Author’s response to reviews

Title: Relative importance of four functional measures as predictors of 15-year mortality in the older Dutch population

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Author’s response to reviews:

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Relative importance of lower-body performance, handgrip strength, lung function, and self-reported functional limitations as predictors of 15-year mortality in the older Dutch population

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BMC Geriatrics

Dr. Tovah Honor Aronin, Editor-in-Chief

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Dear editor, dear Dr. Tovah Honor Aronin,

We appreciate your positive judgement of our manuscript and are very happy with all the good comments which we all considered in order to improve our manuscript.

Below we give our responses with corresponding track changes in the manuscript.

We hope you will consider our manuscript as suitable for publication in The Journal of BMC Geriatrics

Yours Sincerely,

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Concerning Reviewer 1:

Kazuhiro P. IZAWA (Reviewer

1.1 There were several problems on this manuscript. There was not any information of MEDICATIONS in this astusy.

Response: Medication use was mentioned as a potential confounder, we added a description of the methods used to measure medication use to the text in the section of potential confounders:

-Medication use was assessed by asking the participants to show their medication containers to the interviewers. The number of medications was used in the analyses.-

As described in the statistical section on page 10 only the potential confounders associated with both the predictor and the outcome (p<0.1), were added to the model. As the predictive value of the number of medications was highly related to chronic diseases, we chose to include chronic diseases only.

1.2 There were no information of combined sexes data in the present study.

Response: Because one of the tests studied showed an interaction with gender all tests were assessed separately to enable a comparison between all tests. We do not think that, in the presence of such interaction, we should present combined results. In addition, our aim was to determine the optimal test for each gender in predicting mortality risk.

Siti Setiati (Reviewer 2): Overall, the manuscript is good, I appreciate the work on such an interesting topic and the results are also interesting and important. However, there are several things that can be improved in writing this manuscript. Comments will be given per section.

Concerning reviewer 2. Comments for abstract:

2.1.1 The methods section should state the total number of sample (page 4 line 19-21). Also, the sampling method should be mentioned.

Response: We thank the reviewer for his/her attentiveness. We stated the total number of men and women in the sample on page 4 line 19-21.

Regarding the sampling method, the sample was randomly derived from municipal records. This is now stated in the Abstract as well as on p. 8. - sampled from municipal records.-
2.1.2 The result section should state the percentage of subject who died (page 4 line 39).

Response: We added the following percentage: ‘68.5%’

2.1.3 The statistical value of lower body performance and hand grip strength for woman and self-reported physical limitations in men should be reported (page 4 line 50-53).

Response: We added accordingly the following values: In women, lower-body performance (HR 1.66, CI 1.15-2.41) followed by grip strength (HR 1.38, CI 1.02-1.89), and in men, functional limitations (HR 1.43, CI 1.14-1.8) were the other significant predictors of all-cause mortality.

Regarding the Comments on Background:

2.2.1 Overall, explanation about the evidence gap from previous study and the novelty of this study needs to be improved.

Response: We strengthened the novelty by adding the following text

The current study is the first study where a comparison is made among four tests including both objective (lower-body performance tests, grip strength, peak flow measured by an observer) and subjective tests (self-reported by the participant physical function measures, i.e., functional limitations) in one sample of an older community dwelling population to determine the optimal test for each gender in predicting mortality over a period of 15 years in men and women separately.

2.2.2 Background should explain what is physical function and elaborate the effect of ageing and physical function. (page 6 line 6).

Response: The text has been changed into the following sentences - Ageing is accompanied by loss of physical function Physical function is the common term for a combination of endurance, muscle power, balance, and coordination, which capacities are related to exercise, health status, and genetic and environmental factors. With ageing, from early midlife the maximal physical function decreases slowly.

2.2.3 Explanation about tests (its division into objective and subjective and their examples) currently is unclear and needs to be improved/rephrased. (page 6 line 6-13)

Response: the following clarification has been made by adding the following text page 6 line 6-13: ‘’objective (measured by an observer) and subjective (self-reported by the participant).’’
2.2.4 Explanation of self-reported functional limitations as "experienced difficulty doing activity of daily living" needs grammatical correction and should be rephrased for it to make sense. (page 6 line 11-13)

Response: the explanation has been changed into the following sentence on page 6 line 11-13:

"Experienced difficulty in performing activities of daily living."

2.2.5 Confirmation for information on Page 6 line 15-27: were those previous study done in elderly? did it differentiate between men and women? Please mention in the manuscript to highlight the novelty of your study.

Response: Thank you for your good advice. Throughout the manuscript we emphasized the novelty of our study by changing or adding several sentences or words thereby following the good advices of all three reviewer. All changes have been summarized in this letter to the reviewers.

We also added or changed to the text on page 6 and 7 with the following bold words:

P6 - Several studies in older persons have linked poorer physical function with negative health outcomes.

P6 - Two recent studies in older persons compared the ability of four and seven different objective physical function measures in predicting mortality[15, 16].

P6 - One study showed that four physical function tests, among which peak flow, hand grip strength, leg strength and physical activity, were associated with impaired physical ability and disability in activities of daily living in older persons (ADL) [17].

P6- One cross sectional study showed that four physical function tests, among which peak flow, hand grip strength, leg strength and physical activity, were associated with impaired physical ability and disability in activities of daily living in older persons (ADL) [17].

*We already summarized some studies that showed any possible difference between gender in the manuscript but now added as bold text/numbers in the sentence below also all other previous mentioned literature that showed any indication for a difference between gender:

P7 --Stratification by gender may be of importance if there is an indication for gender differences; indeed, gender influences have been observed regarding the predictive values of lower muscle strength, grip strength and functional disabilities for increased mortality risk in older persons [5-7, 9, 11-14, 16-18, 19].
2.2.6 Page 6 line 33-41: you write about previous researches that answer similar question to your own research question, which raise the question on the novelty of your study. There had been studies that examine predictive value of those measurements for mortality, why is the current study still needed? Once again please highlight the novelty of your study by stressing the difference/ remaining gap of knowledge / limitations from previous study that explain the importance of your study.

Response: We agree with the reviewer that we need to highlight our novelty more. We would like to refer to the text we added as described in 2.2.1

2.2.7 Page 7 line 7: please explain what did you mean by "with almost disappearance of significance in woman"

Response: Our apologies, we mean an almost disappearing significance and changed the text from -disappearance of- into the bold words : Indeed t The study by Veronese and colleagues showed gender differences in mortality risk prediction of physical function measures specifically due to the influence of malnutrition in women 2.2.8Page 7 line 11:

2.2.8 I think you may elaborate on previous study on self-reported functional limitations or other subjective measure. You may want to include information from reference no 12-14, 5, 26 that seems to report this topic.

Response: we considered this remark and we have checked this in the previous articles again. Due to their different scopes, different tests, variable results, or only including women [5], we have mainly expanded the text with more background information about the tests as mentioned in the articles as mentioned in 2.2.7; 2.2.9; 2.6.3; 2.6.7

2.2.9 My advice is to to group information related to objective tests into one paragraph and subjective test into another

Response: We changed the text into the following No Among the two previous studies that assessed the association between self-reported measures of physical function and mortality risk only one study [5] showed a difference between sexes [12]. included in the studies cited. Thus, it cannot be deduced which has more relevance for mortality prediction: objective tests or self-reports.
In reference 13 the ADL levels were obtained from caregivers therefore it was not included as a subjective test;

In reference 26 the study was only performed in women

2.2.9.1 I think it's excellent that you mentioned the importance of doing these test to help with clinical decision making (page 7 line 15-17), you should elaborate it and place this information in the opening paragraph instead.

Response: we thank the reviewer for the positive comment. We added the following sentence as new paragraph at the end of this section:- In addition, from our findings a new study might be developed to design a practical scoring system to predict mortality.-

Comments for Methods:

-Aim:

You stated that the aim of the study was to compare objective and subjective physical performance test in predicting mortality and gender effect. There are several things that needs confirmation:

2.3.1 Did your study compare objective versus subjective or did you mean that the comparison was made among those tests that include both objective and subjective tests? I think you need to clarify this, since currently the written aim can be misleading, because the data analysis and result did not compare objective (3 tests) vs subjective (1 test), rather it compared those tests. Please state an aim that best reflect the content of the rest of this paper.

Response: We clarified this by adding the following bold words in the text at the end of the background:- In the current study, a comparison was made among those tests that include both objective and subjective tests in one sample of an older dwelling population to determine the optimal test for each gender in predicting mortality over a period of 15 years.(Page 7)

Because of the repetition, we subsequently deleted the aim of the Method section:

Aim: To compare objective (lower-body performance tests, grip strength, peak flow) and subjective physical performance tests (self-reported physical function measures, i.e., functional limitations) in predicting 15-year mortality risk and its gender effect in older men and women.
2.3.2 Is it physical function test or physical performance test?

Response: it is physical performance test

2.3.2.1. What did you mean by "gender effect" in older men and woman? Did you mean the difference of predictive value of those tests according to the gender? Please clarify/rephrase.

Response we deleted this sentence in the introduction (and added to the final conclusion by adding the following bold words Final Conclusion: -This study investigated the differences in predictive strength and gender effect differences in predictive strength of four measures of physical functioning for mortality in older men and women-

-Study Sample

2.3.3 Please mention the sampling methods

Response: The sample was randomly derived from municipal records. This sentence has been added to the text as mentioned previously.

2.3.4 How many was the total participants in LASA cycle 95-96? How many had sufficient data to be included in this study? Were they all included? What's the reason for exclusion? (page 8 line 1-5)

Response: Starting from 727 men and 778 women, we included all participants with data on each test. This number varied across tests, with a minimum of 680 men and 702 women in the analyses including all tests. See further table 2 for the numbers of men and women included per pair of tests. This information was added to the text as described below.

2.3.5 Please mention the sample calculation for this study to get the number of 680 for men and 702 for women as minimum sample of this study (page 8 line 7-9)

Response: This approach has also been clarified in 2.3.4; we added the following bold information to the text- Starting from 727 men and 778 women, all participants with data on each test were included. This number varied across tests, with a minimum of 680 men and 702 women in the analyses including all tests-. See further table 2 for the numbers of men and women included per pair of tests.
-lower body performance

2.4.1 usually methods for how a test is performed referenced previous study, please include citations for the methods of each tests.


2.4.2 The description of how the test were performed should be improved.

Response: For economy of space we only added the references.

2.4.3 The explanation of how the scoring was done for chair stand test and walking test is made clearer so that it become easier to understand. Please give citation to the scoring system (the quartile or table for scoring).

Response: In line with our Response of 2.4.2 we refer to the reference.

-Hand grip strengths

2.4.4 Please explain the methods to perform the hand grip strength was measured and give citation

Response: As in our response in 2.4.1 and 2.4.2 we added the reference.

-Lung function

2.4.5 Please state the measuring unit for peak flow meter

Response: ml was added to the section lung function* and to Table 1

* The highest score of three measurements in milliliters (ml) was used

-Functional limitations

2.4.6 what questionnaire were used for this measurement? Please give citation to the questionnaire.

- 15-year mortality follow-up

2.5.1 Please explain how did you handle with missing data or lost to follow up

Response: Follow-up data were complete for 1505 out of 1509 persons. This sentence is now added on p. 10.

-potential confounders

2.5.2 Please include citation for the mentioned potential confounders (page 9 line 53-39)


-statistical analysis

2.5.3 Please explain the test that you used for data distribution test (page 10 line 29)

Response: The data distribution test used was the commonly used Kolmogorov-Smirnov test

2.5.4 Please explain the purpose of the second step (page 10 line 33-36)

Response: The purpose of the second analysis step was to assess the interrelations between the four tests. We added this to the text—....to assess their interrelation–.

2.5.5 On the third step, how was the tertiles were obtained? (page 10 line 38-43)
Response: the following sentence was added to the text: - the tertiles were obtained by considering the frequency distribution of each physical function measure for men and women separately –

2.5.6 Page 10 line 54-56: "one model adjusted for age and gender (If no interaction was present)" how about when interaction was present.

Response: Our approach in case an interaction was present is now clarified two sentences earlier. Note, that interaction was present, so that all analyses were stratified by gender.

2.5.7 In the result section in table 4, two models were presented for each gender, please explain the methodology in methods section.

Response: Both models are explained in the statistical analysis as also noted below Table 4. Model 1 is adjusted for age, model 2 is adjusted for age and additionally for all potential confounders.

Comments for Result

2.6.1 Note about data presentation (Page 12 line 54-55) should be included in methods section

Response: In the results we refer to the corresponding table which is a part of the results.

2.6.2 According to the method section, only those with p<0.1 needs analysis with stratification for sex, which means that those with no interaction did not need stratification. Please justify why at the end all measures were further analysis were stratified by sex. (page 15 line 1-5)

Response: our approach has already been better clarified in the method section as described in 1.2: : Because one of the tests studied showed an interaction with gender all tests were assessed separately to enable a comparison between all tests. We do not think that, in the presence of such interaction, we should present combined results.

-Please mention the statistical value of each result in the last paragraph (page 15 line 35-45)

Response: we added these (as bold) values in the text as follows: with the strongest combination of measures of peak flow (HR 1.54, CI 1.18-2.01) and self-reported functional limitations (HR
1.43, CI 1.14-1.8) in men and peak flow (HR 1.45, CI 1.08-1.93) and lower-body performance (HR 1.66, CI 1.15-2.41) and to a lesser extent grip strength (HR 1.38, CI 1.02-1.89).

2.6.3 You may want to highlight the result that Lower body performance is better predictor for woman.

Response: we emphasized this already later in the manuscript, but also added the following sentence:- The test is easy to perform and has often been used in studies.-

2.6.4 Typo in page 15 line 22 should be HR

Response: we thank the reviewer for this attentiveness and changed it accordingly into -HR- p 15 line 22.

2.6.5 Some explanations were unclear Please explain what is model 1 and what is model 2. Please highlight the difference between results in model 1 and model 2 for both men and woman.

Response: We extended the and results of model 1 and model 2 by adding the following sentences to the discussion:

-Adding all confounders to the separate analysis (model 2) reduced the strength of all associations compared to adjusting for age alone (model 1). Adding all confounders to the combined tests analysis reduced the importance of peak flow test in both sexes, of functional limitations in men and turned physical performance in men non-significant

- Table 3 and 4:

2.6.6 the notes should be incorporated into the table for easier reading. For example: lower body performance (0-12), men teritel 1 (0-7), tertile 2 (8-9), tertile 3 (10-12), etc.

Response: the tertiles have been included.

2.6.7 please explain in the text how did those confounders in model 2 were considered relevant to be included in the model.

Response: the confounders we included in model 2 have been derived from previous articles and were included when they were assessed to be relevant (P<0.1) This was added in the method section as -derived from previous studies-.
2.6.8 - figure 1 and 2: please explain what do you mean by separate model and combined model

Response: we added the following sentence: Separately for each test (separate models) and relative if all four tests combined (combined model).

Comments for Discussion

2.7.1 Please describe the relevant confounders on page 15 line 57

Response: Important confounders in the combined model were: no. of chronic diseases, cognitive impairment, body mass index, smoking, alcohol use. These were already added below Table 4.

2.7.2 Page 16 line 10-12 "these remaining as the only significant predictors…" please confirm what did it remain from (i.e. remains after adjusting to what factors?)

Response: we changed this sentence to a clearer translation as follows:, which were the only two remaining significant predictors of mortality in men

2.7.3 Please explain how do the peak flow with least correlation with the others turns out to contribute the most in predicting mortality (page 16 line 20-25)

Response: This argument is now clarified (p. 16). We changed the text by adding the following sentence -Thus, peak flow adds predictive value over the other functional measures.-

And deleting the following sentence: This may explain why peak flow turns out to contribute most, in addition to some of the other measures, in predicting mortality.

The mechanism of how peak flow relates to mortality is explained on page 17 (see also comment 2.7.6).

2.7.4 Page 16 line 38-43: Excellent! you pointed out the importance of your study (difference observed for men and women) Please highlight this and elaborate more.

Response: we thank the reviewer for the positive comment. We have given more attention to this gender difference in Responses 2.2.1; 2.2.5; 2.2.9; 2.3.1; 2.7.7..
2.7.5 Page 17 line 3-9: please explain how grip strength may relate to the mortality.

Response: -We added to the text the following information: -The underlying factors that might relate the decline in muscle power to mortality are yet unclear, but seems to be multifactorial including a chronic low-grade inflammation [19].-

2.7.6 Page 17 line 16-25: very good! You have explain well how peak flow may relate to mortality.

Response: thank you for you positive comment.

2.7.7 About the strength of your study: Don't forget to add the comparison between genders as one of your strength (page 17 line 38-39)

Response: we thank the reviewer for this comment and have added gender as one of our strengths in bold the following words Strengths of the present study include the use of a large population-based, well-characterized study sample -the comparison between four measures separately and combined per gender the long follow-up period and the examination of and correction for effect modification and various confounders –

2.7.8 About the limitation of your study: Pease mention the limitation related to the bias of a retrospective cohort study. (page 17 line 43-45)

Response: The study was performed prospectively, therefore we did not change this

2.7.9 Future study (page 17 line 55-59): future study may be done to developed scoring system to predict mortality from your findings.

Response: we like this idea very much and thank the reviewer for this comment. We added as sentence -In addition, from our findings a new study might be developed to design a practical scoring system to predict mortality-.

2.9.1 Overall, the discussion part contains important information but the information seems scattered. My suggestion is for the discussion to focus first on comparing the prediction values of the measures in men vs women (which I think is one of the most important finding in the study). Then, the discussion is followed by discussing the result of each measures; Group the
information (comparison of your result vs previous result) according to each measures (e.g. one paragraph about each peak flow, lower body performance, handgrip strength and self-reported functional limitation).

Response: we have carefully considered this comment. However, when we changed the text sequence, we experienced it as a loss of our goal.

The purpose of the study was to examine the relative strength of the different tests among each other. Therefore we think it is important to start with the comparison among the different tests initially. Later we discuss the different tests separately.

In bold letters we have added the following words to the discussion to emphasize the differences between men and women:

- The findings demonstrate that although each objective muscle strength measure (lower-body performance, handgrip strength), objective lung function (peak flow), as well as subjective self-reported functional limitations can predict mortality in older people, remarkable differences exist between the strength of the associations for gender and mortality outcome. While decreased lower-body performance was associated with the highest increase of mortality risk in older women, strikingly in older men lower peak flow showed the highest risk-

- To our knowledge, this is the first study that compares objective measures of physical functioning, including peak flow, and self-reported measures in their predictive value for 15-year mortality risk in a large representative sample of Dutch older persons between men and women-

- While prior studies also found gender differences in the relationship between mortality risk and handgrip strength [8, 9], self-reported disability in ADL [12] and functional performance [16], we are the first to show that when combining addressing all four tests the difference in predictive strength for mortality between men and women becomes more clearly apparent.

Comments for Conclusion

2.9.2 The first sentence contained several grammatical errors, please apply some correction.

Response: We changed the sentence into- This study investigated the difference in the predictive strength and gender effect differences in predictive strength of four measures of physical functioning for mortality in older men and women (as described in 2.3.2)
2.9.3 What did you mean by "relative contribution model"

Response: With relative contribution model we mean assigning a relevance grade to each test, we are aiming to judge which of the tests compared to each other is a better predictor.

Soham Al Snih, M.D., Ph.D. (Reviewer 3): Manuscript Number: BGTC-D-18-00469

Title: Relative importance of lower-body performance, handgrip strength, lung function, and self-reported functional limitations as predictors of 15-year mortality in older Dutch population.

Comment:

3.1) The title can be shortened.

Response: We changed the title as follows: Instead of -Relative importance of lower-body performance, handgrip strength, lung function, and self-reported functional limitations as predictors of 15-year mortality in older Dutch population-. into the changed words in bold:- Relative importance of four functional measures as predictors of 15-year mortality in the older Dutch population=

General: This study examined physical function measures as predictors of 15-year mortality among participants from the Longitudinal Aging Study Amsterdam (LASA).

Abstract: Concise and specific.

Introduction: The literature used is pertinent to the study. The study objective was clearly stated.

Methods: Sample description and measures are clear.

3.2) Results: Four tables and two figures well presented.

Comment: The figures are not necessary since the information is provided in the tables.
Response: We do agree with this comment but we think that the figures really contribute to

a better grasp of the results

Discussion:
-Previous pertinent literature was compared with author's findings.
-Study limitations, strengths, and implications were identified.

References: All appropriate.

Where a mandatory Declarations section is not relevant to your study design or article type, please write "Not applicable" in these sections.

Response: we will write ‘’Not applicable’’

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page (see links below).

We already added: Data will be made available upon request. To request data, see www.lasa-vu.nl

The editor might consider to add the Official Statement in LASA data contract: Data from the Longitudinal Aging Study Amsterdam (LASA) are available for use for specific research questions, provided that an agreement is made up. Research proposals should be submitted to the LASA Steering Group, using a standard analysis proposal form that can be obtained from the LASA website: www.lasa-vu.nl. Files with data published in this publication are freely available for replication purposes and can be obtained using the same analysis proposal form. The LASA Steering Group will review all requests for data to ensure that proposals for the use of LASA
data do not violate privacy regulations and are in keeping with informed consent that is provided by all LASA participants

Declarations: all were already addressed in the original manuscript

- Ethics approval and consent to participate
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