Author’s response to reviews

Title: Do self-reported pregnancy complications add to risk evaluation in older women with established cardiovascular disease?

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Author’s response to reviews:

Dear Editor, 2 September 2019

On behalf of my co-authors and myself I would like to submit our revised manuscript with a new/revised title “Do self-reported pregnancy complications add to risk evaluation in older women with established cardiovascular disease?” (BMWH-D-19-00429) for potential publication in BMC Women’s Health. The manuscript has been revised according to the comments from the Reviewers. Below you find detailed answers to each comment. The major changes in the manuscript are indicated in red. We now hope that the manuscript is suitable for publication.

Best wishes,

Elin Täufer Cederlőf
Answers to the comments raised by the reviewers

Reviewer reports:

Morounfolu Thompson (Reviewer 1): Originality

Although not a uniquely original topic, this is an interesting study and may have some contribution to the current medical knowledge available on this topic.

The authors may wish to read this review in supporting their study justification - Hauspurg A, Ying W, Hubel CA, Michos ED, Ouyang P. Adverse pregnancy outcomes and future maternal cardiovascular disease. Clinical cardiology. 2018 Feb;41(2):239-46.

What the authors may contribute though is in terms of risk in older women with already established cardiovascular disease, and their raising the question of a possible link with antepartum haemorrhage. The authors may therefore also wish to reflect this in their study title by adding the word "older" e.g. Do self-reported pregnancy complications add to risk evaluation in older women with established cardiovascular disease.

• Thank you for the suggestion of the article and we have now added it to the background, page 3. We have revised the title of the manuscript, according to the suggestion of the reviewer, to “Do self-reported pregnancy complications add to risk evaluation in older women with established cardiovascular disease?”

Abstract

A couple of adjustments need to be made in this section - a more concise inclusion of the main study objective and the statement in the conclusion that suggests a statistically significant conclusion "The mean age was 67.5 (SD 9.5) years. GHT and/or PE tended to be more common in women with CVD than in women without (20.3% vs 10.8%, p=0.066)” should explicitly state the lack of a statistical correlation.

• We totally agree and have revised the abstract as recommended by the reviewer, page 2.

Introduction and Background

A retrospective questionnaire study investigating a possible link between a previous history of pregnancy complications in menopausal women with or without established cardiovascular disease.

It is unclear whether this was with a view to improving risk assessment in women with already established cardiovascular disease (CVD) or assisting in screening for this. Whatever the case,
this is not clearly presented to the reader and description of the study objectives should be consistent throughout the manuscript. Clearer details are needed in the background section.

It would appear that the authors focused on trying to establish a relationship between multi-systemic cardiovascular disease after the menopause and utero-placental complications in pregnancy. Based on reports of possibly shared pathophysiological mechanisms in terms of vascular function, immunoregulation and metabolic control. On these grounds, the second and third aims need to be better explained in the background section with clearer justification for the study (Page 4, Lines 1-10). The abstract should be re-written with these in mind.

• To clarify the justification for the study we have moved two sections from the discussion to the background as suggested by the reviewer. We have revised the first section in the background, page 3. We also have revised the section were the aims of the study are described, page 4.

Methodology

The data is somewhat confusingly derived from a questionnaire study conducted among post-menopausal women obtained from a composite of three different cohort studies. This is a considered limitation when compared to other similarly retrospective studies in the medical literature that draw direct data from large patient databases. There are however a few published studies with similar numbers.

• We totally agree with the reviewer, as we stated in the section of study limitations, page 11

The pregnancy complications sought examined included previous miscarriage, subfertility, gestational hypertension (GHT), preeclampsia (PE), low birth weight, preterm birth, bleeding in late pregnancy, gestational diabetes mellitus and high birth weight.

The clinical investigation of the three arterial beds was comprehensive, and is well described by the authors, showing a high investigation uptake rate in their population. It is not stated and unclear whether or not the questionnaire employed in this study based on reference #23 (Jacobs and Hubel) is validated.

• To our knowledge there is not a validated questionnaire regarding pregnancy complications and risk assessment for CVD. We based our questionnaire on the recommendation from the above mentioned reference.
The statistical analyses are only described briefly and this section because of its importance requires more detail. A couple of descriptive flow charts may be helpful and the predictive statistics basis explained, although this should be subject to the Statistician's review.

- We have added more details in the section about statistical analyses, page 7, as suggested by the reviewer. We have a flow chart of the study population and have added a new table 3 according to suggestion of the other reviewer and we hope this will clarify the statistical analysis.

There are a couple of typographical errors

P4 Line 10 Predict not predicate
- Yes, this has been changed.

P8 Line 46 - Supplement not supplementary
- Yes, this has been changed throughout the manuscript.

P11 Line 56 - Expected not expectable
- Yes, this has been changed.

P11 Lines 15-18 belongs to the introduction/background where it would make a significant difference in helping the reader to understand why the study was conducted in the first place.
- We totally agree and have moved the above mentioned section to the background to clarify the aims of the study as suggested by the reviewer, page 4

There is an excellent discussion of the study limitations, and some of these statements again e.g. P11 Lines 43-51 would perhaps be more helpful if included in the background section discussing study justification.
- We have moved the section to the background as suggested by the reviewer, page 4

Nonetheless, no clear relationship could be demonstrated between the self-reported pregnancy complications and established cardiovascular disease as stated by the authors, however, any conclusions to be drawn may be limited by the nature of the study and study size. This should be stated in concluding discussion as done on P10 Lines 47-50.
- We have now added this limitation to the concluding discussion, page 11.
Jennifer Tabler (Reviewer 2): Review: In women with established cardiovascular disease, do self-reported pregnancy complications add to risk evaluation?

Summary

* Overall, an interesting application of other literature, and an important research question (can we use past pregnancy as an indicator of cardiovascular risk?)
* I cannot evaluate the medical assessment strategies for MSAD or establishing cohorts, as I am not a clinician.
* Tables need to be edited for clarity (Tables should be standalone from the text)
  • We have edited the tables according to the reviewer comments throughout the manuscript and supplement.

Review

* Small sample of women without CVD should be highlighted more in the limitations—they do mention small sample size, but the non CVD sample is a huge limitation.
  • We have clarified the limitation of small sample size for both women with and without CVD, page 11.

* The premise of the paper is built on null or non-findings, but non-findings is much more likely with a small sample size! It is problematic to conclude that previous pregnancy issues provide no additional value—rephrase to "may not". Make sure to moderate suggestions to "may not" "could not" "might not" rather than use such definitive language throughout.
  • We totally agree and have revised both the abstract and discussion according to the suggestion by the reviewer.

* A p-value of 0.06 is borderline significant, not significant—yet is presented as such in the abstract.
  • This has been revised.
Methodology

* Limitations

- Self-report of fertility complications—this is a huge issue given that the time frame for the self-report is so wide. Asking women about something happening up to 20 years ago, is problematic. You address this in the limitations, but should also emphasize that future studies should try to include longitudinal medical histories (non self-report). (Even if something is the "common" way of doing something, doesn't mean it's the way it should be done).

  • We agree and have added this to the concluding discussion as suggested by the reviewer, page 12

- Other covariates (controls) are excluded, highlight the exclusion of education and income which are known to be associated with CVD in your limitations OR include them in your models if you have them (you do mention lack of some controls broadly, but be specific). (examples of papers looking at education/income and cardiovascular disease: Degano et al., 2017 10.1038/s41598-017-10775-3; Khaing et al., 2017 10.1177/2047487317705916)

  • We did not have information about education and income and we have added that to the limitations, page 12. The small sample size of the study limits the possibly to include too many covariates in the statistical models.

Tables

* Table 1 is potentially unnecessary — you should describe response rate in-text. You already show the process for sample selection in Figure 1. You are presenting too much in Table 1, limit it to describing your analytic sample in Table 1 (the sample you are actually looking at N=307).

  • We agree and have moved the table to the supplement and made some adjustments in the manuscript according to the suggestion by the reviewer.

* Table 2 is messy/hard to read—it isn't clear what is or is not a categorical variable, the swinging sample size (n) is needlessly complicated (ns listed for each individual variable) — I suggest listwise deletion on key covariates, since this will be what's presented in multivariate logistic regression models anyway.
Please restructure and clean up your table 2. Also, please footnote analytic strategy to assess differences between CVD and non-CVD samples (independent t-tests, chi-squared, whatever it is) in the Table.

- We have rearranged the table (now table 1) to make it more readable and clarified the analytic strategies according to the suggestion of the reviewer, page 20.

* Table 3 is not standalone. You cannot interpret the Table without going to the body of the manuscript. What results are even being presented? Logistic regression? Correlations? Reader should know this looking at Table 3.

- We totally agree and have revised the table (now table 2) according to the comments of the reviewer, page 21

* Logistic regression results are not presented in a Table? Make sure to reference Tables in-text more frequently, so the reader knows what Tables they should look at. It seems like not all the results are actually presented in Tables. You can say (not shown) if you do not create a Table (but standard practice is to present all results in a Table format).

- We have added a new table 3 with the above mentioned information according to the suggestion of the reviewer, page 22. We have added some in-text references to tables throughout the manuscript.

* Grammar, please read through carefully and fix small grammatical errors present in the manuscript. Here are some examples:

- Typo in the figure legend for REBUS
  - The capital letters indicates the abbreviation for REBUS

- Run on sentence on lines 40-45 (When describing the cohorts)
  - This has been corrected.

- MSAD "is" defined, not "were" defined (it's singular) lines 27-30.
  - This has been corrected.