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: John Breitner

Reviewer's report:

The authors report an analysis of data from a large population cohort study (ELSA) that divided participants into middle age (60-74) and old-age (75+) participants but exclude those over age 80 (why that exclusion?) From various sorts of data (some self-reported, others more objective) they created a Cardiovascular Risk Factors Score ranging from 0 to 3+. Adjusted linear mixed effects models then indicated association of CVRF count with change over time in episodic memory score. The latter is described as a verbal recall task after distraction, but some further specification might be helpful. The principal finding is that middle-aged persons without CVRF appear to show some capacity for practice effects in their biennial assessments, while those with CVRF do not, or may even decline slightly. Older participants show decline that appears to be relatively homogeneous across CVRF score but with different baseline intercepts. The authors speculate that the apparent effect of CVRFs in "middle age" might portend subsequent vulnerability to dementia, whereas the absence of a CVRF later (where dementia risk is much greater) may have no such implication.

A major concern with this paper is its rather cursory description of the ELSA. I could not find a substantial reference to investigate this, and there is no description given of the focus of the study and the roles of cognitive assessment in its goals. Was episodic memory the only cognitive test used? If so, it would be helpful to know more about how this test was administered and by whom. If this is the only cognitive test in ELSA, one might worry that cognition was a rather cursory consideration in this large and expensive study, and one then wonders about the rigour of its application. By contrast, if more than one cognitive test was used, why have the authors chosen to report this one only? Honestly, I worry about this paper, and the association of these authors with the study. Are the results of ELSA in an open-source format, and if not how is it that these authors have access to the data when so little has been published otherwise from this study (or, if there are publications, they should surely be cited liberally).

As for results themselves, I have some questions. There appears to be a clear cohort effect in the description of characteristics of the older and younger samples. This is not a criticism (it is expected) but it does raise concerns about confounding by some of the differences, especially education which is measured in rather cursory fashion. I'm not sure there won't be some residual confounding by the variables of mental aptitude, social class, etc., or what effect these variables might have on the results. This would be less of a concern if the main outcome (differences in slope of cognitive performance by CVRF score in the two groups) had given a more robust finding. The authors acknowledge that the observed effect is in fact quite small, so that the P values are driven more by the massive size of the sample than by the actual effect itself.

It would be important to know whether contrast in memory decline X CVRF in the two age groups was a primary aim of ELSA, again because this might speak to the care with which the needed variables were acquired.
I have a number of less important comments as well: I'm not sure how this paper adds to the very well summarized prior work on middle aged vs old aged risk factors for dementia or cognitive decline. Several of these earlier works were tightly focused on this topic, and if this was not, then I'm concerned about just how much new information is offered.

Are the various mortality risks discussed initially in fact PAR or some other method of estimation? It's probably misleading to state these estimates as fact.

The authors should avoid at all times language implying cause and effect when what they describe are associations.

It is odd that the authors use reported number of prior cardiac events (CVDs) as a covariate and adjust for it. Why would this information not have been used in the CVRF score??

I thought the use of a completes-vs-non-completers covariate was nifty. I hadn't seen that before.

Because the paper reports a "null" result for the older age group, there is concern about type 2 error. There is mention made of Bonferroni correction, a technique that has fallen out of favour because it over-corrects. Would the same findings hold if a less biased method (FDR?) were used to adjust for multiple comparisons. Then again, if memory effects of CVRFs were the principal objective of the study from the outset, why would one need correction for multiple comparisons (maybe I'm missing something here?) If multiple comparisons are, indeed, a problem, then what are the other comparisons being made (speaks to intent of the ELSA in the first place).

There is no need for detailed text description of the contents of Table 1. Just mention the important contrasts perhaps.

Don't use "conversely" if you mean "by contrast". I think the word "subsequent" memory decline at the beginning of the Discussion is misleading; you mean contemporaneous decline, do you not?

I wonder about the statement, bottom of P. 10, about not expecting memory decline in middle age. Do we have strong prior information here? What does it add to your paper?

**Are the methods appropriate and well described?**

If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**

If not, please specify which controls are required in your comments to the authors.

Unable to assess

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