Reviewer’s report

Title: Slower walking speed, poor balance and reduced gray matter volume predict falls in older adults with mild cognitive impairment

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Reviewer: James E Galvin

Reviewer’s report:

The manuscript describes a longitudinal study assessing the association between baseline physical performance and gray matter volume, and risk of falling in 42 community-dwelling older adults with mild cognitive impairment followed up for a 12-month period – 11 individuals experienced a fall during the study period. The investigators were than able to compare clinical and performance characteristics as well as MRI volumes between those who fell (n=11) vs. those who did not fall (n=31).

Overall, the paper is well written. The findings suggest that poor physical function as measured by walking speed and balance and lower gray matter volume predict incident falls over the follow-up period. Identification of risk factors for falling in the MCI population – an at-risk group is an important issue. Inclusion of brain imaging data adds merit to the project and furthers our understanding of the link between brain structural changes, cognitive impairment, and risk of falling. However, there are some issues that this reader would like to comment on with the goal of improving the quality of the paper.

Major Compulsory Revisions:

1. Although the primary results of the trial have been published, there are details missing from this manuscript that would be helpful to the reader. Nowhere in the methods section is the form of MCI studied (amnestic, non-amnestic, single, multidomain) or how the MCI evaluation was performed is described. MMSE scores are not sufficient to characterize the sample described here.

2. This reviewer therefore assumes that a larger neuropsychological evaluation was performed. Even though MMSE scores were not different between Fallers and Non-fallers, what about other cognitive tasks. For example, were there differences in executive or visuospatial tasks between the groups?

3. History of falling has been identified as a significant predictor of future falling. However, this factor has not been addressed in the manuscript. This reader suggests that this information, if available, should be taken into account in data analysis (added to the multivariate models to control for its impact on fall risk).

4. Given the correlations between structural changes in the brain, physical functionality, and fall risk, it may be important to assess whether the effects of physical performance are independent of gray matter volume or whether the latter confounds the association between the former and fall risk.
Minor Essential Revisions

5. The issue of why increased fall risk is important in the context of mild cognitive impairment should be more emphasized in the background section. This would imply making the connection to the Alzheimer’s Disease/dementia process as well.

6. Given the finding that gray matter volume in certain areas of the brain appears to be an important predictor of fall risk in older individuals with MCI, having something in the background section that addresses the link between different brain areas and fall risk may help provide some direction as to what the expectations were at the onset of the study.

7. Which leg was used to measure isometric knee extension strength and why (page 4)?

8. The ‘magnetic resonance imaging procedure’ section on page 5 could be improved by describing how gray matter atrophy was measured and used in data analysis.

9. Why was the statistical threshold for the VBM analysis set for p<0.001 (page 6)? This looks like a multiple comparison correction, although the authors state this was uncorrected.

10. The results section mentions that fallers and non-fallers were compared in terms of body mass index (page 6). This appears ‘out of the blue’ without a connection had having been made between BMI and fall risk.

11. This reviewer would advice the authors to replace the term ‘reduced’ when describing baseline levels of gray matter volume. Since ‘reduced’ suggests decline in volume over time, a more appropriate term would be ‘lower’. Do this throughout the manuscript.

12. Although the brain imaging findings were understandably emphasized in the discussion section, the findings on physical functionality should not be ‘brushed-off’. The authors could expand the second paragraph on page 7 to discuss the importance of physical functionality on fall risk in the context of MCI. How current findings relate to previous reports should be discussed here.

13. Could the authors elaborate on why muscle strength was not important in predicting fall risk in this population?

14. The authors could elaborate a little more on the last point they make in the conclusions section. Is there evidence that age-related declines in physical function and brain structure can be prevented?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

none