Reviewer’s report

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

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Reviewer: David G Le Couteur

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This is a landmark study that links basic aging biology with frailty and clinical deficits and it will change the way that we approach ageing studies in the future. It brings together the Rockwood group who are leaders in evaluating frailty with the Kirkwood group who are leaders in ageing biology. The Newcastle 85+ study is well established. The results seem unequivocal – that the FI-B predicts mortality as well as FI-CD even though they measure quite different parameters and are not highly correlated.

Minor and discretionary suggestions

1. Explain why a very elderly age group (ie 85+) is relevant for this type of study

2. Is there an element of redundancy in that the FIB parameters were dichotomized on the basis of predicting mortality, then these values used subsequently to predict mortality? Perhaps this could be mentioned in the ‘weaknesses’ section

3. Was there any correlation between FIB and Fried criteria. This might be relevant given the Fried criteria are said to be based on age-related changes in bioenergetics which might be more closely related to ageing biology.

4. The observation that FIB is a stronger predictor of mortality in the non-frail group is really interesting and worth exploring because it might answer the question of whether frailty is ‘end-stage old age’ which can only be avoided by dying prematurely of something else. Do people with a low FICD and high FIB become frail before death.

5. Is there any mechanistic explanation for the difference in the shape of the curves in figure 1? The differences are quite striking.

6. The list of parameters in table1 include strong associations between various markers that are established biomarkers of ageing (eg albumin, CD4/CD8 etc), so it is surprising that IL6 was not significant. Is there any explanation for this?

Quality of written English: Acceptable

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

Declaration of competing interests:
I have no competing interests