Author’s response to reviews

Title: Advanced glycation end products and their ratio to soluble receptor are associated with limitations in physical functioning only in women: results from the CARLA cohort

Authors:

Helen Ebert (helen.ebert@student.uni-halle.de)
Maria Lacruz (elena.lacruz@uk-halle.de)
Alexander Kluttig (alexander.kluttig@medizin.uni-halle.de)
Andreas Simm (andreas.simm@uk-halle.de)
Karin Greiser (h.greiser@dkfz-heidelberg.de)
Daniel Tiller (daniel.tiller@medizin.uni-halle.de)
Nadja Kartschmit (nadja.kartschmit@medizin.uni-halle.de)
Rafael Mikolajczyk (rafael.mikolajczyk@medizin.uni-halle.de)

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Author’s response to reviews:

Dear Dr Popa-Wagner,

Thank you for accepting our manuscript for second review and giving us the opportunity to improve it. We have revised the paper in response to the comments of the reviewer. Please find below a point-by-point response to all the comments. A revised version of the manuscript with highlighted changes made to the original version (tracked changes) as well as responses to the comments marked in bold are attached.

Yours sincerely,

Rafael Mikolajczyk and Helen Ebert

Response to the comments

Reviewer #1. Agustín Aíbar Almazán

1. Please add keywords to your abstract. The keywords are located below the conclusion of the abstract (page 2, line 20).

2. Introduction:

-Please add a hypothesis
We have now included following text: “We hypothesize that there is variation in the above association across the wider age range (particularly, that the associations might be stronger at older ages). Moreover, we await a stronger association between physical functioning and the AGE/sRAGE ratio than with each of the components alone.” (page 4, lines 27-30)

3. Discussion:

- Omit the significant words. We thank the reviewer for this comment and deleted the term “significant” throughout in the Discussion (lines 158, 178)

4. - Was there no limitation in the study? We apologize for the absence of clarity in discussing the study limitations. In our revision, we state this more clearly in the following text: “The main limitation of the current study is that we rely on self-reported impairment of physical functioning. Instead of using an objective measurement, such as walking speed or grip strength we measured physical functioning by questions of the SF-12 questionnaire.” (page 11, line 216-219).

Reviewer #2. Andrea Britta Maier, M.D., Ph.D

1. The authors have to clearly state that physical function was not measured objectively, but by use of questionnaires, which is a major limitation. We agree with the reviewer that this is the major limitation in our study and have stated it more clearly in the discussion “The main limitation of the current study is that we rely on self-reported impairment of physical functioning. Instead of using an objective measurement, such as walking speed or grip strength we measured physical functioning by questions of the SF-12 questionnaire.” (page 11 and lines 216-219). See also reviewer #1, 4th comment.

2. It has to be clearly stated why analysis included the given confounders at page 5. I would strongly suggest including a DAG presenting the confounders. The confounders were chosen due to their reported association with the AGE-RAGE system and physical functioning in the literature. We amended this aspect in the manuscript “Covariates known to affect physical functioning, that were also associated with AGEs were identified from the literature [8, 23-25] and considered as confounders in the analyses.” (page 5 line 64).

3. The data about age (per 10 years), page 9 should be presented (now ' data not shown'). We thank the reviewer for this remark. We have now included a Supplementary Figure 7 showing these data. (page 9, line 151)

4. How do you explain that there is no age difference (line 205) - this should be discussed more extensively. Thank you for this important comment. We explained now that the lack of difference in association between AGEs and physical functioning across age supports the notion of biological age being independent of chronological age: “This finding is interesting as previous studies addressed mainly older participants and extending the evidence to younger age groups appears useful. In women, AGEs are apparently associated with older age, but their association with physical functioning is stable and not restricted to older ages. This supports the notion of AGEs as a marker of biological age, being independent of chronological age – and a potential target of interventions.” (page 11, line 206-211).
5. What is the lesson to learn and clinical implication of the findings? This is not clear. We stated now more clearly how the hypotheses were answered and what are the implications: “There was no considerable difference in terms of effect size between the association of AGEs, and AGE/sRAGE ratio and physical functioning in contrast to previously suggested better performance of the ratio. We also did not observe differences across age, which supports the notion, that AGEs are a marker of biological rather than chronological age.” (page 12, line 235-238)