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 have carefully addressed each of the points raised by the reviewers, and outlined how the revised manuscript addresses each of these comments.

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)

I appreciate the authors’ responses to my previous suggestions. In some cases they rejected the suggestions, and my thoughts on these are below.

Major:

The abstract seems likely to lead readers to believe this is a longitudinal analysis, because you refer to the 10 year risk for incident stroke and you describe ELSA as a prospective cohort. Please clarify that this is a cross-sectional analysis of the association between FSRP scores and several cognitive domains at the baseline ELSA interview. We have revised the abstract to reflect the cross-sectional design.

I disagree with the authors regarding the usefulness of the unadjusted coefficients, since their results demonstrate that the great majority of this association is attributable to age and sex. I am puzzled about why the authors strongly prefer this, because as they point out, the adjusted coefficient is also statistically significant, but much smaller in magnitude. The disagreement may partially arise from uncertainty about whether this is a paper regarding clinical prediction (i.e. identifying patients who are at risk of low cognitive function) or a paper about the etiologic basis of cognitive impairment, or both. If the goal of the paper is strictly about prediction, then the unadjusted results are perhaps useful. For etiologic understanding, they are not relevant. In several places the authors seem to suggest that intervening on vascular health may promote cognitive function (e.g., bottom of pg 10), which leads me to believe they are interested in addressing the etiologic/causal question. Our paper addresses both the clinical utility of the Framingham Stroke Risk Profile and the etiologic basis of poor cognitive function. We have revised the abstract to stress that the association with cognitive function was attenuated though remained significant after adjustment, and now present regression results for both the adjusted and unadjusted models.

The 10-year risk of stroke is not measured in this data set, because these people have not yet been followed for 10 years. The independent variable used in these analyses is the predicted 10-year risk of stroke, based on the FSRP score. This prediction is based on data from Framingham, which as the authors note, may not be generalizable to the ELSA sample. If you dislike referring to the FSRP-score, in the interest of transparency, what if you called this variable the FSRP-predicted 10-year stroke risk? The concept of risk itself incorporates the notions of uncertainty and prediction, as we now make clearer in the methods section. We feel that it would be unnecessary and disrupt the flow of the manuscript considerably to include this additional text throughout. Also in several places it is unclear if you mean a 10% (i.e. the difference between a 20% probability and a 22% probability) or a 10 percentage point (the difference between a 20% risk and a 30% risk) increase in risk. I think you usually mean the latter. We have altered the text throughout to make this clearer.

Minor:

Table 2 is very helpful. It would be convenient to show another decimal place, because at this point the means for men and women in many comparisons appear to be identical but the p-value for test of difference is significant. I assume this is just because the huge sample renders the standard errors very tiny. That is correct. Adding another decimal place to the means should resolve this. We have added another decimal place to Table 2 to clarify this.
The distributions of the dependent variables shown in Table 2 seem to severely violate the assumptions for linear regression (i.e. some of the dependents are discrete variables that range from 0-4 or 0-2). Ordered logistic or poisson models might be preferable. It seems unlikely to change your results, but it would be helpful to note that these results were not sensitive to choice of model. This made no difference to our results for prospective memory and time orientation (the tests limited to a small number of discrete categories). Additional text relating to these secondary analyses has been included.

Thank you for the clarification that all components of the FSRP gathered in ELSA are based on self-report. Given this, it would be helpful to know if there is any evidence on the validity of self-reports of the items in the FSRP, especially atrial fibrillation. Has this ever been studied? Systolic blood pressure (mm Hg) was directly measured and is not based on self-report. While the use of self-reported history of doctor diagnosed conditions (including atrial fibrillation) is commonplace in the biomedical literature we acknowledge this as a limitation in the discussion section. A large number of studies describe considerable overlap between self-reported and measured conditions (e.g. Furberg and colleagues’ 1994 study of atrial fibrillation in the Cardiovascular Health Study).

Adjusting for income and wealth alongside education and the occupational class measure is unlikely to produce much of a collinearity problem. The variables are correlated, but not so strongly as to prevent identification in such a large sample. More importantly, the coefficients for the SES variables are never presented in this paper, they are entirely treated as potential confounders. It is not a problem if you end up with wide confidence intervals for these estimates. The goal is to do the best possible job eliminating potential bias from income or other possible common causes of FSRP and cognition. ELSA and similar studies have many serious limitations for health research (most notably, self-report of all medical information), but these limitations are offset by remarkable strengths, including broad based, representative samples, and comprehensive assessment of socioeconomic conditions. It seems disappointing to write a paper that is vulnerable to all of the limitations and fails to take advantage of one of the primary strengths. The inclusion of income is problematic given that income levels typically drop considerably at retirement, and for that reason is not normally included in ageing research. However, we were able to adjust for wealth (total net non-housing wealth) and we have revised the text accordingly. Also, could you please add a couple of words describing the National statistics-socioeconomic classification 3 for the benefit of non-UK readers? We have inserted additional text in the methodology.

I still feel that the paper would be much stronger if it included results from wave 2 of ELSA, and I question the potential contribution to the literature of a cross-sectional analysis showing that vascular risk factors correlate with cognitive test scores. The results that seem especially interesting (for example: in adjusted models, FSRP did not predict time orientation, prospective memory, attention, or numeracy; and the relationship between FSRP and cognition was not modified by years of education; and neither SBP nor atrial fibrillation predicted cognitive test scores after covariate adjustment) are not emphasized in the abstract or discussion. The latter result, regarding lack of effect modification by education is difficult to discern in the current version of the text. As we have made clear we intend to conduct longitudinal analyses when further information becomes available. The contribution of this article is not to link vascular risk factors to cognitive function; it is to investigate the utility of a widely used clinical measure and the association of combined cerebrovascular risk factors to cognitive function. There is very little literature in this area, and our manuscript represents the first large population based study (other than analyses
based on the highly educated Framingham cohort itself) to investigate this phenomenon.

Our response to reviewer 2 (Matti Viitanen)

Thank you for your feedback (no revisions were requested).