Reviewer’s report

Title: Blood lipids and lipoproteins in relation to incidence and mortality risks for CVD and cancer in the prospective EPIC-Heidelberg cohort

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Reviewer: Seth Martin

Reviewer's report:

I reviewed Katzke et al's manuscript on blood lipids and lipoproteins in relation to mortality for cardiovascular disease and cancer in EPIC-Heidelberg cohort. This is an interesting manuscript as the topic of competing risk between cardiovascular disease and cancer is of increasingly recognized, but understudied. The authors also identify and address an important problem in terms of uncertainties with prior studies of lipid measures and mortality, with some paradoxical signals that have led to confusion.

A strength of this study is the prospective nature. This cohort has been well described. The authors find inverse associations of certain lipid biomarkers with cancer incidence and mortality with the exceptions of HDL cholesterol and Lp(a). HDL-C showed a positive association with breast cancer and Lp(a) had a positive association with prostate cancer. Overall, the observed cancer pattern seems complicated in comparison with the CVD risk pattern. This certainly is something that informs past and future analyses of lipids and lipoproteins with mortality as an outcome.

I have a couple of questions with respect to methods of the study that if addressed may strengthen the paper.

First, my reading of the methods was that standard Cox models were used. I was curious why standard Cox regressions were done rather than using competing risk methods given the obvious competing risk for mortality of cardiovascular disease and cancer?

Secondly, I was wondering whether the authors have access to serial measurements of these lipids/lipoproteins and whether the cumulative exposure to these parameters can be considered rather than one-time values? Given the common use of lipid altering drugs it strikes me that this is a major complicating factor in any prospective cohort studies of lipids and lipoproteins in relation to clinical outcomes. So it would be of interest to consider modeling cumulative exposure to lipids and lipoproteins as the exposure variable in the study since it is really cumulative exposure that is pathophysiologically relevant.

Furthermore, I had two issues that I would like to bring up with respect to the interpretation of results. It seems to me that the sometimes fall into causal statements in this paper, and perhaps this is not their intent or supported by the study design. For example, on page 13 the authors state
as in our study, they all showed a low total cholesterol conferred greater cancer mortality. I wondered if the authors really mean to implicate in a causal fashion lower cholesterol in mortality in their manuscript. In my view, it is not supported by the data, and a statement of association would be more appropriate.

Finally, in terms of the clinical implications, I am curious for the authors to comment on these findings in relation to randomized trials. It strikes me that clinical trials of statins for example, as summarized by the CTTC group, clearly do not show any difference in cancer incidence. How do we reconcile those high-quality data with the findings of this study and the observational literature?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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