Author's response to reviews

Title: Depressive symptoms, Atherosclerotic burden and Cerebral Blood Flow disturbances in a cohort of Octogenarian men from a general population.

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Author's response to reviews: see over
Response to reviewer nr 1, Irene Romera

Here are the corrections made according to reviewers report, in the same order:
- study population has been described more clear in *abstract* and *methods*
- new figure (nr 1) has been made with flow chart of study cohort.
- In abstract, study population and measurements has been separated.
- We added in methods that a neuropsychologist performed MMSE testing and together with geriatrician performed dementia diagnostics.
- In statistics, we explained thoroughly each analysis
- We defined the groups as cases and controls consequently in the whole manuscript
- We rewrote the discussion according to the recommendations.

Except these reviews comments, we made *additional changes*:
- we added table 1, with new background data, described in results, and performed multiple regression analysis as on table 4 adding its description in results section.
- We have studied literature and found that several authors use 45p as lower limit for depression (not 50p), which we changed, and we recalculated scores into indexes (with the same lower limit) as it’s described in methods. Even so, we have had 9 subjects with mild symptoms. We’ve chosen arbitrary 75th percentile as a cut-off to have the power for calculations in the case group alone. So we described both in abstract and the results that our case group comprised 9 subjects with mild depression (ZSDS index 0.55-0.71) and 22 subjects from 88th percentile and above of the normal range (ZSDS index 0.48-0.54). As it’s a population based cohort, we do not expect higher frequencies, which we refer to another, Finnish study. The fact that results are significant in the zds-borderline subjects or those with very mild symptoms is maybe the most interesting finding of the study.
Response to reviewer nr 2, Rita Bella

Here are the corrections made according to reviewers report, in the same order:

1. we précised in methods that subcortical ROI is in subcortical white matter, bilaterally, i.e. one region delineated in both hemispheres. Right basal nuclei précised in abstract

2. We defined hypertension according to WHO guidelines from 1986, i.e. systolic and diastolic brachial blood pressure ≥ 160 mmHg or ≥ 90 mmHg respectively, or medication for hypertension, as these guidelines were used for initiation of therapy at the time for both follow-ups. We added an explanation in methods.

Considering Ankle Brachial Indexes: we described additionally in methods that they were performed by a technician at the department of Clinical Physiology, using standardized method, by placing a cuff around the ankle, and using a Doppler signal on the tibial posterior artery or dorsal foot artery to detect peripheral blood flow. The reference pressure in the arm was calculated using the strain gauge system. ABI values greater than 1.3 were considered abnormal and subjects would be excluded, which was not the case in this group.

3. discussion has been rewritten considering comments on possible CBF regional influences.

Minors:

- The study started when all men were 55, and the first follow up was planned and performed at age 68, and the second and last follow up invited survivors at age 81-82. We added new figure (nr 1) with flow chart of study cohort.

- We excluded cognition from the ‘somatic symptoms’ list.

- We tried to improve the language.

Additionally:

- we added table 1, with new background data, described in results, and performed multiple regression analysis as on table 4 adding its description in results section.

- We have studied literature and found that several authors use 45p as lower limit for depression (not 50p), which we changed, and we recalculated scores into indexes (with the same lower limit) as it’s described in methods. Even so, we have had 9 subjects with mild symptoms. We’ve chosen arbitrary 75th percentile as a cut-off to have the power for calculations in the case group alone. So we described both in abstract and the results that our case group comprised 9 subjects with mild depression (ZSDS index 0.55-0.71) and 22 subjects from 88th percentile and above of the normal range (ZSDS index 0.48-0.54). As it’s a population based cohort, we do not expect higher frequencies, which we refer to another, Finnish study. The fact that results are significant in the zsd-borderline subjects or those with very mild symptoms is maybe the most interesting finding of the study.
Response to reviewer nr 3, Alice Laudisio

Here are the corrections made according to reviewers report, in the same order:

- Considering ZSDS-score levels. We have studied literature and found that several authors use 45p as lower limit for depression (not 50p), which we changed, and we recalculated scores into indexes (with the same lower limit) as it’s described in methods. Even so, we have had 9 subjects with mild symptoms. We’ve chosen arbitrary 75th percentile as a cut-off to have the power for calculations in the case group alone. So we described both in abstract and the results that our case group comprised 9 subjects with mild depression (ZSDS index 0.55-0.71) and 22 subjects from 88th percentile and above of the normal range (ZSDS index 0.48-0.54). As it’s a population based cohort, we do not expect higher frequencies, which we refer to another, Finnish study. The fact that results are significant in the zsd's-borderline subjects or those with very mild symptoms is maybe the most interesting finding of the study.

- We added table 1, with new background data, comparing cases and controls, according to background data, social factors, clinical symptoms and questions on social and physical activity. They were commented in results and in discussion.

- We defined hypertension according to WHO guidelines from 1986, i.e. systolic and diastolic brachial blood pressure ≥ 160 mmHg or ≥ 90 mmHg respectively, or medication for hypertension, as these guidelines were used for initiation of therapy at the time for both follow-ups. We added an explanation in methods.

- English language has been reviewed.
- Tables were corrected. Data in table 2 (both CBF and ABI) are index data, i.e. with no units.

Additionally

- We added new figure (nr 1) with flow chart of study cohort.
- We performed multiple regression analysis as on table 4 adding its description in results section