Author’s response to reviews

Title: Framingham Stroke Risk Profile and Poor Cognitive Function: A Population-Based Study

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Author’s response to reviews: see over
Dear John Kerr,

Thank you for your useful suggestions regarding revisions to our manuscript on the relationship between the Framingham Stroke Risk Profile and cognitive function. We recently presented these findings at the Fifth International Congress on Vascular Dementia where it received second prize for best free oral communication.

We have carefully addressed each of the points raised by the reviewers, and outlined how the revised manuscript addresses each of these comments. We greatly appreciate these points and feel that the subsequent revisions have improved the content of the manuscript.

Please contact us if we can provide any further information or clarification. We look forward to hearing from you regarding the revised manuscript.

Kind Regards,

Dr. David J. Llewellyn
University of Cambridge
Our response to reviewer 1 (Jennifer Manly)

This is a well-written paper summarizing the relationship between a modified version of the Framingham Stroke Risk Profile (FSRP) score and cognitive function in a representative sample of English people aged 50+. The sample is a great strength of this study, and the analyses are relatively straightforward. It is not clear however, how much the results add to the literature.

Major compulsory revisions
1. We already know that some components of the FSRP correlate with cognitive test scores – what is new here? The FSRP, a widely used clinical score, may provide a convenient and cost-effective way to identify vulnerable older adults (we have revised our conclusions to make this clearer – p.12, para.3). Our data provide the first evidence from a large population study that the association between stroke risk and cognitive function is not constrained to the highly educated or the Framingham cohort itself (p.9, para.1 and p.10, para.2). Elias and colleagues themselves argue that further research is necessary to extend their findings to a more representative population. Recent American Heart Association and the American Stroke Association Stroke Council guidelines also stress the need for further research using the FSRP with groups other than the Framingham cohort (p.4, para.1).

2. A second wave of data for ELSA participants should now be available, and it would be much more helpful to see the longitudinal analyses. While we agree that it will also be interesting to conduct longitudinal analyses, we plan to examine cognitive decline separately when additional data becomes available. Given the socioeconomic diversity in ELSA, it might also be helpful to know if the FSRP-cognition relationship varied across social groups. This is an interesting supplement to our initial results, and we now present sensitivity analyses examining the association between stroke risk and cognitive function separately by those with and without educational qualifications (p.10, para.2). The pattern of results observed was highly similar, providing reassuring evidence that the association is also observed in participants with low levels of education.
3. The association between specific components of the FSRP and cognitive outcomes would be interesting. Is there one single factor driving these results or are all of these risk factors operating in the same direction? We agree that this is very interesting to examine, and present results demonstrating that the association was not constrained to just one or two FSRP components (p.9, para.3).

4. Please spend more time describing the cognitive measures. For example show the distribution of the outcomes – the mean and the SE as shown here is not very informative. The SD and range would be helpful and an assessment of ceilings/floors if there are any with these measures. We have supplemented the content of the Methods (p.6, para.2, and p.7, para.1) and Table 2 (p.12) accordingly. Is there just one item on the “prospective memory” assessment? Prospective memory assessment is based upon two tasks as we now make clear in the revised Methods section (p.7, para.1).

5. Please show the fully adjusted results in the tables, along with the age and sex adjusted results currently displayed. Also add results for the global cognitive function measure to Table 3. We have revised Table 3 to include unadjusted and fully adjusted results for each cognitive domain (p.24). We prefer to present results for global cognitive function separately in the main text to maximise the conceptual clarity between results relating to global cognitive function and individual cognitive domains.

6. It seems very misleading to report the unadjusted regression coefficient (0.4) in the abstract and discussion. After adjusting for sex and age, the magnitude of this effect drops by nearly a factor of 5 to .088. Thus, this result probably primarily reflects the fact that older people score worse on global cognition. We do not agree that this is misleading. Indeed it would be strange if our results did not suggest that age accounted for a large proportion of the variance given that age is known to be strongly associated with both cognitive function and stroke. We stress in the abstract and elsewhere that the association was attenuated with adjustment, though the fact that the association remained significant suggests that potentially modifiable risk factors are also important. New analyses with the FSRP components following your suggestions support this conclusion (p.9, para.3).
7. Are all items from ELSA, including atrial fibrillation, assessed with self-report or were medical records available for validation? Cognitive function was directly measured and other items were based on self-reported diagnosed conditions, which we acknowledge as a limitation (p.11, para.3).

Minor Essential Revisions
1. On page 9, 1st sentence of the last paragraph, which cognitive domain is the beta estimate referring to? And why is it <=? These results are now presented in Table 3 following your suggestion (p.24).

2. It probably won’t make much of a difference, but given the range of social data available in ELSA, why have you chosen to control for such a limited set of potential confounders (e.g., why not income and wealth, if they are available)? We control for education and socioeconomic status which are highly correlated with income and wealth. We encounter problems with collinearity in our models if we introduce too many variables that are highly similar. It should also be noted that previous studies have incorporated a more limited set of covariates, and our study is the first to adjust for socioeconomic status. And what is the motivation for selecting the covariates you did choose? CESD score in particular seems to me potentially causally subsequent to the FSRP. We selected variables that are reliably measured in ELSA and known to be associated with levels of cognitive function (p.8, para.1). We also took into account which variables were included as covariates in previous studies in order to ensure that our results were reasonably comparable. Adjusting for depression is common practice in cognitive research, though we acknowledge that we may have effectively over adjusted our final models given the similarity in risk factors for poor cognitive function and stroke (p.11, para.2). The fact that the association remained significant is testament to its robustness.

3. Repeated reference to “probabilities of stroke” instead of “FSRP score” is confusing. We amended a sentence which refers specifically to FSRP scores (p.12, para.2). However, FSRP scores correspond to the 10-year probability or risk of incident stroke (p.6, para.1), and we therefore refer to stroke risk or 10-year stroke risk throughout.
4. How was the subsample of 7716 ELSA participants who provided FSRP information selected? Or do you just mean that the other 4,015 ELSA participants had missing data? Each wave of the Health Survey for England (HSE) is an independent nationally representative sample, and the focus of each wave changes each year. Extensive information on cerebrovascular risk factors has been collected in some waves (e.g. 1998) whereas in other waves with a different emphasis this data was not collected, or was collected for a random subsample of participants.

Our response to reviewer 2 (Matti Viitanen)

This is an interesting article describing the association with stroke risk factor load and cognitive decline.

Background: The authors claim that risk factors for incident stroke such as smoking status and diabetes predispose older adults to cerebral white matter pathology, and biological aging is partly attributable to effects of cerebrovascular disease. Please explain what you mean with cerebral white matter pathology. The point we were making in this introductory statement is that risk factors for incident stroke predispose older adults to subclinical cerebrovascular disease in addition to clinical stroke. We have revised this section to clarify this point (p.3, para.1). I do not agree that biological aging is attributable to effects of cerebrovascular disease. Please explain. This section is taken from the commentaries of Seshadri and others who argue that biological aging of the brain is partly attributable to aging of the cerebrovascular circulation and the effects of these vascular changes on the brain. We have amended this section to make this clearer (p.3, para.1).

Methods: With which examinations the stroke and dementia were excluded and how were stroke and dementia defined. Were the patients with mild cognitive impairment excluded? Were the silent cerebral infarctions included? Those with a self-reported diagnosis of stroke or dementia were excluded, and we acknowledge the use of self-reported diagnosed conditions as a limitation (p.11, para.3). Participants with mild cognitive impairment and silent cerebral infarctions were included, indeed it was essential to include these individuals, and we argue that subclinical cerebrovascular
pathology is likely to account for the observed association between stroke risk and cognitive function.

In the discussion asymptomatic cerebral infarction should be silent cerebral infarction. We have revised this sentence accordingly (p.13, para.2).

Conclusion: Further research is necessary to establish whether 10-year stroke risk can be used to predict whether individuals will become demented in the future I do not understand what you want to say dementia is only a stage of cognitive decline when the cognitive decline interferes significantly with work or usual social activities or relationships with others already mild cognitive deterioration interferes with work. Dementia definition works well in Alzheimer’s disease but in cerebrovascular diseases where the patients have executive dysfunction and relatively intact memory the definition is almost useless especially in the epidemiological studies. We have revised our conclusions following your feedback, and do not now make reference to the prediction of dementia (p.14, para.1).