PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is LDL cholesterol associated with long-term mortality among primary prevention adults? A retrospective cohort study from a large healthcare system
AUTHORS	Kip, Kevin; Diamond, David; Mulukutla, Suresh; Marroquin, Oscar

VERSION 1 – REVIEW

REVIEWER	Szarek, Michael SUNY Downstate Health Sciences University
REVIEW RETURNED	05-Nov-2023

GENERAL COMMENTS	1. For continuous characteristics in Table 2, rather than presenting the mean and median, please provide the median (Q1, Q3). 2. Please provide additional details about the number of individuals that were LTFU. How many were LTFU? Was the risk of being LTFU related to LDL-C concentrations? Are there any indications that LTFU resulted in informative censoring? 3. Rather than looking at risk of death in ordered categories of LDL-C, T-C, etc., a more informative analysis would involve analyses of these relationships with continuous splines of LDL-C, T-C, etc. These splines should reflect adjustment for prognostic characteristics, e.g., age, etc. as well as statin use. 4. Regarding the following sentence in the discussion: Moreover, mortality reductions with recent use of PCSK-9 inhibitors to lower LDL-C have been unimpressive. There was a nominally significant reduction in all-cause death in ODYSSEY OUTCOMES; the corresponding paper should be referenced: DOI: 10.1161/CIRCULATIONAHA.118.038840 5. The relationships between LDL-C, T-C, etc. among the individuals who were excluded due to death within 1 year of baseline should be summarized. 6. How many individuals developed clinically-evident ASCVD during follow-up? Did it correspond with estimated ASCVD 10-year risk at baseline? Given the 10-year risk in Table 2, it seems that a higher percentage of individuals would have been expected to start statin therapy during follow-up.

REVIEWER	Kawamoto, Ryuichi Ehime University
REVIEW RETURNED	25-Jan-2024

GENERAL COMMENTS	This article presents an interesting analysis of statistical data from an American population that demonstrates the potential protective role of LDL in all-cause mortality prevention. Prior studies have demonstrated that LDL has a protective effect against the risk of infectious diseases, especially in populations susceptible to infectious diseases. To enhance the utility of this study, it would be beneficial to examine broader categories of mortality in this population, particularly cardiovascular death. Such an analysis would clarify whether the observed impact on all-cause mortality is specifically related to reductions in other causes of death, such as infectious diseases. The report warns against the conventional treatment guideline of an optimal LDL-C value of 100 mg/dL when the outcome of mortality is sought. This is because many people would have to be treated with statins to actually achieve this value.

REVIEWER	Yi, S.W. The Catholic University of Korea
REVIEW RETURNED	01-Feb-2024

GENERAL COMMENTS	Despite evidence from clinical trials of statins, the causal role of LDL-C in all-cause mortality is not completely clear. More evidence is needed to confirm whether lower LDL-C is better for all-cause mortality and cardiovascular mortality. 1. The Introduction section is too long and contains a lot of unnecessary detail. For example, the section on "Widespread use of the ACC-ASCVD Risk Estimator" can be substantially reduced. Some section can be discussed in the Discussion section rather than in the Introduction section. 2. "high LDL-C may not be a significant cause of ASCVD or premature mortality." Please be clear about what the authors meant. Is it that high LDL-C is not a cause of premature mortality, or that the magnitude of the effect of high LDL-C is not large? 3. Lines 89-91. There have been studies reporing mortality risk reductions with LDL-C reduction in statin trials (e.g. CTT collaboration, 2010). These studies should also be commented on for the sake of balance. Cholesterol Treatment Trialists' CTT Collaboration; Baigent C, Blackwell L, Holland LE, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170, 000 participants in 26 randomised trials. Lancet. 2010;376:1670-1681. 4. A flow chart of the study population may be helpful in understanding the study.

	5. Please report the number of deaths for HR in Table 3, Supplementary Tables 2-5. 6. Figure 2. Please specify adjusted variables. 7. Discussion Lines 237-248. Among the many studies of the association between LDL-C and all-cause and cardiovascular mortality, only one Danish study was commented on. These are the main findings of the study. Other studies worth mentioning include, but are not limited to, a large study reporting the association in 14.9 million Korean adults (Yi et al., 2022, Figure S11) and a US study (Rong et al., 2022). Yi SW, An SJ, Park HB, et al. Association between low-density lipoprotein cholesterol and cardiovascular mortality in statin non-users: a prospective cohort study in 14.9 million Korean adults. Int J Epidemiol. 2022 Aug; 51(4): 1178-1189. Rong S, Li B, Chen L, et al. Association of Low-Density Lipoprotein Cholesterol Levels with More than 20-Year Risk of Cardiovascular and All-Cause Mortality in the General Population. J Am Heart Assoc. 2022 Aug 2;11(15):e023690. 8. Lines 286-288 The statements about statins and a false sense of security may be irrelevant to the study results. 9. The value of T-C/HDL and triglycerides/HDL-C ratios in the CVD risk prediction model should be discussed more thoroughly with citations, as the author emphasised in the conclusion. 10. Sentences related to "ACC-ASCVD Risk Estimator", especially lines 326-329, may be appropriate in the Discussion section, but not in the Conclusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1, Dr. Michael Szarek, SUNY Downstate Health Sciences University		
1	For continuous characteristics in Table 2, rather than presenting the mean and median, please provide the median (Q1, Q3).	Revised as suggested.

2	Please provide additional details about the number of individuals that were LTFU. How many were LTFU? Was the risk of being LTFU related to LDL-C concentrations? Are there any indications that LTFU resulted in informative censoring?	Unlike a true prospective cohort study with fixed follow-up intervals, our analysis is based on passive follow-up within the UPMC system with patient follow-up being derived from the last available record (e.g. office visit, lab results, prescription, etc.) in the EMR. In this regard, we have added text in the results under the subheading of Patient Followup, and these results suggest that censoring was non-informative.
3	Rather than looking at risk of death in ordered categories of LDL-C, T-C, etc., a more informative analysis would involve analyses of these relationships with continuous splines of LDL-C, TC, etc. These splines should reflect adjustment for prognostic characteristics, e.g., age, etc. as well as statin use.	We appreciate the recommendation to examine lipid levels as non-linear continuous variables in relation to long-term risk of mortality. Our preference is to still focus on the 6 defined categories of LDL-C as they represent common thresholds used in clinical practice, such as whether to initiate lipid-lowering therapy. Nonetheless, we have presented secondary results as continuous splines in Supplement Figure 2 and briefly describe the results in the text. In general, these results are consistent with those presented categorically.
4	Regarding the following sentence in the discussion: Moreover, mortality reductions with recent use of PCSK-9 inhibitors to lower LDL-C have been unimpressive. There was a nominally significant reduction in allcause death in ODYSSEY OUTCOMES; the corresponding paper should be referenced: DOI: 10.1161/CIRCULATIONAHA.118.038840	Revised, as suggested.
5	The relationships between LDL-C, T-C, etc. among the individuals who were excluded due to death within 1 year of baseline should be summarized.	While we purposely excluded these patients from the analysis to mitigate potential reverse causality (i.e. very low LDL-C being a marker for serious illness), we have briefly analyzed and described the results for these patients under the subheading of Evaluation of Potential Reverse Causation.

6	How many individuals developed clinicallyevident ASCVD during follow-up? Did it correspond with estimated ASCVD 10-year risk at baseline? Given the 10-year risk in Table 2, it seems that a higher percentage of individuals would have been expected to start statin therapy during follow-up.	These results have been added under the subheading Assessment of ASCVD, and they are generally consistent with the all-cause mortality results. We have added a limitation stating that assessment of ASCVD was based on events documented within the UPMC system (i.e., events for patients treated at non-UPMC hospitals would not be captured) whereas mortality assessment had additional external ascertainment through the Social Security Index. Because our inclusion criteria required no use of statins at baseline or within the first year of follow-up, the sample may have been biased towards individuals generally less likely to initiate lipid-lowering therapy over the long-term. We have added this as a limitation.
Reviewer: 2, Dr. Ryuichi Kawamoto, Ehime University		
1	To enhance the utility of this study, it would be beneficial to examine broader categories of mortality in this population, particularly cardiovascular death. Such an analysis would clarify whether the observed impact on all-cause mortality is specifically related to reductions in other causes of death, such as infectious diseases.	As described, our data does not have information on cause of death. However, we have added new results on the relationship between LDL-C and risk of ASCVD events. These results are somewhat consistent with the all-cause mortality results, yet generally show a less pronounced U-shaped relationship. Thus, we might infer that some of the lower risk of mortality among patients with baseline LDL-C in the range of 100 to 190 mg/dL might be due to reduced risk of death for noncardiac causes. However, such inference is very difficult to reliably estimate from the data, and thus we prefer not to speculate.
2	The report warns against the conventional treatment guideline of an optimal LDL-C value of 100 mg/dL when the outcome of mortality is sought. This is because many people would have to be treated with statins to actually achieve this value.	We have added some context to this statement in the first paragraph of the Discussion.

Reviewer: 3, Dr. S.W. Yi, The Catholic University of Korea		
1	The Introduction section is too long and contains a lot of unnecessary detail. For example, the section on "Widespread use of the ACC-ASCVD Risk Estimator" can be substantially reduced. Some section can be discussed in the Discussion section rather than in the Introduction section.	Revised, as suggested.
2	"high LDL-C may not be a significant cause of ASCVD or premature mortality." Please be clear about what the authors meant. Is it that high LDL-C is not a cause of premature mortality, or that the magnitude of the effect of high LDL-C is not large?	We have clarified the statement.
3	Lines 89-91. There have been studies reporting mortality risk reductions with LDL-C reduction in statin trials (e.g. CTT collaboration, 2010). These studies should also be commented on for the sake of balance. Cholesterol Treatment Trialists' CTT Collaboration; Baigent C, Blackwell L, Holland LE, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170, 000 participants in 26 randomised trials. Lancet. 2010;376:1670-1681.	We have added and described the reference to the 2010 Cholesterol Treatment Trialists' CTT Collaboration meta-analysis. For this earlier meta-analysis, it is important to note that the absolute reduction in all-cause mortality was only 0.2% per 1.0 mmol/L reduction in LDL-C. With the revised text, we believe we have provided adequate balance in review of the literature.
4	A flow chart of the study population may be helpful in understanding the study.	Revised, as suggested (please see Supplement Figure 1).
5	Please report the number of deaths for HR in Table 3, Supplementary Tables 2-5.	Revised, as suggested.
6	Figure 2. Please specify adjusted variables.	The variables that were adjusted for have been added to the figure legend.
7	Discussion Lines 237-248. Among the many studies of the association between LDL-C and all-cause and cardiovascular mortality, only one Danish study was commented on. These are the main findings of the study. Other studies worth mentioning include, but are not limited to, a large study reporting the association in 14.9 million Korean adults (Yi et al., 2022, Figure S11) and a US study (Rong et al., 2022).	We thank the reviewer for these excellent references which have been summarized in the text and generally support our findings and conclusions.

	Yi SW, An SJ, Park HB, et al. Association between low-density lipoprotein cholesterol and cardiovascular mortality in statin non-users: a prospective cohort study in 14.9 million Korean adults. Int J Epidemiol. 2022 Aug; 51(4): 11781189. Rong S, Li B, Chen L, et al. Association of LowDensity Lipoprotein Cholesterol Levels with More than 20-Year Risk of Cardiovascular and AllCause Mortality in the General Population. J Am Heart Assoc. 2022 Aug 2;11(15):e023690	
8	Lines 286-288 The statements about statins and a false sense of security may be irrelevant to the study results.	We have removed these statements from the discussion.
9	The value of T-C/HDL and triglycerides/HDL-C ratios in the CVD risk prediction model should be discussed more thoroughly with citations, as the author emphasised in the conclusion.	We have included and summarized additional citations on the T-C/HDL and triglycerides/HDL-C ratios.
10	Sentences related to "ACC-ASCVD Risk Estimator", especially lines 326-329, may be appropriate in the Discussion section, but not in the Conclusion.	We removed the sentences from the Conclusion, and overall, have placed much less emphasis on this topic. Our main point in discussing how this calculator is routinely used for patient risk estimation is how easily there may be a propensity for clinicians to prescribe statin therapy for middle aged and older adults. Our analysis indicates that LDL-C level, per se, is not very important with respect to mortality risk.

VERSION 2 – REVIEW

REVIEWER	Szarek, Michael SUNY Downstate Health Sciences University
REVIEW RETURNED	12-Mar-2024

GENERAL COMMENTS	responses to prior comments are acceptable

REVIEWER	Kawamoto, Ryuichi Ehime University
REVIEW RETURNED	09-Mar-2024

GENERAL COMMENTS	Comments to the Author: We thank for your careful and extensive revision.

	The authors have revised the manuscript carefully according to the reviewer's comments. The manuscript will be acceptable.

REVIEWER	Yi, S.W. The Catholic University of Korea
REVIEW RETURNED	15-Mar-2024

GENERAL COMMENTS	The authors have adequately addressed the points raised by the reviewer in the previous review.