Reviewer's report

Title: Age-related frailty and its association with biological markers of ageing

Version: 2
Date: 12 May 2015
Reviewer: Jeremy Walston

Reviewer's report:

Please number your comments and divide them into

- Major Compulsory Revisions

The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.

1) Although the authors addressed an important comment in the cover letter, they did not address the following comment in the revised manuscript which may lead to an error in interpretation of the results. The comment stated:

‘Given previous statements and previously reported measurement problems related to the Fried phenotype in this population (stated by this group in a prior manuscript, reference 15), its use as a comparison in the present study does not appear to be indicated. Suggest removal of this or clear rationale for its inclusion given prior statements related to its lack of utility in this population.’

The comparisons of various frailty tools to compare risk of mortality is common and indeed encouraged by the reviewer if the comparisons can be made accurately. This reviewer remains concerned that there are major differences in this subset analyses between the populations which may lead to interpretation error. Given that the authors chose to leave the comparison in the manuscript, it is recommended that the authors more fully address the rationale for the use of this tool in a smaller and likely far more healthy subset of the Newcastle 85+ study. If the authors include it in the manuscript in order to compare mortality prediction between tools, then the number of Fried frailty subjects included should be listed in the frailty measures section along with descriptors of the FI-B and the FI-CD. Reasons for exclusions of individuals for Fried phenotype should also be clearly stated as they were for the other two tools (in this case it appears that the subjects were not able to participate in the cognitive or physical components of the Fried assessment and hence not included in the analysis).

Given that the Fried tool is indicated for use in ambulatory, non-cognitively impaired subjects, it is likely that the sickest, and most functionally and cognitively impaired individuals were excluded from this the analysis of mortality using the Fried tool. It is not clear to this reviewer if this was accounted for in the
ROC. If it was, then this should be articulated more clearly. If it was not, then the revision could be handled in one of two ways. First, a repeat analyses could be performed which is restricted to the same subjects across all the measurements in order to determine a more accurate head to head comparison of mortality prediction between the tools using the same subjects. If the authors can not do that analysis, then a clearer discussion of what it would mean to exclude the sickest most disabled individuals from the mortality calculations using the Fried tool is indicated.

2. IL-6 and TNF-alpha language was clarified and a section added to the discussion section that will be helpful to the reader. However, most readers will interpret ‘basal’ level of these cytokines as serum levels of these markers. Suggest adding PBMC basal to the table to help clarify this important difference.

- Minor Essential Revisions

The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

- Discretionary Revisions

These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.

Please note that both the comments entered here and answers to the questions below constitute the report, bearing your name, that will be forwarded to the authors and published on the site if the article is accepted.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.