Reviewer’s report

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

Version: 1 Date: 07 Jul 2019

Reviewer: John Breitner

Reviewer's report:

The authors have responded adequately, for the most part, to my critique. I do have substantial remaining doubts, however. The main argument here is that accumulation of cardiovascular risk factors has bearing on cognitive performance trajectory in middle life, but not in older age. One of my inquiries was about the possibility that the "statistically significant" result was as much a reflection of the large sample size as it was of real differences in outcomes between the two age groups. The authors have responded that the large sample size may protect against type 1 error, and I agree that occasionally peculiar results can happen in the analysis of smaller samples, but rarely so with larger numbers. But the fact remains that the differences "proven" are quite small. Small differences can become "statistically significant" with large samples where their more fundamental or clinical importance is less certain. Furthermore, what is observed is in fact an apparent reduction in learning or practice effects in the middle aged group with CRF, while there is little or no practice effect in the older group to begin with. It is true that practice effects can in fact reveal a certain form of cognitive ability that may be lost in illness, and it is also true that some authors contend that the ability to learn with practice may be a valid indicator of cognitive abilities. This perspective is by no means without controversy, however, and it reflects a relative weakness in this finding therefore. More worrisome, in fact, is a common occurrence that smaller effects can arise more readily from various sorts of confounding that produce systematic error. It is widely appreciated in epidemiological studies that the convincing demonstration of a relatively small effect requires a very "clean" study design. In this context, I continue to wonder why (now that it is clear that there were several other tests of cognitive domains in the ELSA) the authors chose to conduct their analyses only on episodic memory. A much more convincing argument could have been made if other cognitive test results showed similar trends, especially if some argument (other than sheer speculation) were drawn as to biological plausibility of the findings. All told, despite the clarifications afforded by the authors' responses, I remain rather skeptical about the validity of the argument made here that somehow cardiovascular risk factors have effects in middle age that are not present in older age groups. The finding here is interesting, to be sure, but the considerations above leave me with doubts that there is substantial new knowledge demonstrated here.
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