Reviewer’s report

Title: Trajectories of physical function prior to death and brain neuropathology in a community-based cohort: the ACT study

Version: 0 Date: 23 May 2017

Reviewer: Soo Borson

Reviewer's report:

This is a report from the Adult Changes in Thought study, an important source of longitudinal data on rates and risk factors for incident dementia, which has produced major contributions to the literature over its long study life. This paper offers data from 300+ participants who came to autopsy, with the goal of adding to the literature on the relationship between physical performance (here measured by the SPPB) and neuropathology, including major markers of Alzheimer's disease, vascular brain disease, and Lewy body dementia. The authors find that vascular disease, indexed by infarcts, but not the degenerative neuropathologies evaluated, was associated with poorer SPPB performance 5 years before death. They also found that no pathology measured was associated with rate of decline in SPPB.

This work adds incrementally to what is already known about the relationships between various brain pathologies and physical performance. Assuming that statistical review by experts finds the analytic methods suitable, my main concerns are in three areas:

1. Sample: Characteristics of the ACT cohort. Various strengths and weaknesses of this cohort have been discussed over the many years of the study's tenure; for this paper, the relative good health of the cohort may obscure relationships that would emerge in 'sicker' samples with more vascular and mixed pathology.

2. Measures: I found myself wishing that more components of neuropathology had been measured. For example, one would expect subcortical Lewy bodies and long-tract white matter disease to relate to physical performance. Restriction of examination to AD indicators (including amyloid angiopathy), cortical Lewy bodies, and infarcts limits the contribution of this study.

3. Readability: The paper lacks a clear theoretical framework and set of hypotheses, which, if provided, would ground the dense analytics and rather arcane presentation in important clinical phenomenology and make the work more meaningful to geriatricians.
Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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