

Comments on the paper authored by Group 13 as Refereed by Group 12

RE: Questions of Interest

There are two discrepancies we feel should be addressed in the authors' report with regards to the questions of interest as stated and the actual questions answered.

Based on the questions of interest listed on pages 1 and 2, the authors do not seem interested in prediction of mortality based on demographic, disease, behavioral, organ function covariates, though these analyses appear in many places throughout the paper, along with the argument that they are more predictive than atrophy score. Perhaps a brief sentence or two motivating the inclusion of these analyses in addition to the collaborator's questions of interest could be added below the questions themselves.

Alternatively, the survival and proportional hazards analyses could be dropped for these predictors individually since they do not seem to address the questions of interest. It is noted in the results for descriptive statistics that the variables adjusted for are associated with cerebral atrophy score, and many of them are associated causally with death. On these grounds alone, histories of strokes, heart attacks, etc. are potential confounders (they don't have to be associated with mortality in the sample).

In both the background and questions of interest (Question 3, in particular) there is a focus placed on the association between atrophy score and mortality being independent of the demographic, behavior, disease status and organ system functioning variables. This question seems to go largely unanswered. While demographic variables of age, race, and sex are adjusted for and the adjusted analysis also includes information on diagnosis of CHF, CHD, and strokes, there is no discussion of the association between atrophy score and length of time to death being independent or dependent of behavioral variables, or measures of organ system functioning. If the authors feel that the descriptive statistics address this concern, or do not feel that the question is answerable given the present data, this should be made explicit.

RE: Results, Descriptive Statistics

We have just a few quick clarifications and considerations here:

- Is there a clinical relevance for the stratification of cerebral atrophy score into 0-35, 36-50, 51-100?
- The time period for average alcohol consumption quoted here and in the **Description of the Data** differ. Should it be one or two weeks?
- The authors mention that alcohol consumption and diabetes diagnosis vary across the strata, but they do not join the other covariates in the adjusted model later on. Why not?
- There does seem to be a slight negative correlation between physical activity and atrophy score. This could be of interest as a behavioral covariate.
- White matter changes are mentioned for the first time here, should they be included in the earlier **Description of the Data**?
- What is "12-10%" supposed to be for volume of infarcts?
- When did the study start? The study's end date is given, and 5.80 years is mentioned a few times. Is the 5.80 years the length of follow-up?
- In discussing CHD's survival curves, the curves did overlap (this looks like a typo).

- If there was no data missing for atrophy score or the variables that varied by the atrophy strata, why is it necessary later to state that no individuals missing observations were included when estimating the regression?

RE: Methods/Results, Inferential Statistics

Variable selection in **Methods** says that all variables found to be associated with atrophy would be adjusted for. In **Results** this criteria narrows; the authors only adjusted for what they considered to be potential confounders.

There is some inconsistency in referring to hazard ratios versus instantaneous risk of death throughout the report. We are particularly fond of the interpretations used in the **Summary** for reporting and interpreting estimated hazard ratios.

In the methods section, it may be worth mentioning that “no association” corresponds to the true hazard ratio being one in this analysis.

RE: Figure 1

Since all discussion pertaining to survival time is in units of years, perhaps the observation time could be changed from days to years here as well.