Author’s response to reviews

Title: Serum total cholesterol and risk of cardiovascular and non-cardiovascular mortality in old age: a population-based study

Authors:

Yajun Liang (yajun.liang@ki.se)
Davide Liborio Vetrano (davide.vetrano@ki.se)
Chengxuan Qiu (chengxuan.qiu@ki.se)

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Author’s response to reviews:

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Editor,

This letter refers to online submission of our revised manuscript based on your decision letter dated November 1, 2017. We thank the reviewers for kindly offering valuable comments. The comments and suggestions have now been fully considered, and whenever possible, carefully incorporated into the revised version, as specified below (we first copy the comments, followed by our responses).

Ben Schöttker (Reviewer 1):

Question 1. Page 4, line 10: 'Institution' should be 'institutions'.

Answer: We have now updated the word (see page 4, line 10).

Question 2. Page 5, line 14-25: The authors didn't show how the comparison of baseline characteristics between alive and died participants. The authors should add statistical analyses to this part.
Answer: We added a sentence to describe the statistical analysis for comparison of baseline characteristics between alive participants and died ones (see page 5, lines 22-25).

Question 3. Page 6, line 10: According to table 1, 'had a higher level of total cholesterol' should be 'had a lower level of total cholesterol'.

Answer: We thank the reviewer for carefully pointing this out. We have now corrected the error (see page 6, line 22).

Question 4. Page 6, line 8-14: The text should be rewritten due to the wrong p values in table 1.

Answer: We have added the specific P value to each item other than combing the P values together (see page 6, lines 20-25).

Question 5. Page 15: The P values for current smoking, alcohol drinking, obesity, hypertension, use of cholesterol-lowering drugs and APOE ɛ4 between alive and died group are not correct. Please check them again.

Answer: Regarding that alive participants were significantly younger than those died, we tested the difference of baseline characteristics after controlling for age. We performed univariate analysis of variance for continuous variable and logistic regression or nominal regression for categorical variables after controlling for age (see page 5, lines 22-25, and page 16, line 9). We thank the reviewer for this comment, we have checked and verified all the P values.

Aileen Chan (Reviewer 2):

Question 1. Walking speed was measured by asking a person to walk 6 or 2.4 meters. How to determine the distance selected and why?

Answer: The length of the walk test was determined by asking the participants how fast they normally walk. Subjects who rated themselves as fast or normal walkers did the longer walk and those who self-rated as slow or very slow walkers did the shorter walk test. At home visits, the shorter walk test was always conducted due to space restrictions. We now add the detailed description of measurement on walking speed and cited a previous study (see pages 4-5, referenced no. 12).

Question 2. Did the blood samples for total cholesterol were fasting blood?

Answer: In SNAC-K, we first measured non-fasting serum cholesterol. If total cholesterol level was \(\geq 6.5\) mmol/L, then fasting serum cholesterol was measured. In this study, non-fasting total cholesterol was used. We now add a sentence to the text (see page 5, line 8).
Question 3. The blood lipid profile was lacking, this was important in determining the contributing factors of mortality, such as the 'good' and 'bad' cholesterols.

Answer: We agree with the reviewer that other components of blood lipid profile are also important for determining the contributing factors of mortality. However, we don’t have the data on other components of cholesterol. We acknowledged this as a limitation in this study (see page 9, lines 12-16).

Question 4. Cholesterol-lowering medication compliance was also lacking, this would lead to a mislead result if those noncompliance participants were counted as drug users.

Answer: The information of use of cholesterol-lowering medication was recorded according to self-report, which was further verified by inspecting drug prescriptions and containers (see page 5, lines 11-13). However, the information on compliance was not collected in the SNACK. This could be a limitation and we acknowledged in the discussion (see page 9, lines 16-18).

Question 5. Those died during follow-up were less likely to be currently smoking. This result was different from prior literature. It would be better if history of smoking also being reported, e.g., number of ex-smokers, years of smoking, etc.

Answer: We have added the information of former smoking into table 1 as one of the baseline characteristics (see page 16, table 1). Participants died during follow up were less likely to be former smokers and current smokers at baseline than those alive participants. A healthy survival effect may explain this finding: strong and genetically predisposed participants smokers died before being enrolled in SNACK.

We compared the baseline characteristics of the participants by smoking status and found that current smokers are younger (mean age: 75.4, 71.9 and 69.4 for never, former and current smoker, p<0.001), have lower prevalence of obesity (11.5%, 14.2% and 8.9%, p=0.009), hypertension (78.0%, 74.7% and 69.1%, p=0.001), marginally lower prevalence of diabetes (8.9%, 11.0% and 7.6%, p=0.066), and lower prevalence of cognitive impairment (17.0%, 11.1% and 10.5%, p<0.001) and walking limitation (32.1%, 22.6% and 20.2%, p<0.001) in comparison with never and former smokers.

Furthermore, we assessed the risk of mortality for smoking participants and found that after controlling for age and other covariates, the risk of all-cause mortality was not significant for former smoking (HR=1.05, 95% CI=0.91-1.21) but was significantly higher for current smoking (HR=1.58, 95% CI=1.30-1.91) in comparison with never smoking.

However, we only considered about covariates at baseline. The information on changes and amount of smoking during follow-up were not taken into account, which might also affect the mortality (see page 9, lines 20-22).
Question 6. 12.4% of subjects used cholesterol-lowering drugs at baseline. These subjects might have lower total cholesterol due to drug effects. Some still had high cholesterol level, was that due to not enough dose or noncompliance to drug therapy?

Answer: Among 831 persons who were pharmacologically treated with cholesterol-lowering agents, the rate of reaching the therapeutic goal was 85.8%. The rate was consistent with another paper from SNAC-K [Wang R, et al. PLoS ONE 2015;10(3): e0119582]. As shown in the previous study, the proportions of being treated and effectively controlled for high cholesterol increase with increasing age in high-income countries. Therefore, age may affect adherence to medical treatment. Compared to young and middle aged people, elders are more concerned about their health and, thus, are willing to better adhere to the treatment.

However, there were still 14.2% of those who used cholesterol-lowering drugs but still had higher level of total cholesterol. We agree with the reviewer that uncontrolled cholesterol might be due to the low dosage or noncompliance might also affect the control rate of high cholesterol. Unfortunately, we didn’t have the information on dose of cholesterol-lowering drugs and compliance of drug therapy. We acknowledged this as a limitation of this study (see page 9, lines 16-18).

Question 7. When assessing association between total cholesterol and mortality, did smoking also being controlled, as it showed lower mortality? May need discussion on the lower mortality of current smoker.

Answer: Yes, we controlled for smoking when assessing the association between total cholesterol and mortality. Please also refer to Question 5. We assessed the risk of mortality for smoking participants and found that after controlling for age and other covariates, the risk of mortality was not significant for former smoking (HR=1.05, 95% CI=0.91-1.21) but was significantly higher for current smoking (HR=1.58, 95% CI=1.30-1.91) in comparison with never smoking.

Question 8. Overall impression: The manuscript did not add much new knowledge. The conclusion was similar to prior findings as the results had been well addressed in literature that cholesterol had inverse association with mortality. The major weaknesses, though addressed as limitations, were the incomplete information on blood lipid profiles and medications for lowering cholesterol. These were the main factors that affected the results.

Answer: Indeed, lack of blood lipid profile and detailed information for cholesterol-lowering medications is the main weakness of this study. Despite of these limitations, our study, as stated in the discussion (see page 9), does add some knowledge to the research area of total cholesterol and mortality regarding the cause-specific mortality and application of competing risk regression models that have been rarely addressed in the previous studies. The findings implied that caution might be needed for therapeutic control of blood cholesterol among elderly people in the perspective of long-term risk for cardiovascular and non-cardiovascular mortality.
Finally, we have made careful editorial revisions. We have also updated the references by adding one more reference (Ref no. 13) and deleting one reference. Accordingly, all the references have been carefully reorganized. All major revisions have been highlighted in red color. We would like again to thank our reviewers for the relevant suggestions to further improve the manuscript. We hope that the paper is now acceptable for publication in the journal. We look forward to hearing from you soon.

Sincerely,

Yajun Liang, PhD

Department of Public Health Sciences
Karolinska Institutet
Widerströmska huset
171 77 Stockholm
Gävlegatan 16
113 30 Stockholm
SWEDEN
Tel.: +46 86905816
Fax: +46 86905954
E-mail: yajun.liang@ki.se

cc.: Dr. Chengxuan Qiu (chengxuan.qiu@ki.se)