Dear Editor,

We thank you for giving us the opportunity to revise our manuscript, for the second time, according to comments received by the reviewers. Listed below are detailed replies to all the questions and comments raised by Professor Angelo Scuteri, who had some additional queries to the previous version.

We now hope that the manuscript has improved sufficiently to meet the standards of your Journal, and that acceptance is possible. However, we are still prepared to make further adjustments, if necessary.

Sincerely yours,

Elin Dybjer, MD
For all the co-authors

Reviewer reports:

Angelo Scuteri (Reviewer 1):

The research hypothesis is relevant and well formulated. The study population allows testing it.

Reply: Thank you for this acknowledgement.

1. It seems the statistical approach and the data modelling is somehow redundant and, accordingly, not easy to read. This also impacts on the dilution of the potential implications of the main findings.

For instance, it is not clear the added value of having GLM models and multiple regression models as well as so many models, each of group testing different populations because of missing values (PWV), exclusion (stroke cases, diabetes for 2h glucose), adjustment.

Testing a unique study population will simplify presentation and comprehension.

Reply: We have now revised our Tables and made several re-calculations to modify and simplify the data presentation. One unique aspect of our study population is that we have not only used a golden standard measure of evaluation glucose tolerance (OGTT), but also golden standard measure of arterial stiffness (c-f PWV) in addition to a set of more conventional risk factors/markers for evaluating associations with two cognitive tests, the MMSE (a test of global cognitive function) and AQT (a test of processing speed and executive functioning). Other studies may have used even better test batteries for cognitive function, but lack one or two of the other golden standard components.

We have made the following changes to the analyses:

- We have reduced the number of adjustment models to two instead of three. Model 1 is adjusted for demographics and lifestyle factors, and Model 2 for demographics, lifestyle factors, and cardiovascular factors.

- The categories of glucose metabolism have now been simplified into ‘NGT’, ‘pre-diabetes’ and ‘diabetes’ as suggested, see the analyses presented in Table 1-2.

- The previous Table 2 with four categories of participants, in which people with diabetes are further sub-divided into long-term and short-term diabetes, can be regarded as a post-hoc analysis, and is now moved to the Supplement (Table S1).
• We have excluded the Table of corresponding regression analyses equivalent to the GLM analyses in Table 2, as suggested.

• The analysis in which stroke patients were excluded has also been excluded. However, we still find it relevant to mention this analysis in the manuscript although data are not shown, as it is interesting to see if the findings are significant also regardless of stroke.

• Table 3 (with continuous glucose measurements as exposure, cognition as outcome) has been changed. Results of cognitive domains as outcome are moved to Table S2, Supplement and results in the sub-population of participants without diabetes has been included in the Table, as these are important findings.

• Table 4 and Table S3 that were previously adjusted for age, sex and education are now adjusted for factors in the new version of Model 1.

We mentioned in the previous reply letter to the editor that we also performed a complementary analysis in which we did not impute missing data. We only performed this analysis because one of the reviewers questioned the fact that we used multiple imputation for missing data in covariates. This is still mentioned in this version of the manuscript.

2. The main point is whether the relationship between alteration in glucose "metabolism" and cognitive function is continuous or is specific for diabetic subjects.

Cognitive tests' scores across groups of "glucose tolerance" do not allow answering the question. What about a post-hoc analysis, to identify which Group differs.

Similarly, having two main set of models - one with glucose as continuous variable and one with multinomial categorical variable (NFG, prediabetes, diabetes) will simplify presentation and comprehension, highlighting the strengths of the study.

Reply: Thank you for this suggestion. As mentioned in the list above, we have simplified the categories into ‘NGT’, ‘pre-diabetes’ and ‘diabetes’ and moved the previous Table 2 to the supplement, as a post-hoc analysis including diabetes with long and short duration.

Already in the previous version we had two main sets of models, one with categories of glucose metabolism and one with continuous glucose measurements (Tables 2-3). This also applies to this version, but with the simplified categories as suggested.

3. Accordingly, the Discussion section also should be shortened and more focused.

Reply: The Discussion has now been revised and shortened, with a more focused approach, as requested.
4. Speculations about mechanisms linking glucose to cognition, likely via arterial stiffening/aging, might include - depending on the final results of the proposed models - discussion about:

- glucose-independent (Nutr Metab Cardiovasc Dis. 2008; 18:349-56) and glucose-direct endothelial damage in diabetes (Stroke. 2009; 40: 306-8);

- subclinical inflammation impact on arterial stiffness, independent of metabolic alterations (Atherosclerosis. 2011; 215: 459-64);

- a systemic multiple organs damage "witnessed" by stiffer artery (Int J Cardiol. 2018; 263: 132-137);


Reply: We have now added a selection of the most appropriate of these references after reading, as suggested. Thank you!

Gang Liu (Reviewer 2):

The authors have well addressed my questions. I have no more comments.

Reply: Thank you.