Author’s response to reviews

Title: Handgrip Strength, Depression, and All-Cause Mortality in Korean Older Adults

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In Responses to the Reviewers’ Comments/Critics

We thank the editors and reviewers for giving us an opportunity to revise the manuscript. We did our best to address the comments and critics point-by-point. Our responses and corrections to the comments/suggestions are highlighted in Yellow in the text and Tables. Three references are added and listed in the last page. The order of references is renumbered accordingly. Our responses to the reviewers' reports are also attached as a separate file in supplement.

In our responses to the comments/suggestions made by reviewer #1

Q1) Abstract line 12: "ratio"

ANS1) Thanks for the comment. Ration is now corrected as ratio.

Q2) Results line 2: "heavier" suggest higher body mass, in fact it relates to BMI

ANS2) Thanks for the comment. It is now corrected as suggested in Results (line 13).
In our responses to the comments and critics made by reviewer #2

[Major concern]

The content of this manuscript seriously deviated from its main findings. According to the result section and tables, whether depression or low HGS predicts elevated risk for all-cause mortality has never examined by Cox regression. However, the authors spent a lot of space to introduce and to discuss the independent effect of depression and low HGS on mortality risk. Just reflecting the authors' review, the relationship between depression and low HGS with mortality risk has been well-known in the literature. In this study, the most interesting finding, which has opportunity to add to the literature, should be that 'sex moderates the synergic effect of depression and low HGS on mortality risk' (Table 3). Unfortunately, the authors failed to provide background for this observation and did not discuss this main finding at all. For example, the authors discussed a lot regarding why sex moderated the relationship between depression and mortality risk- a point which was not illustrated in the analyses.

ANS) Thanks for the comments. We tested the interaction between depression and low HGS separately and found a significant interaction in men but not in women. Table 4 is reconstructed to illustrate the independent and joint effects of depression and low HGS in total, men only, and women only. Description of Table 3 in the Results and Discussion is completely rewritten (please refer to our responses to Question #6 in [Minor Concern]).

[Minor concern]

Q1) In the second paragraph of the Introduction section (lines 39), gender is a moderator, not a confounder. Besides, in this paragraph, the evidence of the cited article did not adequately support the hypothesis- sex may play a role in determining the relationship of low HGS and depression with the mortality risk.

ANS1) Thanks for the comments. Sex is restated as a moderator. Additional references (#12-14) are added to illustrate that sex as a moderator may play a role in determining the relationship of low HGS and depression with the mortality risk.
Q2) In the Methods section, which hand was used to test HGS?

ANS2) Thanks for the comment. We measured handgrip strength of each participant’s dominant hand. The following statement is now added to the Methods; “We measured HGS to the nearest kilogram of each participant’s dominant hand” using a hand grip dynamometer (TANIATA No. 6103, Tokyo, Japan)”

Q3) In the Methods section (determinants of confounders), the authors introduced frailty as a confounder (line 35). However, in the following analyses, including illustrations in tables, I failed to identify this variable. In contrast, physical activity, which was estimated by International Physical Activity Questionnaire, was included in the analysis. Is frailty erroneously depicted?

ANS3). We are sorry for this error. Physical activity but not frailty was included as a confounder in the regression model. Accordingly the statement is corrected as follows: Additionally, health behavioral factors were measured and including alcohol consumption and smoking, nutritional status, number of comorbidities, disability, cognitive impairment, and physical activity.”

Q4) In Statistics, the proportional hazard assumption should be examined.

ANS4) Thanks for the suggestion. We tested the proportional hazard assumption with handgrip strength (HGS) as a continuous variable, as shown below. The Time Varying Covariates (T_COV) is greater than 0.05 (p=0.190), indicating the proportional hazard assumption is satisfied.

Q5) Obviously, the present study aimed to illustrate a three-way interaction effect, i.e. moderated moderation. According to Table 4, the authors seemed attempt to illustrate how sex moderates the moderation effect of depression on the relationship between low HGS and elevated mortality risk. However, the authors did not examine this 3-way interaction terms (sex x depression x HGS). At least, the authors should examine the statistical significance of interaction term (depression x HGS) among both sex.

ANS5) Thanks for the comments. We tested the interaction between depression and low HGS separately and found a significant interaction in men but not in women. Table 4 is reconstructed to illustrate the independent and joint effects of depression and low HGS in total, men only, and women only.
Q6) The authors claimed that both low HGS and depression were significantly associated with increased all-cause mortality risk (lines 9-12, the first paragraph of Discussion section). However, this statement was not supported by the description in the Result section. Except for univariate analysis in table 2 and 3, no Cox regressions examining the independent effect of low HGS and depression on mortality risk were illustrated.

ANS6) Thanks for the comment. As suggested, the independent and joint effects of the exposures on all-cause mortality were now examined and presented in Table 4. The outcomes are restated in the Results and Discussion as follows;

(Results)

“Table 4 represents the independent and joint effects of low HGS and presence of depression at baseline on the risk of all-cause mortality stratified by gender. In the total sample, individuals with depression only (HR=1.505, 95% CI=1.129-2.006, p=0.005) or low HGS only (HR=1.628, 95% CI=1.344-1.973, p<0.001) or both exposures (HR=3.194, 95% CI=2.635-3.871, p<0.001) had significantly higher risk of all-cause mortality, compared with individuals with no depression and high HGS (HR=1). The independent effect of depression only (HR=1.366, 95% CI=1.033-1.807, p=0.029) as well as the joint effect of depression plus low HGS (HR=1.961, 95% CI=1.409-2.736, p<0.001) remained statistically significant even after adjustments for age, sex, BMI, income, education, alcohol consumption, nutritional risk, K-ADL and MMSE scores, and physical activity.

Gender-stratified analysis showed that men with depression only (HR=1.682, 95% CI=1.107-2.554, p=0.015) or low HGS only (HR=1.786, 95% CI=1.395-2.287, p<0.001) or both exposures (HR=4.259, 95% CI=3.308-5.483, p<0.001) had significantly higher risks of all-cause mortality, compared with men with no depression and high HGS (HR=1). In addition, the independent effect of depression (HR=1.376, 95% CI=1.029-1.841, p=0.031) as well as the joint effect of depression plus low HGS (HR=1.861, 95% CI=1.306-2.651, p=0.001) remained statistically significant even after adjustments for all the measure covariates.

Women with depression only (HR=1.597, 95% CI=1.070-2.386, p=0.022) or low HGS only (HR=1.394, 95% CI=1.026-1.894, p=0.034) or both exposures (HR=2.670, 95% CI=1.985-3.591, p<0.001) had significantly higher risks of all-cause mortality, compared with women with no depression plus high HGS (HR=1). However, the independent and joint effects of depression and low HGS were no longer significant when adjustments for all the measured covariates.”
In this population-based prospective study, we investigated the independent and joint effects of depression and low HGS at baseline on the risk of 3-year all-cause mortality in Korean older adults. Overall, we found that depression independently contributed to increased all-cause mortality risk in Korean older adults, and the increased all-cause mortality risk was exacerbated by presence of low HGS at baseline. However, our gender-stratified analysis showed that the independent and joint effects of depression and low HGS were only the case for men. In women, the independent and joint effects of the exposures on the risk of all-cause mortality were not observed at statistical significance levels. Together, the current findings suggest that depression as well as depression plus low HGS are significantly and independently associated with increased all-cause mortality risk in Korean older adults, and the associations are differently modulated by gender.”

Q7) The current form of Discussion section was more likely an introduction to the background. The authors should discuss more about why and how sex moderated the moderation effect of depression on the relationship between low HGS and elevated mortality risk.

ANS7) Thanks for the comment. Rerunning the cox regression analysis, we found that depression itself was independently and significantly associated with all-cause mortality risk in men but not women. In addition, the association was magnified by presence of low HGS in men but not in women. We provided some explanations for the gender difference in the independent effect of depression as well as the joint effect of depression plus low HGS with all-cause mortality stated in Discussion (please refer to 2-4th paragraphs). However, we recognize that the nature of this population-based association study limits our explanations for the gender difference. And this should be further examined in a future study.

Q8) In the 5th paragraph, there is a typo (line 48, "Om the other hand").

ANS8) Thanks for the comment. It is now corrected as “On the other hand”, which is now in 3th paragraph (line 4).

9. Through table 1 to table 3, the subtotal of participants who consumed alcohol is not equal to the numbers shown above the saddle lines. However, the percentages for these two levels (no drinking and two times a week) were summed up to 100%.
ANS9) Thanks for the comments. Some data are missing due to subjects’ refusal to answer the questions related to education and alcohol consumption. So, the percentages of education and alcohol consumption in Tables 1-3 are now corrected (refer to Tables 1-3).

10. In table 3, the p-value for alcohol consumption in women is lost.

ANS10) Thanks for the comment. p-value of <0.001 is now added in Table 3.

11. I suggest reorganize table 4 to support the content of this manuscript…………..

ANS11) Thanks for the comment. We rerun the cox regression analysis to examine the independent and joint effects of depression and low HGS on all-cause mortality risk. So Table 4 is completely reconstructed to illustrate the independent and joint effects of the exposures (refer to Table 4).

List of References newly added.

