Reviewer's report

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

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Reviewer: Jeremy Walston

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Major Compulsory Revisions:

1. Is the question posed by the authors new and well defined?

In regards to definition, there is a lack of definition of the aging biology that the authors state that they are attempting to capture with the biological index that should be addressed by rationalizing the choice of measures or reanalyzing the data as detailed below. Although the title of the manuscript is ‘Age-related frailty and its association with Biological markers of Intrinsic Ageing’, many of the biological domains and measurements chosen to be included in this intrinsic aging index are not considered part of intrinsic aging per se. Many of the domains could be construed as being related to chronic infections or specific clinical disease states (CMV, WBC, inflammatory) rather than aging per se. For example, WBC and inflammatory measures, haemoglobin and even immunosenesence markers in the case of chronic HIV or CMV can be altered in younger individuals who are chronically ill, weakening the specificity and utility of this grouping of measures and the claim that they are related to intrinsic aging. This should be further clarified in both the analytical section and in the discussion section.

If the goal of the authors is to identify the relevance of the accumulation of aging-related deficits or intrinsic aging, then clearer, more rationalized measurement choices should be made for the construction of this index rather than the broad mixed clinical and research array as presented. There are individual markers included in this manuscript that could be identified as markers of ‘intrinsic aging’ such as DNA methylation, DNA repair, and telomere length. A reanalysis of just these ‘intrinsic aging’ measurements and its relationship to the frailty index and to mortality would be novel and potentially informative for the identification of an ‘intrinsic aging’ mechanistic framework that the authors are seeking.

Another suggestion for getting at the ‘mechanistic framework’ more fully rationalize the development of the domains, rationalize their biological plausibility in the underlying construct, and compare their individual and aggregate relationship with both the clinical frailty index and with each other. This may help to determine which of the biological/clinical domains is most important in this
model and in predicting mortality, and highlight the most important mechanistic pathways.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

This group has previously utilized the index approach and applied it to many different populations. They have long-standing expertise in mathematical modelling of frailty as defined by clinical and more biologically relevant indices. The approach could be replicated if more detailed measurement and analytical methods were provided.

As to the overall design of the study, the authors previously published a manuscript in 2012 that states that the Fried frailty measurement could not be determined in over 1/3 of this population in part because of the large amount of pre-existing mobility disability and pre-existing conditions. They also stated that this ‘significantly limits the utility of the Fried model in very old people’. Given these previous statements and previously reported measurement problems related to the Fried phenotype in the same publication, 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.

3. Are the data sound and well controlled? As to the inflammatory domain data, there appears to be either model or measurement errors reported in table 1. Serum levels of IL-6 and TNF-alpha, which were related to frailty index in a prior publication by the same group, are not significantly associated with frailty index in this study. Upon examination of table 1, shows that nearly all of the participants had an IL-6 level over 15 pg/ul, and were included in the ‘at risk’ group. While those over 85 years of age would be expected to have higher levels than younger individuals, the information in table 1 would suggest a mean IL-6 level that is well over what is considered a ‘normal range’ for even the oldest subset of adults. It is theoretically possible that most of the participants had these very high levels; however, most prior population studies of older adults, even up in to this age group, have shown levels of serum IL-6 levels have a mean level of between 1.5 and 3.0 pg/ul. The values suggested here that 1) either the vast bulk of the participants have a very high chronic disease burden or were acutely ill when they were sampled, 2) there is measurement error perhaps associated with using a low sensitivity ELISA kit, or 3) there is an error in the way that this has been displayed or modelled (perhaps only 27 rather than 676 individuals had value over 15 pg/ml). Given the importance of IL-6 in predicting adverse outcomes and mortality in almost every previous publication on IL-6 and its relationships to adverse outcomes in older adults, this data and the modelling should be checked very carefully. If it is found to be accurate, then a very clear explanation of why this is thought to be accurate should be provided to the reader. The same issue applies for TNF-alpha. One would expect the results from both of these cytokines to look more like the results from high sensitivity CRP results and similar to the
previously published data from the 2012 Mechanisms of Aging and Development paper from the same group.

6. Are the discussion and conclusions well balanced and adequately supported by the data?

The authors make a claim in the discussion section that a ‘significant step has been taken to provide a framework through the FI-B that might provide the mechanistic connections between frailty and the underlying biology of intrinsic aging.’ Because many if not most of the markers chosen for the FI-B have no clear connection in the literature to ‘intrinsic aging’, this claim is overstated. In addition, there is minimal information from the the authors in the discussion section related to potential concerns of including many highly related variables and what that might mean in this model. For example, low haemoglobin is known to associate with low albumin, lower leptin and adipokine levels, and high inflammatory mediators and mortality. This is especially relevant for readers who are not familiar with index development and may question the importance of including these variables that are known to be highly associated in chronically ill individuals.

Given the choice of a large subset of the domains of markers (inflammatory, hematologic, CMV), an articulation or discussion from the authors as to why this constructed index is not simply a marker of severe chronic illness or end stage disease that could be ascertained in a simple clinical exam would be useful, as would an articulation of the potential clinical or interventional utility of such a tool in the future.

7. Do the title and abstract accurately convey what has been found? The title does not accurately represent what is in the manuscript in that most of the measurements are not markers of intrinsic aging as discussed above given the inclusion of CMV markers, inflammatory markers, hematology markers, and metabolic markers as articulated above. Title should be changed to more accurately reflect the chosen biological markers unless the paper is revised to just include intrinsic aging biomarkers. The conclusion of the abstract overreaches what is stated in the paper in that it suggests that the results ‘may indicate the nature of underlying causal deficits’. This abstract statement goes well beyond the authors’ conclusion section of the manuscript itself. Suggest altering the conclusion section of the abstract to better reflect the findings of the manuscript and better match the conclusion section of the manuscript.

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.