Author's response to reviews

Title: Family history and stroke outcome in a bi-ethnic, population-based stroke surveillance study

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Author’s response to reviews: see over
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Dear Editor,

Thank you for the opportunity to revise our manuscript “Genetic epidemiology of ischemic stroke: a bi-ethnic, population-based stroke surveillance study” (MS: 2083797098706543). Below is a point-by-point description of the changes made to the manuscript. Revisions are highlighted in the text for ease of identification.

Sincerely,

Lynda Lisabeth, PhD

Major Compulsory Revisions

1. “It appears that patients with strokes prior to the study were included in the analysis. Cases of recurrent stroke could demonstrate different relationships from incident/first ever cases and their inclusion hampers interpretation of the results and potential comparisons with other studies. It would be desirable to clarify this issue.”

The Reviewer is correct that both incident and recurrent strokes were included in the analysis. Table 2 (page 21) now includes information on the proportion of cases with a history of stroke or TIA, as well as the p-value for the chi-square test of association between family history and history of stroke/TIA. As this relationship was not significant, history of stroke/TIA does not appear to confound the relationship between family history and the outcomes studied.

2. “A substantial proportion (37%) of the family history interviews were conducted with proxies, primarily spouse or child of the case. Although prior work established the agreement between patient/proxy interviews for other historical elements, agreement for family history has not been examined. Proxy interviews are presumably a maker of stroke severity and could be correlated with stroke subtype and with completeness of family history. For this reason, proxy status could be a confounder. This could be examined empirically, for example, by determining the quantitative change in the odds ratio for the association between family history and each outcome, before and after adjustment for proxy status.”

We agree that the use of proxy subjects could confound the observed associations. We have added a section to the Statistical Analysis (page 8) and the Results (page 11) to evaluate the degree to which confounding is present. We conducted a chi-square test to determine the association between proxy use and family history which was insignificant suggesting proxy use is not a confounder by definition. We also added an indicator for proxy use to the multivariable models as the Reviewer suggested and
include the results in Table 6 (page 25). Further, we conducted a chi-square test to determine the association between subtype and use of proxies. Proxy use does not appear to confound the associations between family history and the outcomes, with the exception of age at stroke onset. However, family history remained insignificant in this model.

Discretionary Revisions

1. “There is a rather striking finding in Table 2 of increased family history of stroke among female stroke cases compared to men (p=0.0006) that is not commented upon in the results or discussion.”

We have added a sentence to the Results (page 9) to point out the gender difference in family history. We have previously reported on this finding and have added the reference for the interested reader to the Results.

2. The title is somewhat misleading since the main exposure of interest “family history” is not mentioned.

“The title has been changed to ‘Family history and stroke outcome in a bi-ethnic, population-based stroke surveillance study’.”

Other Changes

We have added a recent reference on the topic of the manuscript to the Discussion where appropriate (page 12).