Author's response to reviews

Title: Lifestyle risk factors and residual life expectancy at age 40: a German cohort study

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Author's response to reviews:

Revisions
Dear editor of BMC,

We appreciate all the comments/suggestions from the two reviewers, some of which have been incorporated in the revised manuscript. Below you will see our point-by-point responses to reviewers’ questions.

Best regards,
Kuanrong Li

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Reviewer: Evelyn Wong

Major Compulsory Revisions

1) With regards to low body weight being associated with reduced RLE, it would be worthwhile to explore further with some sensitivity analyses:

a. If low body weight was defined as BMI<18.5kg/m2

In our cohort, only a small number of people had a BMI below 18.5 (men: 22/10235, women: 173/12234), therefore it seems not possible/necessary to perform such a sensitivity analysis. Nevertheless, we added this information in the Discussion part (page 15, line 341- 344)

b. Is it possible that the low body weight group was dominated by heavy smokers and therefore a reduced RLE was observed? Did the authors analyse the effect of body weight on RLE in never smokers only?

Compared with other BMI groups, the low body weight group did show a relatively higher percentage of heavy smokers (27.8% in low body weight group, 18.7% in optimal body weight group, 16.4% in overweight group, and 15.2% in obese group).

Also as a response to the comments from reviewer 2, we further stratified the analysis by smoking status, and found that the effect of low body weight on RLE
became weaker for never smokers (particularly female never smokers) but become in current smokers (results are shown in a new table, i.e. Table 4). Regarding this new analysis, we have added some words in Abstract (page 2, line 47-49), Statistical analysis (page 10, line 216-223), Results (page 13, line 280-284), and Discussion (page 16, line 350-355).

c. If participants who died within 1-3 years of baseline were excluded. There may have been weight loss due to undiagnosed disease such as cancer and by re-analysing with this exclusion, the possibility of reverse causation can be somewhat accounted for.

There were 48 deaths in men and 33 deaths in women documented in the first two years of the follow-up period. We re-analyzed the data after excluding these deaths, and the corresponding descriptions have been added in Statistical analysis (page 10, line 214-216), Results (page 13, line 278-280), and Discussion (page 15, line 344-page 16, line 348).

As we have excluded participants who had pre-existing cardiovascular diseases and cancer in the original analysis, and therefore reverse causality for low body weight might play a minor role in this study (page 5, line 103-105).

2) In the multivariate models, the authors adjusted for education as a confounder. What was the hazards ratio and 95% CI for all-cause mortality? Was it statistically significant? If it was, what would the effect be of calculating RLE for all risk factors combined with fixed education at ‘secondary/professional’? Are some risk factors such as cigarette smoking higher in lower socio-economic position (in this study measured by education) and lower education/socio-economic groups have lower RLEs? If so, how much of the lowered RLE for each risk factor is driven by lower socio-economic position?

In men, the hazard ratio (95% CI) for all-cause mortality is 0.92 (0.80, 1.05) for secondary/professional education, and 0.69 (0.58, 0.81) for university education, using the no/primary education as the reference. In women, the hazard ratios for these two educational levels are 0.96 (0.80, 1.16) and 1.02 (0.79, 1.32), respectively.

For men, the expected absolute residual life expectancy with fixed educational degree at secondary/professional education will be significantly shorter than that with fixed education degree at a higher level (university). But the choice of educational degree will have no effect on the expected reduction in RLE associated with lifestyle risk factors, as we have already mentioned in the manuscript (page 9, line 191-195).

Since our multivariable model mutually adjusted for all the selected risk factors/confounders, the reduction in RLE therefore can be associated to each lifestyle factor alone. The significantly reduced mortality due to high education suggests that socio-economic position may have its own independent effect on RLE, but the focus of this paper is lifestyle factors, and thus we decided not to mention it.
Minor Essential Revisions
1) Last paragraph of ‘Results’ – spelling ‘covariantes’ – change to covariates
This wrong spelling has been corrected (page 13, line 287).

2) Paragraph 8 in ‘Discussion’ discussing the effect of food groups, change the word ‘confirms’ to ‘confirmed’ in the sentence, “Low fruit/vegetable consumption has also been associated with increased mortality rate in a study based on the entire EPIC cohort [31], but we only confirms this finding among men by showing a loss of RLE by 1.3 (95% CI: 0.4, 2.1) years associated with the low consumption.”
We accepted this change (page 17, line 390).

Discretionary Revisions
1) In the abstract, under ‘Results’, perhaps the word ‘ignorable’ could be replaced with ‘negligible’.
We accepted this change (page 3, line 50).

2) It may be worthwhile classifying physical activity by WHO recommendations (Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. Ref: http://www.who.int/dietphysicalactivity/factsheet_adults/en/index.html)
According to WHO, moderate-intensity physical activity is defined as about 3-6 METs, and vigorous-intensity physical activity was defined as > 6 METs. Therefore, physical activity level recommended by WHO for age 18-64 is equivalent to at least 7.5 METS-hours/week. This recommendation seems too loose for our study population (only 54 men and 13 women failed to meet this recommendation). Thus we decided to choose the median to classify our study population.

Reviewer: Michael Leitzmann

Major Compulsory Revisions
Previous research has shown that the relation of body mass to mortality varies markedly according to smoking status. Thus, it would be desirable to examine potential effect modification of the association between adiposity and RLE by smoking status and present results stratified by smoking status.
We performed a stratified analysis by smoking status (new results presented in Table 4) and added some texts accordingly [please see Abstract (page 2, line 47-49), Statistical analysis (page 10, line 217-223), Results (page 13, line 280-284), and Discussion (page 16, line 350-355)].

Also, the observation of a strong association between underweight and RLE
suggests the possibility of reverse causation due to pre-existing but undiagnosed chronic disease (i.e. wasting). Please consider presenting results of a sensitivity analysis that excludes the initial years of follow-up.

This question has also been asked by Reviewer 1, so please refer to above our response to that question.

The quality of the manuscript would be enhanced if the Methods section included data on the validity and reproducibility of the main exposures.

Information on validity and reproducibility of exposure measurement was only available for food groups, which was measured by food frequency questionnaire and by 24-hour dietary recall as a calibration tool. Relevant information has been added (page 7, line 148-152).

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Other revisions:

1. Page 8, line 176-177 and Page 18, line 411- page 19, line 414: we described briefly how the proportionality assumption was checked, and corresponding change was made in the Discussion.

2. Page 19, line 426-430: We add some texts to describe that the validity of our findings is likely to be compromised by inaccuracy of risk factor assessments. This is relevant to Reviewer 2’s question about validity and reproducibility of exposure measurements, which, in this study, were largely unknown.

3. Figure 1 was redrawn to make it look shaper.