	1.7	7.9	15.1	3518	1.0	1.0	-----
Patients aged 50-69								
Quintile 1	29314	0.6	3.1	5.9	1213	0.53	0.73	0.68 – 0.79
Quintile 2	29313	0.8	3.9	7.3	1458	0.66	0.82	0.76 – 0.88
Quintile 3	29213	0.9	4.4	8.5	1634	0.76	0.89	0.84 – 0.96
Quintile 4	29425	1.0	4.7	9.3	1775	0.83	0.91	0.85 – 0.97
Quintile 5	29302	1.3	5.8	10.8	2131	1.0	1.0	-----
Patients aged 70-89								
Quintile 1	6169	2.8	15.9	30.7	1232	0.80	0.84	0.77 – 0.91
Quintile 2	6180	3.2	16.4	31.9	1256	0.83	0.87	0.80 – 0.94
Quintile 3	6176	3.7	17.9	33.6	1357	0.91	0.93	0.87 – 1.01
Quintile 4	6180	3.7	18.5	34.6	1375	0.93	0.96	0.89 – 1.04
Quintile 5	6179	4.1	19.4	37.0	1467	1.0	1.0	-----

Model: Adjusted for age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, glucose, and the following medications in the past year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin initiation >1 year after baseline cholesterol measurement.



Supplement Figure 1.
Flow diagram of selection of patients for the study cohort.

338x190mm (96 x 96 DPI)



Supplement Figure 2.
Continuous spline plots of the relationship between different lipid parameters and adjusted risk of long-term mortality. The spline includes 95% confidence bands, with narrower bands indicating a higher prevalence of patients with the given lipid value. X-axis values below the horizontal line with 0.0 value indicate lower risk of mortality; X-axis values above the line indicate higher risk of mortality.

338x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Research Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, Paragraphs 1-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, Paragraph 5
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, Paragraphs 1,3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, Paragraphs 1-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods, Paragraphs 3,5,6 Suppl. Figure 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Paragraphs 2-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, Paragraphs 2-5
Bias	9	Describe any efforts to address potential sources of bias	Methods, Paragraph 3
Study size	10	Explain how the study size was arrived at	Methods, Paragraph 1, Suppl. Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, Paragraphs 4-7

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, Paragraphs 6,7
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, Paragraph 8
		(*c*) Explain how missing data were addressed	Methods, Paragraph 3
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Suppl. Figure 1
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Suppl. Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	Results Paragraph 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (e.g., average and total amount)	Results Paragraph 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results Paragraphs 3,4 Tables 2,3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results Tables 2,3 Suppl. Tables 3-6
		(*b*) Report category boundaries when continuous variables were categorized	Results Tables 1-3, Suppl. Tables 3-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results Paragraphs 5-8
Discussion			

Key results	18	Summarise key results with reference to study objectives	Discussion Paragraphs 1,3
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion Paragraphs 1,5,6,7
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion Paragraph 6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.