Reviewer’s report

Title: The association of APOE genotype and cognitive decline in interaction with risk factors in a 65-69 year old community sample

Version: 1 Date: 29 March 2008

Reviewer: Janet Johnston

Reviewer’s report:

This is a well written article reporting on a well done and important study. The majority of my comments have to do with organization or missing details regarding the analytic methods.

Major Compulsory Revisions

1. A reference should be added for the Reaction test, as well as for the method used for handling outliers.

2. What statistical tests were used for Table 1? It would be best to use a test for trend to test whether there is a greater effect with two E4 alleles as opposed to one.

3. I was not clear exactly how the clinical diagnosis was used as an exclusion criteria. Was everyone with any diagnosis of mild cognitive impairment, age associated memory impairment, age associated cognitive decline, or mild neurocognitive disorder excluded when the analyses were repeated. And what happened when they were excluded. I do not see two sets of results (one with the 127 people with clinical diagnosis and one without) reported.

4. Please explain how missing data was handled.

5. Please provide more details regarding model fitting and what diagnostics were used.

6. Please comment on whether the APOE genotype was in Hardy-Weinberg equilibrium.

7. I found the last two sentences of the Bivariate models paragraph in the Results section to be confusing. The second to last sentence talks about those homozygous for *E4 while the last sentence talks about those homozygous or heterozygous for *E4. From Table 2 the reader can only tell that there was some effect of the APOE genotype, but cannot tell anything about differences between homozygotes and heterozygotes. I would prefer to see regression coefficients and 95% confidence intervals for the significant models, rather than a table of mostly non-significant statistical test values and p-values.

8. In Figure 1, the error bars for the *E4 homozygotes in panels C and D include 0, making me question your statement that they showed greater decrease in
MMSE and SDMT than all other groups. It is true that the genotype/head injury interaction was statistically significant, but the figure does not show a significant interaction for that group.

9. The authors provide a relatively long introduction with a good review of the literature; however, they then do not talk about how the results fit into the literature in the discussion. I recommend shortening the introduction and including more information about other studies and where these results fit in the discussion.

Discretionary Revisions

10. It would have been nice to be able to distinguish between stroke and TIAs in the analysis. Given that only one question was asked, it does not seem possible to change that for this analysis. However, for the future I would recommend getting more detailed information about stroke vs. TIA.

11. The cutpoints for hypertension seem high, particularly given current hypertension definition of SBP $\geq 140$ and DBP $\geq 90$. Would consider re-doing analysis with lower cutpoints.

12. Because of the relatively small number of participants who are homozygous for the E4 allele, the authors may want to consider dichotomous analyses where the two groups are no E4 allele vs any E4 allele. This might help shrink the confidence intervals when you start looking at interactions.

13. I would divide Table 1 into two tables, either Table 1 and Table 2 or Table 1A and 1B, with the Wave 2 test scores and change in test scores in the second table. I would also leave out the value of the test statistic and just include the p-value. The tables are very busy, making them a little overwhelming to read.

14. In many longitudinal studies of cognitive function there is a learning effect where scores may actually increase the second time a test is given. I find it interesting that almost all of the test scores went down from Wave 1 to Wave 2. This may be due to the age of your participants. You might want to comment on this in the discussion. If you have completed Wave 2 for your younger groups of participants, it would be interesting to know whether the scores also fell from Wave 1 to Wave 2 for those groups.

15. I think it is a good idea to use figures to show the effect of the interactions, however, I think the figures would be easier to read if you flipped the groupings. For example, I would have had an easier time reading the figures if in panel A the first group was everyone with education 0 to 12 years and then there were 3 bars in that group showing the different APOE genotypes.

16. In looking at Figure 1, there are many instances where there are large error bars that include zero, especially for the E4 homzygotes. Again, I would suggest combining the heterozygotes and homozygotes in hopes of shrinking the error bars and being able to report more robust findings.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.