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

Version: 1
Date: 8 March 2015

Reviewer: Alexander Kulminski

Reviewer's report:

This is a well-written paper which extends the approach of a clinical deficits frailty index (FI-CD) to a new and important domain of a biomarker-based frailty index (FI-B). Why this is important? Chiefly, this is because biomarkers have a potential: (i) to resolve pre-clinical conditions well before the occurrence of diseases later in life and (ii) to finely characterize age-related changes in an organism. The results are clearly important as well, because they document that FI-B and FI-CD have additive property, i.e., they complement each other and, thus, greatly improve predictive power. Furthermore, the FI-B can help in better discriminating the changes in health and the risks of mortality in individuals with no apparent clinical manifestations, i.e., at low levels of the FI-CD. Even so this study is limited to a specific population, this does not undermine its strengths.

Some minor comments which can strengthen this paper:

1) Page 10: Estimates of HR have low resolution. It can be improved by rescaling FIs, i.e., by considering larger units of change in the FIs, e.g., 10% instead of 1%.
2) AUC measures should be also given in a table/figure.
3) It would be interesting to include also Fried’s FI to see whether or not there is an improvement in AUC.
4) Page 12. The authors discuss the results for 95th and 99th centiles whereas they do not appear in the results section
5) Page 12, line 7 from the bottom. I am not sure that the authors correctly used the word “significant” there because it does not look like there is significant difference in the estimates of AUC=76 (CI=0.71-0.80) and AUC=71 (CI=0.66-0.76).
6) Figure 2: Why the authors selected those specific cut-points? Why, e.g., they did not include mean or median values?

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