Reviewer’s report

Title: Cardiovascular risk factors and memory decline in middle-aged and older adults: The English Longitudinal Study of Ageing

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Reviewer: Kathleen Welsh-Bohmer

Reviewer's report:

This study explores the relationship of cardiovascular risk factors to memory decline in middle aged and older adults in a large epidemiological study. The sample included over 4000 individuals who were between the ages of 50-64 and 3000 between the ages of 65-79 at baseline all of whom were followed every 2 years over 10 years. The results show expected effects of age and education on neurocognitive function at baseline. With repeated memory evaluation, the anticipated test-retest improvement effect was seen in the younger groups but the effect was muted within the group that had cardiovascular risk factors. In the older group there was an absence of the test-retest effect and there was monotonic decline over repeated observations that was amplified by the presence of cardiovascular risk factors in a dose dependent fashion. The latter effects were not significant. The findings suggest that CVD risk factors have a deleterious effect on memory in midlife but that this effect is not seen in older age.

The study seems well done and carefully considered. It tackles an important question that has been difficult to resolve. This particular work makes an important contribution and while the question of CVD risk in older age is not completely resolved, this study has the advantage of 10 years of follow-up data in a very large group of well characterized older adults.

Several suggestions to consider that would improve the interpretation of the main findings.

1) First, some clarification of retention over the longitudinal course of study needs to be considered when looking at slope of change. It is not clear from the data provided how many people contribute to the later time points. It would be useful to know the n's at the various waves by CVD risk factors, to better understand the models that provide trajectories of longitudinal change.

2) Second, some further consideration of chronic diseases and the protracted effects of CVD are needed. The 2 age groups appear to be starting at a different level of health, it may be that a lifetime of CVD risk is playing some role on later life cognitive health. Some further discussion is probably warranted about the effects of chronic disease. Then, there is also the worrisome effect of undetected cognitive disorders at baseline, a problem that will be a bigger issue in the older group. While there was some effort to remove diagnosed cases of cognitive disorder, it is not clear that there was any ongoing surveillance of cognitive conditions. Is the prevalence and incidence of dementia and MCI in the ELSA cohort known? Presence of significant cognitive disorders could contribute to lower baseline cognitive scores and a muting of the test-retest effect at follow-up in the older group. Some discussion of these issues is needed before drawing the inference that CVD has no impact on cognition in later life.

3) In this context, it is also very important that the reader knows a bit more about the psychometrics of the primary endpoint (memory change). It is not clear if the investigators used a well validated
measure. And the absence of test/retest effect on memory in healthy older adults is particularly puzzling. This causes worry about potential issues in reliability and in scaling. In the methods it would be helpful to know that the alternative forms used had high reliability. And since there could be problems with floor effects in the older group for delayed recall it would be useful to present the data for the immediate and delayed recall trials by group (perhaps even by CVD subgroup) at the baseline visit in order to get a better appreciation of the group differences and how the measure is performing.

**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

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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