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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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5 2 **Assessment of LDL Cholesterol and Long-Term Mortality Among Primary Prevention**
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7 **Adults: A Cohort Study with Implications for Risk Assessment and Patient Counseling**
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12 5 Kevin E. Kip, Ph.D.

13
14 6 Clinical Analytics, UPMC, Pittsburgh, Pennsylvania

15
16 7 kipke2@upmc.edu
17
18

19 8
20
21 9 David M. Diamond, Ph.D.

22
23 10 University of South Florida, Tampa, Florida

24
25 11 ddiamond@usf.edu
26
27

28 12
29
30 13 Suresh R. Mulukutla, MD

31
32 14 Heart and Vascular Institute, UPMC, Pittsburgh, Pennsylvania

33
34 15 mulukutlasr@upmc.edu
35
36

37 16
38
39 17 Oscar C. Marroquin, MD

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41 18 Clinical Analytics, UPMC, Pittsburgh, Pennsylvania

42
43 19 marroquinoc@upmc.edu
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3 **21 Abstract**
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5 **22 Objectives.** Among primary prevention-type adults not on lipid-lowering therapy, results are
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8 **23** conflicting on the relationship between low density lipoprotein cholesterol (LDL-C) and long-
9
10 **24** term mortality. We sought to evaluate the relationship between LDL-C and all-cause long-term
11
12 **25** mortality in a real-world evidence population of adults.

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14 **26 Design.** Retrospective cohort study of adults during the period January 4, 2000 through
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17 **27** December 31, 2022.

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19 **28 Setting.** Large U.S. health care system.

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21 **29 Participants.** Non-diabetic adults aged 50 to 89 years not on statin therapy at baseline or within
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24 **30** 1-year and classified as primary prevention-type patients (e.g., no prior history of ASCVD). To
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26 **31** mitigate potential reverse causation, patients who died within 1-year or had baseline total
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28 **32** cholesterol (T-C) ≤ 120 mg/dL or LDL-C < 30 mg/dL were excluded from analysis.

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30 **33 Main Exposure Measure.** Baseline LDL-C categories of 30-79, 80-99, 100-129, 130-159, 160-
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33 **34** 189, or ≥ 190 mg/dL.

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35 **35 Main Outcome Measure.** The primary outcome was all-cause mortality with follow-up starting
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37 **36** 365 days after baseline cholesterol measurement.

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39 **37 Results.** Over a mean of 6.1 years of follow-up, a U-shaped relationship was observed between
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42 **38** the 6 LDL-C categories and mortality with crude 10-year mortality rates of 19.8%, 14.7%,
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45 **39** 11.7%, 10.7%, 10.1%, and 14.0%, respectively. Adjusted mortality hazard ratios as compared to
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47 **40** the referent group of LDL-C 80-99 mg/dL, were: 30-79 mg/dL (1.23), 100-129 mg/dL (0.87),
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49 **41** 130-159 mg/dL (0.88), 160-189 mg/dL (0.91), ≥ 190 mg/dL (1.19), respectively. Unlike LDL-C,
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51 **42** both T-C/HDL cholesterol and triglycerides/HDL cholesterol ratios were independently
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54 **43** associated with long-term mortality.

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3 44 **Conclusions.** Among non-diabetic primary prevention-type patients aged 50 to 89 years and not
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5 45 on statin therapy, the lowest risk for long-term mortality appears to exist in the wide LDL-C
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7 46 range of 100-189 mg/dL which is much higher than current recommendations and does not
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9 47 support the prevailing premise that “lower LDL-C is better”. For counseling of these patients,
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11 48 minimal consideration should be given to the LDL-C concentration.
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7**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.

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52 INTRODUCTION

53 Heart disease (HD), which includes atherosclerotic cardiovascular disease (ASCVD) as
54 its primary component, is the leading cause of death in the United States.¹⁻² A near universal but
55 not absolute belief³ is that high total cholesterol (T-C), low density lipoprotein cholesterol
56 (LDL-C) in particular (the so-called “bad” cholesterol), is a root cause of ASCVD,⁴ and that
57 “lower is better” with a suggested optimal LDL-C level at or below 100 mg/dL.⁵⁻⁶ In this regard,
58 the American College of Cardiology (ACC) unequivocally implicates elevated LDL-C as a *de-*
59 *facto* cause of ASCVD (and hence mortality) by stating that lowering of LDL-C with moderate
60 intensity generic statins allows for efficacious and cost-effective primary prevention for those
61 patients with an estimated 10-year risk of ASCVD $\geq 7.5\%$.⁷

62 An individual’s risk of ASCVD (within 10 years) is routinely estimated by health
63 professionals using the online ACC-ASCVD Risk Estimator which incorporates not only T-C,
64 LDL-C, and high-density lipoprotein cholesterol (HDL-C), but also age, sex, race, systolic and
65 diastolic blood pressure, smoking and diabetes history, and current treatment (anti-hypertensive,
66 statin, and/or aspirin therapy).⁸ For primary prevention of ASCVD among adults ages 40-75
67 years who are classified at 10-year “intermediate risk” of ASCVD) (estimated risk 7.5% to
68 <20.0%), the ACC/AHA guidelines recommend that moderate-intensity statin therapy be
69 considered with the goal of reducing LDL-C by 30-49%.⁹ Again, the premise of this
70 recommendation is that elevated LDL-C is an important causal risk factor for ASCVD and
71 mortality.

72 The overall belief that “lower LDL-C is better” for primary prevention of ASCVD is
73 supported by the 25.5% estimated prevalence of use of statins in this setting for adults aged 40 to
74 75 years.¹⁰ This frequent use of statins for primary prevention of ASCVD in adults may be

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3 75 attributed, in part, to routine use of the ACC-ASCVD Risk Estimator in clinical practice. To
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5 76 illustrate, **Table 1** shows ASCVD 10-year risk calculations for primary prevention by age, race,
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7 77 and sex for a hypothetical non-diabetic patient with approximate guideline-driven “normal”
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9 78 values for all clinical variables used in the risk equation. As seen, all males aged 59 years and
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11 79 older will be classified as being of at least “intermediate risk” of ASCVD principally because of
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13 80 their age and despite “normal” risk factor values, and hence, would potentially be referred for
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15 81 statin therapy per the ACC/AHA guidelines.⁹ Parenthetically, **Table 1** unexpectedly shows a
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17 82 much more restricted range for 10-year risk estimates across years of age for blacks (males in
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19 83 particular).

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24 84 In the backdrop of the generally accepted belief that “lower LDL-C is better,” multiple
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26 85 sources of information suggest that high LDL-C may not be a significant cause of ASCVD or
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28 86 premature mortality. First, in brief, in an extensive recent meta-analysis of 60 randomized
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30 87 controlled trials that compared either placebo, usual care or less-intensive therapy to active or
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32 88 more potent lipid-lowering therapy, the number needed to treat (NNT) to reduce one death with
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34 89 active or more potent lipid-lowering therapy was exceptionally high at 754 persons. Moreover,
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36 90 there was no relationship between LDL-C percent lowering and risk of cardiovascular
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38 91 mortality.¹¹ In the context of lipid-lowering therapy, these findings do not support the belief that
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40 92 “lower LDL-C is better.”

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44 93 Second, acute coronary syndromes (ACS) routinely occur in patients with “normal”
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46 94 LDL-C. For example, in a large cohort of 136,905 patients hospitalized with CAD (79%
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48 95 attributed to ACS), of whom, 21% were on lipid-lowering therapy at admission, less than one-
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50 96 quarter had an admission LDL-C >130 mg/dL.¹² In addition, women are generally considered to
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52 97 be at overall lower risk of CHD mortality than men (e.g.,¹³), yet tend to have higher T-C and

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3 98 LDL-C,¹⁴ which is counterintuitive to higher LDL-C being associated with ASCVD and
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5 99 premature mortality.
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8 100 Third, the field of life insurance medicine, which focuses principally on predicting
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10 101 mortality hazards,¹⁵ arguably conducts the most robust actuarial analyses of life expectancy
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12 102 (since organizational profit is directly related to prediction accuracy). Notably, in this field, the
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14 103 T-C/HDL-C ratio has been shown to be the best single measure of all-cause mortality risk among
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16 104 various lipid tests, including LDL-C.¹⁶ This is further supported by examination of selected life
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18 105 insurance underwriting guidelines (obtained publicly and summarized) from a large US
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20 106 insurance company.¹⁷ As seen in **Supplement Table 1**, T-C and HDL-C are used jointly in
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22 107 policy underwriting, whereas LDL-C is not used, and lipid-lowering therapy is not emphasized.
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24 108 Moreover, notwithstanding other important patient factors (e.g., blood pressure, smoking, etc.),
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26 109 **Supplement Table 1** shows that a person 70 years of age or older can potentially qualify for a
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28 110 “preferred-plus” life insurance policy having a T-C value as high as 300 mg/dL so long as the T-
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30 111 C/HDL-C ratio is 5.0 or lower (i.e., HDL-C \geq 60 mg/dL). This aligns with meta-
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32 112 analyses/systematic reviews that report HDL-C to be inversely associated with all cause and
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34 113 CVD mortality risks.¹⁸⁻¹⁹
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40 114 The above-described examples of conflicting beliefs and findings, along with general
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42 115 propensity for health professionals to prescribe LDL-C lowering therapies for primary
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44 116 prevention based in part through routine risk assessment with ACC-ASCVD Risk Estimator, call
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46 117 for a critical appraisal and analysis of the relationship between LDL-C and long-term risk of
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48 118 mortality in adults. Therefore, within a large, “real-world” healthcare system, we sought to
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50 119 evaluate the relationship between LDL-C and all-cause long-term mortality among non-diabetic
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3 120 primary prevention-type adults aged 50 to 89 years. The analysis did not focus on the use of
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5 121 statin therapy for primary prevention.
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10 123 **METHODS**

12 124 We conducted a retrospective cohort study of adults aged 50 to 89 years with hospital
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14 125 and/or office visit data captured through the University of Pittsburgh Medical Center (UPMC)
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16 126 electronic medical record (EMR) system. The date period for analysis was January 4, 2000
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18 127 through December 31, 2022. The Quality Improvement Review Committee and Institutional
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20 128 Review Board provided ethical review and approval of the study as an exempt protocol, and all
21
22 129 data remained deidentified for this analysis. Conduct and dissemination of results from this
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24 130 observational study were performed in accordance with the STROBE (STrengthening the
25
26 131 Reporting of OBServational studies in Epidemiology) statement (see **Appendix**).
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30 132 **Data Sources**

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33 133 Health-related data captured in the UPMC EMR and its ancillary clinical systems were
34
35 134 aggregated and harmonized in a clinical data warehouse, as previously described.²⁰⁻²¹ For all
36
37 135 patients, we accessed sociodemographic data, medical history, and billing charges for all
38
39 136 outpatient and inpatient encounters with diagnoses and procedures coded based on the
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41 137 International Classification of Diseases, Ninth and 10th Revisions.²²⁻²³ Deaths were identified
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43 138 using hospital discharge dispositions of “ceased to breathe” sourced from the inpatient medical
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45 139 record system; deaths after discharge were identified via the Death Master File from the Social
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47 140 Security Administration’s National Technical Information Service.²⁴
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51 141 **Eligibility Criteria**

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3 142 The index date for selection and analysis of patients aged 50 to 89 years was the first date
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5 143 of cholesterol measurement performed whether through hospitalization or in conjunction with an
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7 144 office visit. For analysis, we required non-missing laboratory values for T-C, LDL-C, and HDL-
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9 145 C. The patient population was restricted to “primary prevention” patients, defined as no prior
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11 146 history of diabetes, coronary artery disease (CAD), carotid artery disease, peripheral vascular
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13 147 disease, cardiac arrest, hemorrhagic or ischemic stroke, or transient ischemic attack (TIA). Other
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15 148 eligibility criteria included: self-reported race of either white or black (due to very low
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17 149 prevalence of other races), and not on statin therapy at baseline or within 1-year of follow-up. In
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19 150 addition, to help offset potential bias due to reverse causation (i.e., very low cholesterol being a
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21 151 marker for malnutrition and overall poor health), we excluded patients who died within 1-year of
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23 152 the baseline cholesterol measurement, as well as those with baseline T-C and/or LDL-C values
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25 153 of ≤ 120 or < 30 mg/dL, respectively.

154 **Classification of Lipids**

155 From the baseline measurement, we classified patients into mutually exclusive lipid-level
156 categories using common thresholds²⁵ including LDL-C (30-79, 80-99, 100-129, 130-159, 160-
157 189, or 190 mg/dL or higher) and T-C (121-160, 161-200, 201-240, 241-280, or 281 mg/dL or
158 higher). In supplemental analyses, we classified the T-C/HDL-C ratio as ≤ 3.0 , $> 3.0-4.0$, $> 4.0-$
159 5.0 , $> 5.0-6.0$, or > 6.0 , and triglycerides/HDL-C ratio into quintiles. Again, to potentially mitigate
160 potential bias due to reverse causation, we selected the LDL-C category of 80-99 mg/dL as the
161 referent group, rather than the lowest LDL-C group (30-79 mg/dL).

162 **Primary Outcome**

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

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3 165 who did not die, their length of follow-up was calculated starting 365 days after the baseline
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5 166 cholesterol measurement and until their last record in the EMR system.
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7 167 **Statistical Analysis**

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10 168 For patients within the respective study-defined baseline LDL-C categories, means and
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12 169 medians for continuous variables and counts and percentages for categorical variables are
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14 170 presented. For each LDL-C category, the Kaplan-Meier method was used to calculate cumulative
15
16 171 mortality rates at 1-, 5-, and 10-year follow-up, with survival curves plotted at 6-month intervals
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18 172 out to 12 years. Patients who did not die were censored at last date of follow-up. Cox regression
19
20 173 was used to estimate hazard ratios (and corresponding 95% confidence intervals) of mortality
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22 174 over the full follow-up period by LDL-C. A crude model was first fit followed by an adjusted
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24 175 model that included covariates selected by a forward stepwise approach using an entry *p*-value of
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26 176 < .01 A second adjusted model was fit that added initiation of statin use any time after 1-year of
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28 177 follow-up. Separate estimates for the relationship between initiation of statin use and mortality
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30 178 are not presented due to expected immortal time bias (i.e., requirement to be alive during follow-
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32 179 up to initiate statin use). Secondary analyses of lipid parameters used the same methods as for
33
34 180 LDC-C and included categories of the T-C/HDL-C and triglycerides/HDL-C ratios.
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40 181 **Subgroup Analyses**

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42 182 Subgroup analyses for estimation of the relationship between LDL-C category and
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44 183 mortality included age (50-69, 70-89), sex (female, male), and baseline ASCVD risk
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46 184 classification (low/borderline, intermediate, high, risk not determined).
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49 185 We used SAS, version 9.4 (SAS Institute) for all analyses.
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53 187 **RESULTS**

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3 188 The prevalence of patients within the six LDL-C categories was as follows: 30-79
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5 189 (9.1%), 80-99 (18.3%), 100-129 (39.1%), 130-159 (24.4%), 160-189 (7.1%), or 190 mg/dL or
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7 190 higher (2.0%) (**Table 2**). The mean age of patients ranged nominally across the six LDL-C
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9 191 categories from 60.7 to 61.7 years. There was a general indication of overall higher baseline risk
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11 192 in the group of patients with LDL-C from 30-79 mg/dL (**Table 2**) (consistent with the stated
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13 193 concern of potential reverse causation). This included a numerically higher prevalence of current
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15 194 smokers and those with a history of various comorbidities (e.g., atrial fibrillation, arrhythmia,
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17 195 congestive heart failure, chronic obstructive pulmonary disease), as well as nominally higher
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19 196 prevalence of selected medication use (e.g., ACE inhibitors, beta-blockers, diuretics, opioids,
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21 197 direct oral anticoagulants). History of cancer was slightly higher in the two lowest LDL-C
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23 198 categories, whereas estimated 10-year ASCVD risk was highest in those with baseline LDL-C
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25 199 ≥ 190 mg/dL.
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30 **Overall Assessment of Mortality**

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33 201 The mean and median follow-up after excluding the study requirement to have survived
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35 202 at least 1-year after baseline cholesterol measurement was 6.1 and 5.9 years, respectively, and
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37 203 17% of patients had 10 or more years of follow-up. In ascending order from lowest LDL-C
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39 204 category (30-79 mg/dL) to highest LDL-C category (≥ 190 mg/dL), 10-year cumulative mortality
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41 205 rates were U-shaped at 19.8%, 14.7%, 11.7%, 10.7%, 10.1%, and 14.0% (**Table 3, Figures 1**
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43 206 **and 2**). Adjusted mortality hazard ratios (HR) (model 2), as compared to the referent group of
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45 207 LDL-C 80-99 mg/dL, were as follows: 30-79 mg/dL (1.23), 100-129 mg/dL (0.87), 130-159
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47 208 mg/dL (0.88), 160-189 mg/dL (0.91), ≥ 190 mg/dL (1.19), respectively. Thus, the 3 LDL-C
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49 209 categories within the range of 100-189 mg/dL showed similar, slightly lower mortality risk
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52 210 compared to the referent group of LDL-C 80-99 mg/dL.
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211 Subgroup Analyses

212 For the 2 different age groups, the 3 LDL-C categories within the range of 100-189
213 mg/dL showed relatively similar and slightly lower mortality risk compared to the referent group
214 of LDL-C 80-99 mg/dL (**Table 3, Figure 2**). In a similar manner for both females and males, the
215 3 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and slightly
216 lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Supplement Table**
217 **2**). Males with LDL-C ≥ 190 mg/dL did not have a significantly higher risk of mortality than
218 those with LDL-C 80-99 mg/dL (adjusted HR = 1.06, 95% CI: 0.85-1.32). When stratified by
219 10-year ASCVD risk score, again, the 3 LDL-C categories within the range of 100-189 mg/dL
220 showed relatively similar and statistically lower mortality risk compared to the referent group of
221 LDL-C 80-99 mg/dL (**Supplement Table 3**).

222 Secondary Lipid Measures

223 Patients with a T-C/HDL-C ratio >6.0 had a significantly higher risk of mortality than
224 those with a T-C/HDL-C ratio ≤ 3.0 (adjusted HR = 1.28, 95% CI: 1.18-1.38, **Supplement Table**
225 **4**), with similar results by age (**Figure 2**). For the 3 T-C/HDL-C ratio categories ≤ 3.0 , $>3.0-4.0$,
226 and $>4.0-5.0$, risk of mortality was similar. The triglycerides/HDL-C ratio showed the most
227 consistent evidence of a gradient relationship with mortality with lower values (quintiles)
228 progressively conferring lower risk of mortality (**Supplement Table 5**) and similar results by
229 age (**Figure 2**). Compared to patients in the highest quintile of triglycerides/HDL-C ratio (value
230 of ≥ 3.44), those in the lowest quintile (value of ≤ 1.06) had an estimated 24% lower risk of
231 mortality (adjusted HR = 0.76, 95% CI: 0.72-0.81). Thus, in aggregate and irrespective of age,
232 the secondary lipid measures of T-C/HDL-C ratio and triglycerides/HDL-C ratio appeared to be

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

235

236 **DISCUSSION**

237 In this analysis among non-diabetic primary prevention-type patients aged 50 to 89 years
238 not on statin therapy at baseline, we found no evidence of a gradient relationship between LDL-
239 C and long-term mortality risk. Instead, we observed that within the entire LDL-C range of 100-
240 189 mg/dL, mortality risk was similar and slightly lower than the referent LDL-C category of 80-
241 99 mg/dL. These data conflict with the prevailing belief that “lower LDL-C is better”⁵⁻⁶ yet align
242 closely with results from a large general population study from Denmark among adults with a
243 mean age of 58 years.²⁶ In that study, a U-shaped relationship between LDL-C and long-term
244 mortality was also observed, and the concentration of LDL-C associated with the lowest risk of
245 all-cause mortality among individuals not receiving lipid lowering treatment was 140 mg/dL.
246 Collectively, these results indicate that the “optimal” or “normal” range for LDL-C for primary
247 prevention among adults is likely wide and considerably higher than the suggested optimal LDL-
248 C level of ≤ 100 mg/dL.⁵⁻⁶

249 For multiple reasons, we chose to evaluate a population of non-diabetic primary
250 prevention type adults aged 50 to 89 years not on statin therapy. First, both the prevalence and
251 potential indication for initiating lipid-lowering therapy is relatively high in this population.^{9,10,27}
252 Second, prevailing guidelines and philosophy for initiating lipid-lowering therapy for secondary
253 prevention of ASCVD and among persons with diabetes are well entrenched.²⁸⁻³⁰ Third,
254 consideration of initiating lipid-lowering therapy for primary prevention, particularly among
255 older adults, should be carefully weighed based on empirical data³¹⁻³² and potential side effects,

256 including but not limited to muscle pain or weakness³³ and increased risk of developing
257 diabetes.³⁴⁻³⁶

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

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

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3 279 LDL-C lowering therapies, they are most likely not causally related to LDL-C lowering, but
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5 280 potentially to more broad pleiotropic effects. For example, statin use has been shown to reduce
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7 281 inflammatory markers,⁴⁸ reduce vascular endothelial growth factor (VEGF) concentrations,⁴⁹
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9 282 reduce platelet activity,⁵⁰ and increase nitric oxide bioavailability and stabilize atherosclerotic
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11 283 plaques.⁵¹ These potential mechanisms of statins, rather than concomitant lowering of LDL-C per
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13 284 se, may be expected to result in some reduction of ASCVD events.
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17 285 Arguably, it is irrelevant to patients as to the exact mechanism(s) by which use of statins
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19 286 may result in small absolute reductions in mortality risk. However, research suggests that use of
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21 287 statins (and possibly other LDL-C lowering therapies) may provide some patients with a false
22
23 288 sense of security,⁵² as expressed by higher caloric and fat intake and faster increase in BMI for
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25 289 statin users than for nonusers.⁵³ This observation places a premium on health professionals
26
27 290 promoting established (causal) mechanisms that reduce future risk of major ASCVD events,
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29 291 including weight, blood pressure, and blood sugar control, physical activity, avoidance of
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31 292 smoking, and stress reduction. Similarly, our results suggest that adult non-diabetic patients
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33 293 counselled for primary prevention of ASCVD be apprised of their estimated future risk of
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35 294 ASCVD with minimal consideration of their LDL-C concentration and more consideration of the
36
37 295 T-C/HDL and triglyceride/HDL-C ratios along with other known causes of ASCVD (e.g.,
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39 296 smoking, physical inactivity). Moreover, use of coronary artery calcium scoring in primary
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41 297 prevention is supported by a wealth of data showing that it substantially improves risk prediction
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43 298 including when combined with traditional risk factors and scores.⁵⁴⁻⁵⁶ Lastly, our analysis
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45 299 indicates that the routinely used ACC-ASCVD Risk Estimator over-emphasizes patient risk
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47 300 simply on age (i.e., intermediate or high-risk classification) when in the context of having
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3 301 “normal” parameters otherwise, and that the equation itself may have differential validity by
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5 302 race.

8 303 **Limitations**

10 304 Our study has limitations. First, we were unable to assess cause-specific mortality which
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12 305 would have provided additional insight into the relationship between LDL-C and CVD mortality.
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14 306 Second, we chose the index date for follow-up mortality assessment to begin 1-year after
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16 307 baseline cholesterol measurement to ideally minimize potential bias due to reverse causation
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18 308 (i.e., low LDL-C being an overall marker of malnutrition and poor health). However, low LDL-C
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20 309 has been frequently reported in cancer patients (e.g.,^{25,57,58}) and many cancers have a viral
21
22 310 etiologic component⁵⁹ and with potentially long latency. Theoretically, some patients with the
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24 311 lowest LDL-C values in our analysis may have been in the early stages of cancer development
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26 312 and hence elevated long-term mortality risk. This is why we chose LDL-C 80-99 mg/dL as the
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28 313 referent group (rather than 30-79 mg/dL), and the observation that mortality risk was similar
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30 314 across a wide range of LDL-C values (100–189 mg/dL) argues against appreciable bias due to
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32 315 reverse causation. Third, absence of statin use at baseline and within the first year of the study
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34 316 (inclusion criterion) was based on patient reported data in the EMR and not from prescription
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36 317 data – this leaves open the possibility for some misclassification. Lastly, we cannot rule out
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38 318 potential residual confounding despite statistical adjustment for a large set of covariates
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40 319 associated with mortality.

47 320 **Conclusions**

49 321 Our analysis indicates that among non-diabetic primary prevention-type patients aged 50
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51 322 to 89 years and not on statin therapy, the lowest risk for long-term mortality exists in the wide
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53 323 LDL-C range of 100-189 mg/dL which is much higher than current recommendations. Our

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3 324 analysis also shows that lower T-C/HDL-C and triglycerides/HDL-C ratios are independently
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5 325 associated with lower mortality risk, whereas LDL-C appears to be of limited to no predictive
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8 326 value. Lastly, our analysis indicates that the ACC-ASCVD Risk Estimator routinely used to
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10 327 estimate 10-year risk of ASCVD, and corresponding risk classification (with corresponding
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12 328 pharmacological treatment implications), overemphasizes individual patient risk by age alone
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15 329 and may have differential validity by race. Collectively, these observations suggest that adult
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17 330 non-diabetic patients counselled for primary prevention of ASCVD be apprised of their
18
19 331 estimated future risk of ASCVD with minimal consideration of their LDL-C concentration and
20
21 332 more consideration of the T-C/HDL and triglycerides/HDL-C ratios along with other established
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24 333 causes of ASCVD (e.g., high blood pressure, smoking, physical inactivity) and potentially
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26 334 coronary artery calcium scoring.
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30 336 **Figure Legends**

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33 337 **Figure 1.** Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up
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35 338 by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories
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37 339 (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C
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39 340 categories (130-159, 160-189, ≥ 190 mg/dL).

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42 341 **Figure 2.** Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals
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44 342 (vertical lines) across categories of LDL cholesterol (top), total cholesterol to
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46 343 HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio
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48 344 (bottom). The left side of the graph is for patients aged 50-69 years; the right side
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50 345 is for patients aged 70-89 years. The dashed line reflects the referent group null
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52 346 value (1.0) for the HR. Q: quintile.
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3 348 **Author Affiliations.**
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5 349 Kevin E. Kip, Ph.D.
6

7
8 350 Clinical Analytics, UPMC, Pittsburgh, Pennsylvania
9

10 351 kipke2@upmc.edu
11

12 352
13

14
15 353 David M. Diamond, Ph.D.
16

17 354 University of South Florida, Tampa, Florida
18

19 355 ddiamond@usf.edu
20

21 356
22

23
24 357 Suresh R. Mulukutla, MD
25

26 358 Heart and Vascular Institute, UPMC, Pittsburgh, Pennsylvania
27

28 359 mulukutlasr@upmc.edu
29

30 360
31

32 361 Oscar C. Marroquin, MD
33

34
35 362 Clinical Analytics, UPMC, Pittsburgh, Pennsylvania
36

37 363 marroquinoc@upmc.edu
38

39 364
40

41
42 365 **Corresponding Author.**
43

44 366 Kevin E. Kip, PhD, Vice President of Clinical Analytics, UPMC Health Services Division, 3600
45

46 367 Forbes & Meyran, Forbes Tower, 9th Floor, Suite 9030, Pittsburgh, PA 15213; e-mail,
47

48 368 kipke2@upmc.edu
49

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3 371 **Contributors.**
4

5 372 Kevin E. Kip, Ph.D. Conception, statistical analysis, writing, and editing
6

7 373 David M. Diamond. Ph.D. Conception, critical review, and editing
8

9 374 Suresh R. Mulukutla, MD. Critical review, and editing
10

11 375 Oscar C. Marroquin, MD. Conception, critical review, and editing
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11
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14 398 information and will not be available.
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584 **Table 1. ASCVD 10-Year Risk Calculations for Primary Prevention* by Age, Race, and Sex**

Age	White Male		Black (AA) Male		White Female		Black (AA) Female	
	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

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586 *Defined as non-diabetic persons with approximate guideline-driven “normal” values for total cholesterol
587 (190 mg/dL), LDL cholesterol (125 mg/dL), HDL cholesterol (45 mg/dL for males, 55 mg/dL for
588 females), systolic blood pressure (125 mmHg), diastolic blood pressure (75 mmHg), no history of
589 smoking, not on anti-hypertensive medications, not on statin therapy, not on aspirin therapy.

590
591 <https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/>
592

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

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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 arrhythmia, 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

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3	ACE Inhibitor, n, (%)	2060, (12.7)	3992, (12.3)	8024, (11.6)	4454, (10.3)	1205, (9.5)	328, (9.1)
4	Angiotensin receptor blocker, n, (%)	1028, (6.4)	2017, (6.2)	3927, (5.7)	2018, (4.7)	558, (4.4)	156, (4.4)
5	Beta blocker, n, (%)	2747, (17.0)	4827, (14.8)	8969, (12.9)	4709, (10.9)	1352, (10.7)	430, (12.0)
6	Calcium blocker, n, (%)	1931, (11.9)	3501, (10.8)	6612, (9.5)	3534, (8.2)	956, (7.5)	297, (8.3)
7	Diuretic, n, (%)	2662, (16.5)	4763, (14.6)	8814, (12.7)	4717, (10.9)	1257, (9.9)	390, (10.9)
8	Anti-depressant, n, (%)	3497, (21.6)	6504, (20.0)	13784, (19.9)	8624, (19.9)	2628, (20.8)	797, (22.2)
9	Opioids, n, (%)	3319, (20.5)	5400, (16.6)	9688, (14.0)	5711, (13.2)	1599, (12.6)	523, (14.2)
10	Anti-platelet agent, n, (%)	2209, (13.7)	4319, (13.3)	9006, (13.0)	5057, (11.7)	1267, (10.0)	402, (11.2)
11	Aspirin, n, (%)	3082, (19.1)	6087, (18.7)	12511, (18.0)	7117, (16.4)	1922, (15.2)	586, (16.3)
12	Direct oral anticoagulant, n, (%)	423, (2.6)	684, (2.1)	1086, (1.6)	479, (1.1)	133, (1.1)	33, (0.9)
13	ASCVD 10-year risk, mean, median	10.0, 6	10.0, 6	9.6, 6	9.6, 6	10.1, 7	12.0, 9
14	ASCVD 10-year risk, n, (%)						
15	Low	6204, (58.8)	12166, (58.3)	25457, (58.6)	15048, (57.3)	4144, (54.1)	900, (43.0)
16	Intermediate	2887, (27.4)	5804, (27.8)	12514, (28.8)	8161, (31.1)	2596, (33.9)	839, (40.0)
17	High	1459, (13.8)	2888, (13.8)	5472, (12.6)	3045, (11.6)	913, (11.9)	356, (17.0)
18	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)
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596 **Table 3. Risks and Hazard Ratios of Death by LDL Cholesterol Level at Baseline**

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LDL cholesterol (mg/dL)	n	Cumulative incidence (%)			Crude HR	Adj. HR Model 1	Adj. HR Model 2	95% C.I.
		1-year	5-year	10-year				
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

598

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

603 **Model 2:** Adjusted for Model 1 covariates + statin initiation >1 year after baseline cholesterol measurement.

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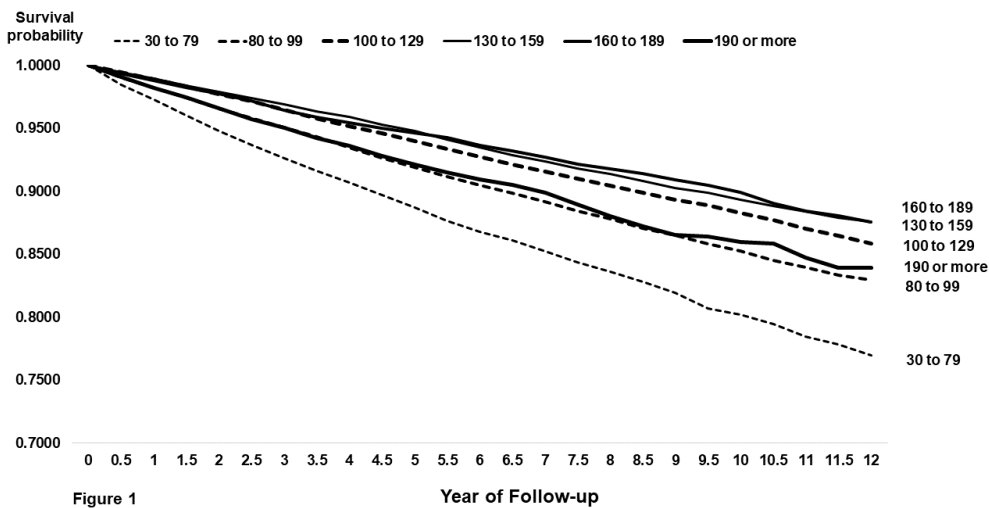


Figure 1. Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C categories (130-159, 160-189, >=190 mg/dL).

855x481mm (38 x 38 DPI)

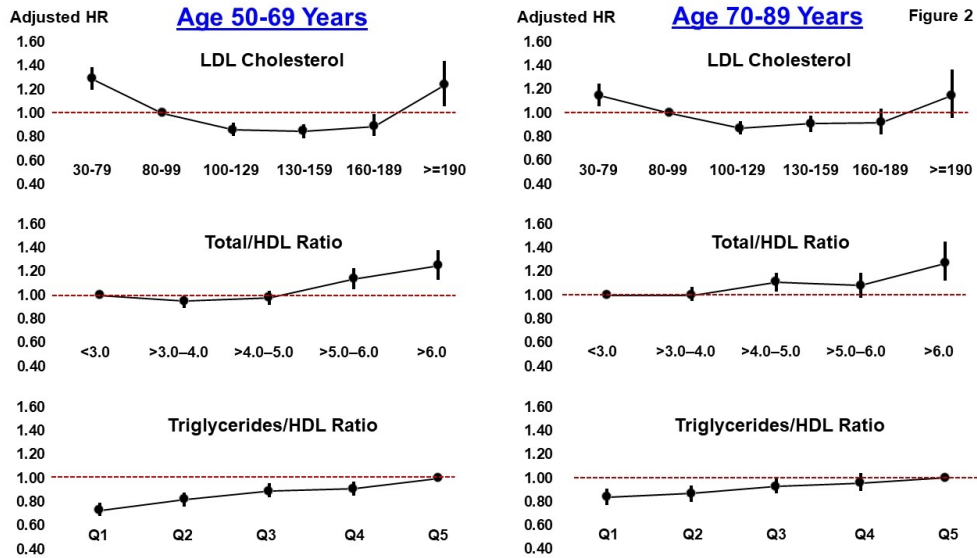


Figure 2. Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals (vertical lines) across categories of LDL cholesterol (top), total cholesterol to HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio (bottom). The left side of the graph is for patients 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

LDL Cholesterol (mg/dL)	n	Cumulative incidence (%)			Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year			
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, arrhythmia, 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 (%)			Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year			
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, arrhythmia, 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

Total/HDL Cholesterol Ratio	n	Cumulative incidence (%)			Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year			
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, arrhythmia, 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 (%)			Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year			
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, arrhythmia, 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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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.

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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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3 1 **Is LDL cholesterol associated with long-term mortality among primary prevention adults?**

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5 2 **A retrospective cohort study from a large healthcare system**

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10 4 Kevin E. Kip, Ph.D.

11
12 5 Clinical Analytics, UPMC, Pittsburgh, PA, USA

13
14 6 kipke2@upmc.edu

15
16
17 7
18 8 David M. Diamond, Ph.D.

19
20 9 University of South Florida, Tampa, FL, USA

21
22 10 ddiamond@usf.edu

23
24
25
26 11
27 12 Suresh R. Mulukutla, MD

28
29 13 Heart and Vascular Institute, UPMC, Pittsburgh, PA, USA

30
31 14 mulukutlasr@upmc.edu

32
33
34
35 15
36 16 Oscar C. Marroquin, MD

37
38 17 Clinical Analytics, UPMC, Pittsburgh, PA, USA

39
40 18 marroquinoc@upmc.edu

41
42
43
44 19
45 20 **Correspondence to:**

46
47 21 Kevin E. Kip, PhD, Vice President of Clinical Analytics, UPMC Health Services Division, 3600

48
49 22 Forbes & Meyran, Forbes Tower, 9th Floor, Suite 9030, Pittsburgh, PA 15213, USA

50
51 23 E-mail: kipke2@upmc.edu

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2
3 **25 Abstract**
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5 **26 Objectives:** Among primary prevention-type adults not on lipid-lowering therapy, conflicting
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8 **27** results exist on the relationship between low density lipoprotein cholesterol (LDL-C) and long-
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10 **28** term mortality. We evaluated this relationship in a real-world evidence population of adults.

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12 **29 Design:** Retrospective cohort study.

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14 **30 Setting:** Electronic medical record data for adults, from January 4, 2000, through December 31,
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17 **31** 2022, were extracted from the University of Pittsburgh Medical Center healthcare system.

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19 **32 Participants:** Non-diabetic adults aged 50-89 years not on statin therapy at baseline or within 1-
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22 **33** year and classified as primary prevention-type patients. To mitigate potential reverse causation,
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24 **34** patients who died within 1-year or had baseline total cholesterol (T-C) ≤ 120 mg/dL or LDL-C
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26 **35** < 30 mg/dL were excluded.

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28 **36 Main exposure measure:** Baseline LDL-C categories of 30-79, 80-99, 100-129, 130-159, 160-
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31 **37** 189, or ≥ 190 mg/dL.

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33 **38 Main outcome measure:** All-cause mortality with follow-up starting 365 days after baseline
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36 **39** cholesterol measurement.

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38 **40 Results:** 177,860 patients with mean (SD) age of 61.1 (8.8) years and mean (SD) LDL-C of 119
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41 **41** (31) mg/dL were evaluated over mean of 6.1 years of follow-up. A U-shaped relationship was
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44 **42** observed between the six LDL-C categories and mortality with crude 10-year mortality rates of
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47 **43** 19.8%, 14.7%, 11.7%, 10.7%, 10.1%, and 14.0%, respectively. Adjusted mortality hazard ratios
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49
50 **44** (HRs) as compared with the referent group of LDL-C 80-99 mg/dL were: 30-79 mg/dL (HR
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52 **45** 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),
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55 **46** 160-189 mg/dL (0.91, 0.84-0.98), ≥ 190 mg/dL (1.19, 1.06-1.34), respectively. Unlike LDL-C,
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3 47 both T-C/HDL cholesterol and triglycerides/HDL cholesterol ratios were independently
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5 48 associated with long-term mortality.
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8 49 **Conclusions.** Among non-diabetic primary prevention-type patients aged 50-89 years and not on
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10 50 statin therapy, the lowest risk for long-term mortality appears to exist in the wide LDL-C range
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12 51 of 100-189 mg/dL, which is much higher than current recommendations. For counseling these
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14 52 patients, minimal consideration should be given to LDL-C concentration.
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7**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.

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56 INTRODUCTION

57 Heart disease (HD), which includes atherosclerotic cardiovascular disease (ASCVD) as its
58 primary component, is the leading cause of death in the United States.[1-2] A near universal but
59 not absolute belief[3] is that high total cholesterol (T-C), low density lipoprotein cholesterol
60 (LDL-C) in particular (the so-called “bad” cholesterol), is a root cause of ASCVD,[4] and that
61 “lower is better” with a suggested optimal LDL-C level at or below 100 mg/dL.[5-6] In this
62 regard, the American College of Cardiology (ACC) unequivocally implicates elevated LDL-C as
63 a *de-facto* cause of ASCVD (and hence mortality) by stating that lowering of LDL-C with
64 moderate intensity generic statins allows for efficacious and cost-effective primary prevention
65 for those patients with an estimated 10-year risk of ASCVD $\geq 7.5\%$.[7] Risk of ASCVD is often
66 estimated using the online ACC-ASCVD Risk Estimator,[8] and as seen in **Supplement Table**
67 **1**, all males ages 59 and older even in the presence of “normal” ASCVD risk factors (lipids
68 included) may be classified at intermediate or high risk of ASCVD, and thus candidates for
69 LDL-C lowering therapy.

70 The overall belief that “lower LDL-C is better” for primary prevention of ASCVD is
71 supported by the 25.5% estimated prevalence of use of statins in this setting for adults aged 40 to
72 75 years.[9] Despite the generally accepted belief that “lower LDL-C is better,” meta-analyses
73 indicate that high LDL-C is associated with at most a small increased absolute risk of ASCVD or
74 premature mortality. First, in brief, in an extensive recent meta-analysis published in 2023 of 60
75 randomized controlled trials that compared either placebo, usual care or less-intensive therapy to
76 active or more potent lipid-lowering therapy, the number needed to treat (NNT) to reduce one
77 death with active or more potent lipid-lowering therapy was exceptionally high at 754 persons.
78 Moreover, there was no relationship between LDL-C percent lowering and risk of cardiovascular

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3 79 mortality.[10] Similarly, whereas an earlier meta-analysis published in 2010 indicated that both
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5 80 use and dose of statin therapy reduced the relative risk of major vascular events and all-cause
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7 81 mortality, absolute risk reductions were very small (e.g., 0.2% absolute risk reduction in all-
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9 82 cause mortality per 1.0 mmol/L reduction in LDL-C).[11] In the context of lipid-lowering
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11 83 therapy, these findings call into question the prevailing belief that “lower LDL-C is better” at
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13 84 least in terms of any appreciable clinical benefit.
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17 85 Second, acute coronary syndromes (ACS) routinely occur in patients with “normal”
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19 86 LDL-C. For example, in a large cohort of 136,905 patients hospitalized with CAD (79%
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21 87 attributed to ACS), of whom, 21% were on lipid-lowering therapy at admission, less than one-
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23 88 quarter had an admission LDL-C >130 mg/dL.[12] In addition, women are generally considered
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25 89 to be at overall lower risk of CHD mortality than men (e.g.,[13]), yet tend to have higher T-C
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27 90 and LDL-C,[14] which is counterintuitive to higher LDL-C being associated with ASCVD and
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29 91 premature mortality.
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33 92 Third, the field of life insurance medicine, which focuses principally on predicting
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35 93 mortality hazards,[15] arguably conducts the most robust actuarial analyses of life expectancy.
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37 94 Notably, in this field, the T-C/HDL-C ratio has been shown to be the best single measure of all-
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39 95 cause mortality risk among various lipid tests, including LDL-C.[16] This is further supported by
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41 96 examination of selected life insurance underwriting guidelines (obtained publicly and
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43 97 summarized) from a large US insurance company.[17] As seen in **Supplement Table 2**, T-C and
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45 98 HDL-C are used jointly in policy underwriting, whereas LDL-C is not used, and lipid-lowering
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47 99 therapy is not emphasized. Moreover, notwithstanding other important patient factors (e.g., blood
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49 100 pressure, smoking, etc.), **Supplement Table 2** shows that a person 70 years of age or older can
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51 101 potentially qualify for a “preferred-plus” life insurance policy having a T-C value as high as 300
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3 102 mg/dL so long as the T-C/HDL-C ratio is 5.0 or lower (i.e., HDL-C \geq 60 mg/dL). This aligns
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5 103 with meta-analyses/systematic reviews that report HDL-C to be inversely associated with all
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7 104 cause and CVD mortality risks.[18-19]
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10 105 The above-described examples of conflicting beliefs and findings, along with general
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12 106 propensity for health professionals to prescribe LDL-C lowering therapies for primary
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14 107 prevention based in part through routine risk assessment with the ACC-ASCVD Risk Estimator,
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16 108 call for a critical appraisal and analysis of the relationship between LDL-C and long-term risk of
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18 109 mortality in adults. Therefore, within a large, “real-world” healthcare system, we evaluated the
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20 110 association between LDL-C and all-cause long-term mortality among non-diabetic primary
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22 111 prevention-type adults aged 50 to 89 years. The analysis did not focus on the use of statin
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24 112 therapy for primary prevention.
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30 114 **METHODS**

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33 115 We conducted a retrospective cohort study of adults aged 50 to 89 years with hospital and/or
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35 116 office visit data captured through the University of Pittsburgh Medical Center (UPMC)
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37 117 electronic medical record (EMR) system. The date period for analysis was January 4, 2000,
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39 118 through December 31, 2022. The Quality Improvement Review Committee and Institutional
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41 119 Review Board provided ethical review and approval of the study as an exempt protocol (Project
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43 120 ID: 4565), and all data remained deidentified for this analysis. Conduct and dissemination of
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45 121 results from this observational study were performed in accordance with the STROBE
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47 122 (STrengthening the Reporting of OBServational studies in Epidemiology) statement.
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51 123 **Data sources**

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3 124 Health-related data captured in the UPMC EMR and its ancillary clinical systems were
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5 125 aggregated and harmonized in a clinical data warehouse, as previously described.[20-21] For all
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7 126 patients, we accessed sociodemographic data, medical history, and billing charges for all
8
9 127 outpatient and inpatient encounters with diagnoses and procedures coded based on the
10
11 128 International Classification of Diseases, Ninth and 10th Revisions.[22-23] Deaths were identified
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13 129 using hospital discharge dispositions of “ceased to breathe” sourced from the inpatient medical
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15 130 record system; deaths after discharge were identified externally via the Death Master File from
16
17 131 the Social Security Administration’s National Technical Information Service.[24] Cause of death
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19 132 was unavailable for analysis. In secondary analyses, a composite outcome of ASCVD was
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21 133 ascertained from UPMC hospital admission/discharge records, defined as the occurrence of
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23 134 myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft
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25 135 surgery, or peripheral vascular disease.

30 136 **Eligibility criteria**

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33 137 The index date for selection and analysis of patients aged 50 to 89 years was the first date of
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35 138 cholesterol measurement performed whether through hospitalization or in conjunction with an
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37 139 office visit (**Supplement Figure 1**). For analysis, we required non-missing laboratory values for
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39 140 T-C, LDL-C, and HDL-C. The patient population was restricted to “primary prevention”
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41 141 patients, defined as no prior history of diabetes, coronary artery disease (CAD), carotid artery
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43 142 disease, peripheral vascular disease, cardiac arrest, hemorrhagic or ischemic stroke, or transient
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45 143 ischemic attack (TIA). Other eligibility criteria included: self-reported race of either white or
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47 144 black (due to very low prevalence of other races), and not on statin therapy at baseline or within
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49 145 1-year of follow-up. In addition, to help offset potential bias due to reverse causation (i.e., very
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51 146 low cholesterol being a marker for malnutrition and overall poor health), we excluded patients
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3 147 who died within 1-year of the baseline cholesterol measurement, as well as those with baseline
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5 148 T-C and/or LDL-C values of ≤ 120 or < 30 mg/dL, respectively.
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8 149 **Classification of lipid levels**

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10 150 From the baseline measurement, we classified patients into mutually exclusive lipid-level
11
12 151 categories using common clinical thresholds[25] including LDL-C (30-79, 80-99, 100-129, 130-
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14 152 159, 160-189, or 190 mg/dL or higher) and T-C (121-160, 161-200, 201-240, 241-280, or 281
15
16 153 mg/dL or higher). In supplemental analyses, we classified the T-C/HDL-C ratio as ≤ 3.0 , > 3.0 -
17
18 154 4.0, > 4.0 -5.0, > 5.0 -6.0, or > 6.0 , and triglycerides/HDL-C ratio into quintiles. Again, to
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20 155 potentially mitigate potential bias due to reverse causation, we selected the LDL-C category of
21
22 156 80-99 mg/dL as the referent group, rather than the lowest LDL-C group (30-79 mg/dL).
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26 157 **Outcome measures**

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28 158 The main outcome measure was all-cause mortality with the number of days and years of follow-
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30 159 up calculated starting 365 days after the baseline cholesterol measurement. For patients who did
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32 160 not die, their length of follow-up was calculated starting 365 days after the baseline cholesterol
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34 161 measurement and until their last record in the EMR system. In secondary analyses, the composite
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36 162 outcome of occurrence of ASCVD was evaluated.
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40 163 **Statistical analysis**

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42 164 For patients within the respective study-defined baseline LDL-C categories, median and
43
44 165 interquartile range (IQR) for continuous variables and counts and percentages for categorical
45
46 166 variables are presented. For each LDL-C category, the Kaplan-Meier method was used to
47
48 167 calculate cumulative mortality rates at 1-, 5-, and 10-year follow-up, with survival curves plotted
49
50 168 at 6-month intervals out to 12 years. Patients who did not die were censored at last date of
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52 169 follow-up. Cox regression was used to estimate hazard ratios (and corresponding 95%
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3 170 confidence intervals) of mortality over the full follow-up period by baseline LDL-C. A crude
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5 171 model was first fit followed by an adjusted model that included covariates selected by a forward
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8 172 stepwise approach using an entry p -value of $< .01$ and initiation of statin use any time after 1-
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10 173 year of follow-up. Separate estimates for the relationship between initiation of statin use and
11
12 174 mortality are not presented due to expected immortal time bias (i.e., requirement to be alive
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14 175 during follow-up to initiate statin use). Secondary analyses of lipid parameters used the same
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16 176 methods as for LDL-C and included categories of the T-C/HDL-C and triglycerides/HDL-C
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18 177 ratios.

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21 178 In addition to the clinical categories used to define and evaluate baseline lipid levels, in
22
23 179 secondary analyses, each lipid parameter was evaluated in relation to mortality risk by use of
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25 180 non-parametric generalized additive models using smoothing splines adjusting for the same
26
27 181 covariates used in the Cox regression models. The smoothing parameters including the number
28
29 182 of degrees of freedom were optimized by use of generalized cross validation (GCV).
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33 183 We used SAS, version 9.4 (SAS Institute) for all analyses.
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35 184 **Subgroup analyses**

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37 185 Subgroup analyses for estimation of the relationship between LDL-C category and mortality
38
39 186 included age (50-69, 70-89), sex (female, male), and baseline ASCVD risk classification
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41 187 (low/borderline, intermediate, high, risk not determined).
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44 188 **Patient and public involvement**

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46 189 None.
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50 51 191 **RESULTS**

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3 192 The mean (SD) LDL-C was 119 (31) mg/dL, and the prevalence of patients within the six LDL-
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5 193 C categories was as follows: 30-79 (9.1%), 80-99 (18.3%), 100-129 (39.1%), 130-159 (24.4%),
6
7 194 160-189 (7.1%), or 190 mg/dL or higher (2.0%) (**Table 1**). The median age of patients was 59
8
9 195 years and mean age ranged nominally across the six LDL-C categories from 60.7 to 61.7 years.
10
11 196 There was a general indication of overall higher baseline risk in the group of patients with LDL-
12
13 197 C from 30-79 mg/dL (**Table 1**) (consistent with the stated concern of potential reverse
14
15 198 causation). This included a numerically higher prevalence of current smokers and those with a
16
17 199 history of various comorbidities (e.g., atrial fibrillation, arrhythmia, congestive heart failure,
18
19 200 chronic obstructive pulmonary disease), as well as nominally higher prevalence of selected
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21 201 medication use (e.g., ACE inhibitors, beta-blockers, diuretics, opioids, direct oral
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23 202 anticoagulants). History of cancer was slightly higher in the two lowest LDL-C categories,
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25 203 whereas estimated 10-year ASCVD risk was highest in those with baseline LDL-C \geq 190 mg/dL.
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31 **Patient follow-up**

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33 205 The mean and median follow-up after excluding the study requirement to have survived at least
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35 206 1-year after baseline cholesterol measurement was 6.1 and 5.9 years, respectively, and 17% of
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37 207 patients had 10 or more years of follow-up. Across the six LDL-C categories, the mean years of
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39 208 follow-up among patients who did not die ranged from 5.8 to 6.4 years. In total, 48.9% to 55.5%
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41 209 of patients had their first LDL-C measurement in calendar year 2015 or earlier, and the
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43 210 percentage of patients with their last follow-up extending into calendar year 2023 ranged from
44
45 211 57.8% to 63.4%, thereby suggesting non-informative censoring.
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49 **Overall assessment of mortality**

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51 213 In ascending order from lowest LDL-C category (30-79 mg/dL) to highest LDL-C category
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53 214 (\geq 190 mg/dL), 10-year cumulative mortality rates were U-shaped at 19.8%, 14.7%, 11.7%,
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3 215 10.7%, 10.1%, and 14.0% (**Table 2, Figures 1 and 2**). Adjusted mortality hazard ratios (HR)
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5 216 and 95% confidence intervals (CI) (**Table 2**), as compared to the referent group of LDL-C 80-99
6
7 217 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),
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9 218 130-159 mg/dL (0.88, CI:0.84-0.93), 160-189 mg/dL (0.91, CI:0.84-0.98), \geq 190 mg/dL (1.19,
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11 219 CI:1.06-1.34), respectively. Thus, the 3 LDL-C categories within the range of 100-189 mg/dL
12
13 220 showed similar, slightly lower mortality risk compared to the referent group of LDL-C 80-99
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15 221 mg/dL. When evaluated as a continuous variable, the relationship between LDL-C and mortality
16
17 222 was mostly U-shaped, with the lowest risk of mortality in the range of approximately 110 to 190
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19 223 mg/dL (**Supplement Figure 2, upper left**).

24 224 **Assessment of ASCVD**

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26 225 In ascending order from lowest LDL-C category (30-79 mg/dL) to highest LDL-C category
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28 226 (\geq 190 mg/dL), 10-year cumulative rates of ASCVD were U-shaped at 6.5%, 5.3%, 4.7%, 4.8%,
29
30 227 5.1%, and 7.6% (**Table 3, top half**). Adjusted HRs of risk of ASCVD as compared to the
31
32 228 referent group of LDL-C 80-99 mg/dL, were as follows: 30-79 mg/dL (1.10, CI:1.00-1.20), 100-
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34 229 129 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,
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36 230 CI:0.88-1.08), \geq 190 mg/dL (1.23, CI:1.06-1.43), respectively. Thus, the 3 LDL-C categories
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38 231 within the range of 100-189 mg/dL showed similar yet nominally lower risk of ASCVD
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40 232 compared to the referent group of LDL-C 80-99 mg/dL. Similar results were observed for the
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42 233 composite outcome of ASCVD/mortality (**Table 3, bottom half**.) Baseline ASCVD risk
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44 234 categories of low, medium, and high risk were strongly associated with 10-year rates of ASCVD
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46 235 (1.9%, 4.9%, 9.8%, respectively).

51 236 **Subgroup analyses**

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3 237 For the two different age groups, the 3 LDL-C categories within the range of 100-189 mg/dL
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5 238 showed relatively similar and slightly lower mortality risk compared to the referent group of
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7 239 LDL-C 80-99 mg/dL (**Table 2, Figure 2**). In a similar manner for both females and males, the 3
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9 240 LDL-C categories within the range of 100-189 mg/dL showed relatively similar and slightly
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11 241 lower mortality risk compared to the referent group of LDL-C 80-99 mg/dL (**Supplement Table**
12
13 242 **3**). Males with LDL-C ≥ 190 mg/dL did not have a significantly higher risk of mortality than
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15 243 those with LDL-C 80-99 mg/dL (adjusted HR = 1.06, CI: 0.85-1.32). When stratified by 10-year
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17 244 ASCVD risk score, again, the 3 LDL-C categories within the range of 100-189 mg/dL showed
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19 245 relatively similar and statistically lower mortality risk compared to the referent group of LDL-C
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21 246 80-99 mg/dL (**Supplement Table 4**).

247 **Secondary lipid measures**

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

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3 260 When evaluated as continuous variables, the relationship between T-C and adjusted risk
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5 261 of mortality was mostly U-shaped (similar to LDL-C), whereas other lipid/mortality relationships
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7 262 presented in a mostly gradient manner (**Supplement Figure 2**). Specifically, lower HDL-C
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10 263 generally indicated higher adjusted risk of mortality, whereas higher triglycerides, total to HDL-
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12 264 C ratio, and triglycerides to HDL-C ratio indicated higher adjusted risk of mortality.

14 265 **Evaluation of potential reverse causation**

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17 266 By study design, the 2,494 patient deaths that occurred from baseline LDL-C measurement to
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19 267 365 days were excluded from the primary analysis. Among these excluded patients, the
20
21 268 percentage of deaths distributed by LDL-C (mg) category was: 30 to 79 (30.4%), 80 to 99
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23 269 (20.1%), 100 to 129 (26.5%), 130 to 159 (14.6%), 160 to 189 (5.9%), 190 or higher (2.5%). The
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25 270 30.4% of deaths in the 30 to 79 mg/dL category is much higher than the 9.1% prevalence of
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27 271 patients in the 30 to 79 mg/dL category (see **table 1**) observed in the primary analysis. Similarly,
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29 272 14.1% of deaths excluded in the first year had a total cholesterol value of 40 to 120 mg/dL
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31 273 compared to 1.6% prevalence of patients in the primary analysis. These results validated the need
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33 274 to remove the influence of potential reverse causality and early deaths and patients with very low
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35 275 baseline cholesterol values from the analysis.
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42 277 **DISCUSSION**

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45 278 In this analysis among non-diabetic primary prevention-type patients aged 50 to 89 years not on
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47 279 statin therapy at baseline or within 1-year, we found no evidence of a gradient relationship
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49 280 between LDL-C and long-term mortality risk. Instead, we observed that within the entire LDL-C
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51 281 range of 100-189 mg/dL (about two-thirds of the total patient population), mortality risk was
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53 282 similar and slightly lower than the referent LDL-C category of 80-99 mg/dL. These data conflict
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3 283 with the prevailing belief that “lower LDL-C is better”[5-6] yet align with results from multiple
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5 284 studies. A large general population study of adults from Denmark showed a U-shaped
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7 285 relationship between LDL-C and long-term mortality, with lowest risk of all-cause mortality
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9 286 (among individuals not receiving lipid lowering treatment) being an LDL-C value of 140
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11 287 mg/dL.[26] Similarly, a large cohort study among Korean adults not on statin therapy showed a
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13 288 U-shaped relationship between LDL-C and CVD mortality, with an optimal LDL-C range of 90
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15 289 to 149 mg/dL.[27] Moreover, in a 20-year prospective cohort study of adults ages 18 and older
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17 290 derived from the National Health and Nutrition Examination Survey III (NHANES III), the
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19 291 lowest relative risk for all-cause mortality was for LDL-C in the range of 130 to <190
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21 292 mg/dL.[28] Collectively, these results indicate that the “optimal” or “normal” range for LDL-C
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23 293 for primary prevention of mortality among adults is likely wide and considerably higher than the
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25 294 suggested optimal LDL-C level of ≤ 100 mg/dL.[5-6]

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27 295 For multiple reasons, we chose to evaluate a population of non-diabetic primary
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29 296 prevention type adults aged 50 to 89 years not on statin therapy. First, both the prevalence and
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31 297 potential indication for initiating lipid-lowering therapy is relatively high in this
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33 298 population.[9,29,30] Second, prevailing guidelines and philosophy for initiating lipid-lowering
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35 299 therapy for secondary prevention of ASCVD and among persons with diabetes are well
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37 300 entrenched.[31-33] Third, consideration of initiating lipid-lowering therapy for primary
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39 301 prevention, particularly among older adults, should be carefully weighed based on empirical
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41 302 data[34-35] and potential side effects, including but not limited to muscle pain or weakness[36]
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43 303 and increased risk of developing diabetes.[37-39]

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45 304 Beyond our principal finding of no indication that “lower LDL-C is better,” other
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47 305 prominent findings were that overall and independent of age, the T-C/HDL-C and
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3 306 triglycerides/HDL-C ratios were predictive of long-term mortality risk, the latter of which
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5 307 presented in a gradient manner. A study derived from NHANES data showed a U-shaped
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7 308 relationship between T-C/HDL-C ratio and risk of all-cause mortality,[40] whereas results from
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9 309 our analysis were unidirectional with elevated risk of mortality evident among adults with a T-
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11 310 C/HDL-C ratio more than 5.0. Similar to our results, a large study among Korean adults showed
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13 311 a gradient relationship between triglycerides/HDL-C ratio and risk of ischemic heart disease.[41]
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15 312 Importantly, the triglyceride/HDL-C ratio has recently been reported to be a stronger predictor of
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17 313 10-year development of type 2 diabetes (strongly associated with mortality risk) than LDL-C,
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19 314 HDL-C, or triglycerides alone.[42]

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24 315 The importance of high HDL-C alone, or in conjunction with other lipids, has been
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26 316 extensively recognized. In brief, oxidative stress and inflammation are integral in the
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28 317 pathophysiology of atherosclerosis and cardiovascular disease.[43] Importantly, HDL-C exerts
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30 318 several physiological roles, prevents oxidation of LDL, and inhibits expression of pro-
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32 319 inflammatory cytokines by macrophages, as well as expression of adhesion molecules by
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34 320 endothelial cells,[44-46] and it is inversely associated with both all cause and CVD mortality
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36 321 risks.[18-19] Moreover, it is likely not coincidental nor trivial that the field of life insurance
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38 322 medicine recognizes and prioritizes the importance of HDL-C over LDL-C in determining
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40 323 underwriting classifications.[16,17,47] Unfortunately, from a public health perspective, a meta-
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42 324 analysis of 31 randomized controlled trials on the use of HDL-C modifying treatments showed
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44 325 little to no effect on cardiovascular and all-cause mortality.[48]

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49 326 There is an overall lack of consensus on the magnitude and statistical and clinical
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51 327 interpretation of the reduction in mortality risk potentially achieved with the use of LDL-C
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53 328 lowering therapies. Multiple reviews suggest that absolute mortality risk reductions from
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3 329 treatment with statins are small as compared to the more frequent reporting and emphasis of
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5 330 relative risk reductions.[49-52] Moreover, mortality reductions with recent use of PCSK-9
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7 331 inhibitors to lower LDL-C have been mixed and of low absolute risk.[53,54] Our postulate from
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9 332 both this review (e.g.,[10]) and empirical analysis is that whatever small absolute reductions in
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11 333 mortality risk may occur with use of LDL-C lowering therapies, they are most likely not causally
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13 334 related to LDL-C lowering, but potentially to more broad pleiotropic effects. For example, statin
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15 335 use has been shown to reduce inflammatory markers,[55] reduce vascular endothelial growth
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17 336 factor (VEGF) concentrations,[56] reduce platelet activity,[57] and increase nitric oxide
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19 337 bioavailability and stabilize atherosclerotic plaques.[58] These potential mechanisms of statins,
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21 338 rather than concomitant lowering of LDL-C, per se, may be expected to result in some reduction
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23 339 of ASCVD events.

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28 340 Arguably, it is irrelevant to patients as to the exact mechanism(s) by which use of statins
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30 341 and other lipid-lowering therapies may result in small absolute reductions in mortality risk.
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32 342 Rather than focusing on LDL-C level, per se, we submit that health professionals should promote
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34 343 established (causal) mechanisms that reduce future risk of major ASCVD events, including
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36 344 weight, blood pressure, and blood sugar control, physical activity, avoidance of smoking, and
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38 345 stress reduction. Similarly, our results suggest that adult non-diabetic patients counselled for
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40 346 primary prevention of ASCVD be apprised of their estimated future risk of ASCVD with
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42 347 minimal consideration of their LDL-C concentration and more consideration of the T-C/HDL
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44 348 and triglyceride/HDL-C ratios along with other known causes of ASCVD (e.g., smoking,
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46 349 physical inactivity). Moreover, use of coronary artery calcium scoring in primary prevention is
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48 350 supported by a wealth of data showing that it substantially improves risk prediction including
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50 351 when combined with traditional risk factors and scores.[59-61]
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352 **Limitations**

353 Our study has limitations. First, we were unable to assess cause-specific mortality which would
354 have provided additional insight into the relationship between LDL-C and CVD mortality.
355 Similarly, our assessment of risk of ASCVD in relation to baseline LDL-C levels is based on
356 ascertainment of events within UPMC hospitals and not external facilities – there is certainly
357 some unknown level of ascertainment of ASCVD events. Second, we chose the index date for
358 follow-up mortality assessment to begin 1-year after baseline cholesterol measurement to ideally
359 minimize potential bias due to reverse causation (i.e., low LDL-C being an overall marker of
360 malnutrition and poor health). However, low LDL-C has been frequently reported in cancer
361 patients (e.g., [25,62,63]) and many cancers have a viral etiologic component[64] and with
362 potentially long latency. Theoretically, some patients with the lowest LDL-C values in our
363 analysis may have been in the early stages of cancer development and hence at elevated long-
364 term mortality risk. This is why we chose LDL-C 80-99 mg/dL as the referent group (rather than
365 30-79 mg/dL), and the observation that mortality risk was similar across a wide range of LDL-C
366 values (100–189 mg/dL) argues against appreciable bias due to reverse causation. Third, absence
367 of statin use at baseline and within the first year of the study (inclusion criterion) was based on
368 patient reported data in the EMR and not from prescription data – this leaves open the possibility
369 for some misclassification. In addition, the study requirement for absence of statin at baseline or
370 within one year may have resulted in a patient population generally less likely to initiate lipid-
371 lowering therapy in the long-term. Lastly, we cannot rule out potential residual confounding
372 despite statistical adjustment for a large set of covariates associated with mortality.

373

374 **CONCLUSIONS**

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3 375 Our analysis indicates that among non-diabetic primary prevention-type patients aged 50 to 89
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5 376 years and not on statin therapy, the lowest risk for long-term mortality exists in the wide LDL-C
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7 377 range of 100-189 mg/dL which is much higher than current recommendations. Our analysis also
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9 378 shows that lower T-C/HDL-C and triglycerides/HDL-C ratios are independently associated with
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11 379 lower mortality risk, whereas LDL-C appears to be of limited to no predictive value.
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14 380 Collectively, these observations suggest that adult non-diabetic patients counselled for primary
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16 381 prevention of ASCVD be apprised of their estimated future risk of ASCVD with minimal
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18 382 consideration of their LDL-C concentration and more consideration of the T-C/HDL and
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20 383 triglycerides/HDL-C ratios along with other established causes of ASCVD (e.g., high blood
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22 384 pressure, smoking, physical inactivity) and potentially coronary artery calcium scoring.
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31 **Contributors**

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33 388 Kevin E Kip: conception, statistical analysis, writing, and editing. David M Diamond:
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35 389 conception, critical review, and editing. Suresh R Mulukutla: critical review and editing. Oscar C
36
37 390 Marroquin: conception, critical review, and editing.
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41

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46
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51 **Competing interests**

52 396 None.
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5 399 **Patient consent for publication**6
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8 400 Not applicable.9
10 40111
12 402 **Ethics approval**13
14 403 The Quality Improvement Review Committee and Institutional Review Board at the University
15 404 of Pittsburgh Medical Center provided ethical review and approval of the study as an exempt
16
17 405 protocol (Project ID: 4565), and all data remained deidentified for this analysis.
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22 40623
24 407 **Provenance and peer review**25
26 408 Not commissioned, externally peer reviewed.27
28 40929
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31 410 **Data availability statement**32
33 411 *Study protocol:* No separate study protocol was required a priori, as this retrospective analysis
34
35 412 was deemed a quality improvement initiative with ethical review and approval granted by the
36
37 413 UPMC Quality Improvement Review Committee and Institutional Review Board. *Statistical*
38
39 414 *code:* Selected statistical code may be requested from Dr. Kevin Kip (e-mail,
40
41 415 kipke2@upmc.edu). *Dataset:* The dataset contains protected health information and will not be
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43 416 available.
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3 616 **FIGURE LEGENDS**
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5 617 **Figure 1.** Plot of cumulative mortality rates in 6-month intervals over 12 years of follow-up
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8 618 by baseline LDL-C category. Dashed lines depict the 3 lowest LDL-C categories
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10 619 (30-79, 80-99, 100-129 mg/dL) and solid lines depict the highest LDL-C
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12 620 categories (130-159, 160-189, ≥ 190 mg/dL).
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14 621 **Figure 2.** Plot of mortality hazard ratios (HR, filled circles) and 95% confidence intervals
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16 622 (vertical lines) across categories of LDL cholesterol (top), total cholesterol to
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18 623 HDL cholesterol ratio (middle), and triglycerides to HDL cholesterol ratio
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20 624 (bottom). The left side of the graph is for patients aged 50-69 years; the right side
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22 625 is for patients aged 70-89 years. The dashed line reflects the referent group null
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24 626 value (1.0) for the HR. Q: quintile. Each model is adjusted for: age, race, sex,
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26 627 BMI, current smoker, former smoker, history of the following in the past year:
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28 628 hypertension, atrial fibrillation, arrhythmia, congestive heart failure, cancer,
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30 629 chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic
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32 630 and diastolic blood pressure, glucose, and the following medications in the past
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34 631 year: ACE Inhibitors, beta-blockers, calcium blockers, any SBP lowering
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36 632 medication, diuretics, aspirin, DOACS, anti-depressants, opioids, and statin
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38 633 initiation >1 year after baseline cholesterol measurement.
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47 635 **Supplement Figure 1.** Flow diagram of selection of patients for the study cohort.
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49 636 **Supplement Figure 2.** Continuous spline plots of the relationship between different lipid
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51 637 parameters and adjusted risk of long-term mortality. The spline
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53 638 includes 95% confidence bands, with narrower bands indicating a
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3 639 higher prevalence of patients with the given lipid value. X-axis
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5 640 values below the horizontal line with 0.0 value indicate lower risk
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8 641 of mortality; X-axis values above the line indicate higher risk of
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10 642 mortality.

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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 arrhythmia, 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 (%)			Total # deaths	Crude HR	Adjusted HR	95% C.I.
		1-year	5-year	10-year				
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, arrhythmia, 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 (%)			Total # events	Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year				
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, arrhythmia, 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.

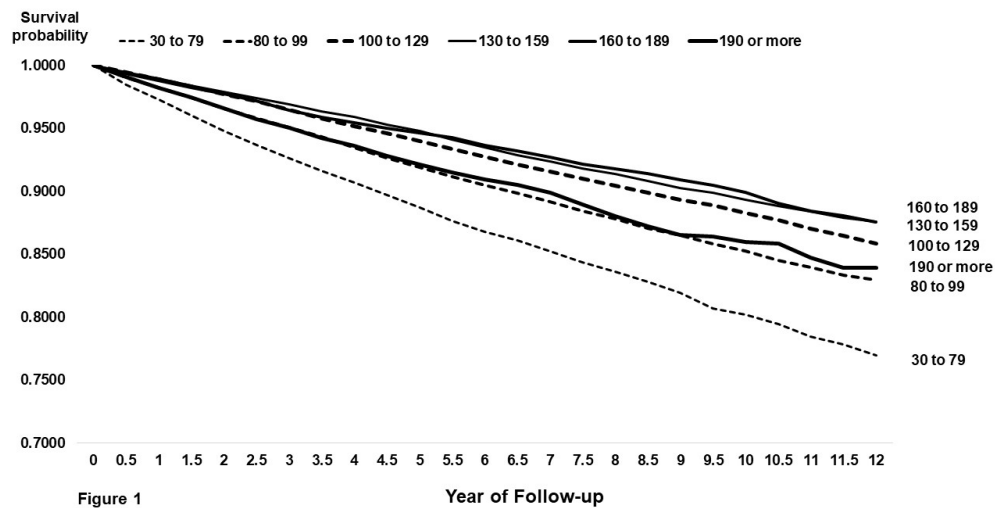


Figure 1.

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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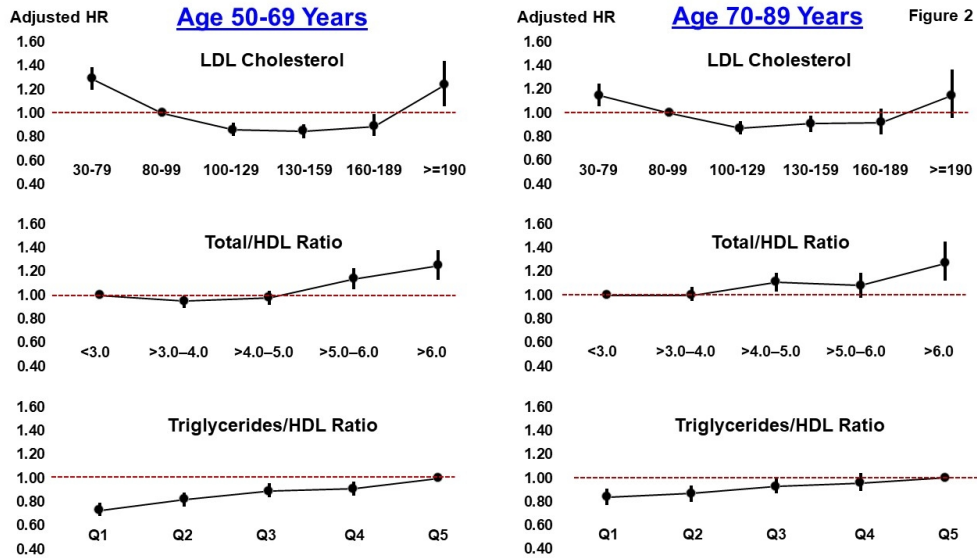


Figure 2.

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, arrhythmia, 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

Age	White Male		Black (AA) Male		White Female		Black (AA) Female	
	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 (%)			Total # deaths	Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year				
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, arrhythmia, 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 (%)			Total # deaths	Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year				
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, arrhythmia, 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

Total/HDL Cholesterol Ratio	n	Cumulative incidence (%)			Total # deaths	Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year				
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

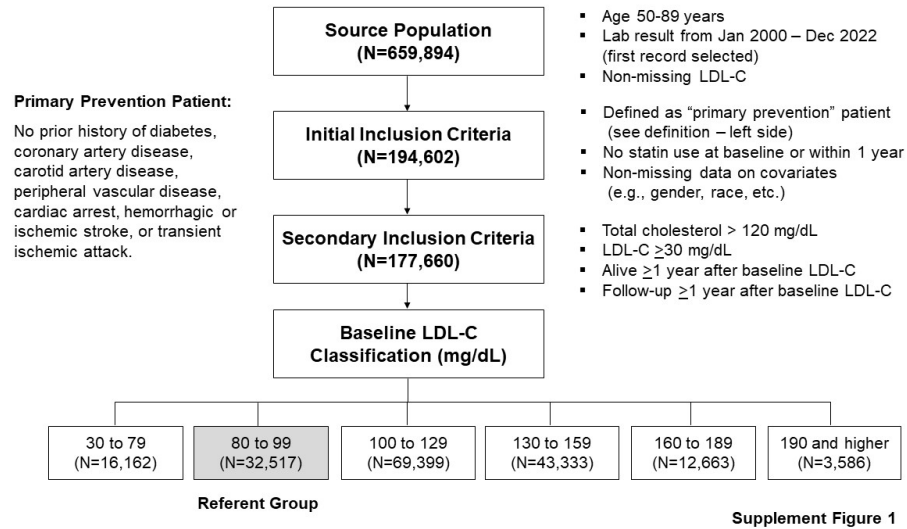
Model: Adjusted for age, race, sex, BMI, current smoker, former smoker, history of the following in the past year: hypertension, atrial fibrillation, arrhythmia, congestive heart failure, cancer, chronic obstructive pulmonary disease, chronic kidney disease, baseline systolic and diastolic blood pressure, 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 (%)			Total # deaths	Crude HR	Adj. HR Model	95% C.I.
		1-year	5-year	10-year				
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, arrhythmia, 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.

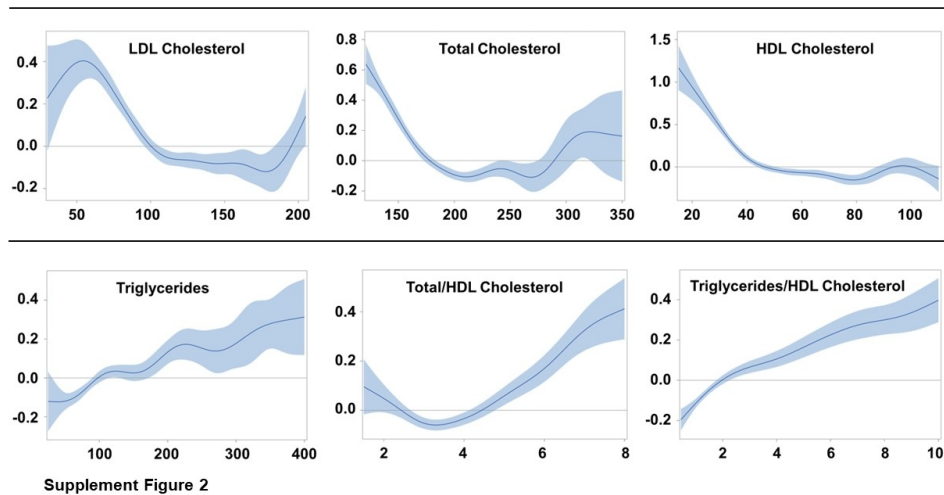
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Supplement Figure 1

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

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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.