Author’s response to reviews

Title: Cardiac ventricular dimensions predict cognitive decline and cerebral blood flow abnormalities in aging men.

Authors:

Linda Furuäng (linda.furuang@med.lu.se)
Per Wollmer (per.wollmer@med.lu.se)
Arkadiusz Siennicki-Lantz (arkadiusz.siennicki-lantz@med.lu.se)
Sölve Elmståhl (solve.elmstahl@med.lu.se)

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

Thank you for your valuable and interesting comments concerning our manuscript: *Cardiac ventricular dimensions predict cognitive decline and cerebral blood flow abnormalities in aging men.*

We have carefully discussed and revised our manuscript. Please, see our answers to the reviewers´ comments down below.

Best regards,

Linda Furuäng¹,

Per Wollmer MD², PhD, Arkadiusz Siennicki-Lantz MD, PhD¹, Sölve Elmståhl MD, PhD¹.

¹Division of Geriatric Medicine, Department of Health Sciences, Lund University, Skåne University Hospital, Malmö, Sweden, E-mail: Solve.Elmstahl@med.lu.se, E-mail: Arkadiusz.Siennicki-Lantz@med.lu.se. ²Division of Clinical Physiology, Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden, E-mail: Per.Wollmer@med.lu.se.

Corresponding author:

Linda Furuäng, ¹Department of Health Sciences, Division of Geriatric Medicine, Lund University, Skåne University Hospital, Jan Waldenströms gata 35, SE-205 02 Malmö, Sweden. Fax +46 40 39 13 13, telephone number +46 40 39 13 03, mail linda.furuang@med.lu.se
1. Reviewer's report

Reviewer: Andreana Haley

Reviewer's report:
This manuscript reports data from the population study “Men born in 1914.” The authors analyze baseline cardiac ventricular dimensions in relation to baseline and follow-up cognitive test performance as well as follow-up regional cerebral blood flow (rCBF). They conclude that cardiac ventricular dimensions predict cognitive decline and CBF abnormalities in aging men. Considering the importance of cognition for ensuring quality of life in older age, the topic is of interest. However, the statistical analyses need to be revised before we can reasonably assess if the relationships reported by the authors are truly there. I provide some suggestions below, but also recommend a consultation with a biostatistician, as there are multiple issues to be dealt with here including multiple outcomes, repeated measures, covariates, non-random drop out from the longitudinal portion, and lack of baseline measurements for rCBF.

- Major Compulsory Revisions

Abstract:

- Methods paragraph states that “Cognitive performance and CBF were analysed … in subjects …, deceased before 1st follow up and in survivors.” How is this possible if CBF was only measured in survivors per previous sentence?

This sentence has been changed to:
Cognitive performance at baseline and at 1st follow up and CBF at 1st follow up were analysed in relation to left ventricular internal dimension in diastole (LVIDd mm/m²) and fractional shortening (FS).

Introduction:

- The second sentence of the introduction implies that we have much knowledge of the mechanisms which link hypertension to poor cognitive function; yet, the cited paper (Elias et al., 1993) merely examined the correlations between blood pressure and cognition (among many other factors) and did not measure any variables that may serve as mediators or suggested mechanisms. In fact, the authors proceed to offer many more references linking LVH to cognitive dysfunction and cerebral hypoperfusion than they do for hypertension where they
claim a greater body of evidence exists. Please revise the statement or offer different references.

We agree with referee and have removed that sentence as well as the cited reference (Elias et al. 1993). Hypertension is however, an important confounder to both CBF and cognitive performance.

- Please introduce FS earlier in the introduction (before the specific study aims) and explain its functional significance for cognition.

We agree with referee and have added information about FS earlier in the introduction.

“Fractional shortening (FS) is one parameter of assessing left ventricular systolic function. In the study of Lauer et al. 1992, low fractional shortening was associated with an increased risk for new events of cardiovascular disease [Lauer et al. 1992]. Studies on the relationship between FS and cerebral function remain however sparse. Left ventricular ejection fraction (LVEF) is nowadays assessed in order to describe left ventricular function. Low but also high LVEF have been suggested to be associated with poorer cognitive performance [Jefferson et al. 2011].”

- The fact that CBF was available only at follow-up and only on a sub-set of survivors should be made clear in the introduction.

That’s an important remark and we have altered the sentence in order to make this fact clearer to the reader.

“The aims of this study are to examine, in a cohort of men, possible associations between their left cardiac ventricular measures in sixth decade and cognitive performance, both cross sectionally and longitudinally, and to assess if left cardiac ventricular measures could predict changes in cerebral blood flow in those men who reached age 83.”
Method:

- Why was HTN defined as HBP>160 mmHg rather than HBP>140 mmHg as in other publications related to the same study (e.g., André-Petersson et al., 2001)?

These cutoffs were used in accordance to current guidelines for hypertension at the time, according to WHO (1986 guidelines for the treatment of mild hypertension: memorandum from a WHO/ISH meeting, J Hypertension 1986;4:383-6). Participants on antihypertensive medication received this according to current guidelines. These limits are well above current cutoffs defining hypertension and participants defined as hypertensive in our study may therefore had a more advanced vascular disease.

- Why was education dichotomized rather than used as a continuous variable or classified as in previous publications related to the same study as 0-6, 7-9, 10-13, >13?

We have initially chosen to dichotomize this variable since there were small sizes of subgroups. However, after your suggestion, we performed all analyses using 4-groups classification and these data are now presented in the table 1 as well.

- Please provide inter-rater reliability statistics for the two ultrasonographers.

Unfortunately this cannot be provided. However, the consequences of a low inter-rater reliability would have resulted in a difficulty of showing associations.

- Reference 11 is not appropriate for describing the rCBF measurement done by this team.

Unfortunately a typing mistake and this has been changed to reference 13 instead.

- Some data reduction strategy or multiple comparisons correction is warranted given the number of conducted comparisons (3 cardiac variables x 8 ROIs x 5 cognitive tests).

- The analytic strategy needs to be drastically revised. As stated above, I recommend a consultation with a biostatistician.

1. A t-test comparison of cognitive performance between high LVIDd and normal LVIDd (as described in the Statistics Section) without any adjustments
for age, education, other cardiovascular risk variables, and depressive symptoms is inadequate. There are published data out from the same cohort showing cognitive differences related to blood pressure among many other things. The fact that we have multiple outcome variables and repeated testing on some but not all measurements as well as significant non-random drop out also need to be seriously considered and taken into account in the analytic strategy.

3. All rCBF relationships also need to be adjusted for age, blood pressure and other relevant covariates.

The effect of non-random selection cannot be excluded, and therefore, the data on deceased subjects are presented. It can be shown that the effect of LVID remain among the survivors. A separate drop-out analysis is also given. Concerning multiple outcomes, neuropsychological assessment and cerebral blood flow (CBF) merely strengthen findings since data can be noted with both assessments. However the lack of CBF at baseline is of course a limitation. To our knowledge, there has not been any studies with 13 years follow-up of CBF yet.

However, following your suggestion on statistics, we cut out the correlations analyses and chose a General Linear Model for both analysis, i.e. LVIDd vs. Cognition and LVIDd vs. CBF and made a new calculations. We made adjustments for several variables which should partly diminish the risk of repeated testing problem in the cognitive part. (whole cohort has the same age and gender). The significance of data in CBF analysis are so clear and widespread in the whole brain in normotensives, that the repeated-testing-problem should not influence the results.

We discuss the drop-out problem also in the discussion.

4. It may be a good idea to explore non-linear effects, especially where blood pressure and rCBF are concerned.

We have handled the non-linear effect of hypertension by stratifying for hypertension.

5. If differences in rCBF are going to be pitched as a potential mechanism driving the poor cognitive function, a mediation model should be tested.

We have not discussed rCBF as a mechanism and therefore not tested. Measurements at baseline are missing.

6. The reported statistics need to match what is proposed in the Statistics
section. For example, right now, we have tables reporting statistics stratified by hypertension status, but that is not at all described in the Statistics section.

We have made changes as described above.

2. Reviewer's report

Reviewer: Robert Paul

Reviewer's report:

The most significant problem with the manuscript is that the strength of the relationships are weak and statistically significant based on power, but not meaningful in terms of effect sizes. As an example, the difference in performance on the Benton Visualization Retention Test is 5.3 vs. 5.9 when categorized by FS, and 3.7 vs. 4.7 when categorized by LIVIDd. The difference on Symbol Digits is 32 vs. 35, a difference that is not clinically meaningful.

A decline of 1 point on Digit Symbol Substitution test corresponds to a 8 year-old age dependent decline. Whereas 1 point decline on Benton Visual Retention corresponds to a 10-year old age dependent decline. (Reference: “Test battery for investigating functional disorders –the TUFF battery. Ekberg K, Hane M.”)

Otherwise, we have made substantial changes in statistics and used General Linear Model instead of correlation, and adjusted for several vascular factors including blood pressure. The presentation of results should be much more clearer that way too.