PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between parity and persistent weight gain at age 40-60 years: a longitudinal prospective cohort study
AUTHORS	Zoet, Gerbrand; Paauw, Nina; Groenhof, Katrien; Franx, Arie; Gansevoort, Ron T.; Groen, Henk; Van Rijn, Bas; Lely, Titia

VERSION 1 – REVIEW

REVIEWER	Seana Gall University of Tasmania
REVIEW RETURNED	12-Jun-2018

GENERAL COMMENTS	This manuscript uses data from a study on renal disease and cardiovascular disease to explore associations between parity and cardiovascular disease risk factors in women. The paper is well written but some further details in some sections would strengthen the paper, as outlined below. I have provided comments in chronological order. 1. The sample for the entire study was derived from 40,856 responders. There is mention of 7,768 with albumin>=10mg/L and 3,394 with albumin<10mg/L or 11,162 people. It is not clear what happened to the remaining participants? I suggest amending the flow chart perhaps starting with the exclusion of men and working from there to arrive a the final sample of 4,320. 2. There are several variables mentioned in the statistical analysis section or table 1 that are not defined in the measurements and visits section - education, alcohol, smoking status. Please revise. 3. How were height and weight measured? 4. What was the rationale for stratifying by age and why these particular groups? 5. How was the kilogram weight equivalence for the BMI unit change determined? 6. Were there measures of waist circumference? Can the authors calculate the metabolic syndrome as a way of capturing the potentially higher burden of cardio-metabolic risk factors? 7. There is an extra word in line 208, page 10 - 'was' 8. Sentence on line 213 is worded awkwardly. I suggest revising. 9. There is mention of the potentially mediating effect of weight or BMI change. Why can't this be explored in the current analyses? 10. There should be further discussion of the reasons for different effects in different age groups. Is this an age, period or cohort effect? 11. There is mention of a sensitivity analysis in the discussion using albuminuria but this is not described in the methods. Please include.

REVIEWER	Professor Deborah Davis University of Canberra and ACT Government Health Directorate

REVIEW RETURNED	28-Jun-2018

GENERAL COMMENTS	Thank you for the opportunity to review this paper. It reports on an interesting study and while it does make a contribution to the field there are some issues and limitations. Aspects of the methods are unclear; * Sample Were 85 thousand invited or agreed to participate in original study? Did about 40 thousand participate (lines 105) and if so why are there only 4 thousand women available for this study before reducing this further with additional criteria. Is the information on albumin concentration (lines 105-106) relevant to this study? In general the paper requires more detail on how the sample was derived. * Length of follow up (6 years? or 12 years?), the sentence on line 129 does not illuminate this point. * Categories It is interesting that women with 2+ children were placed in the same category. I would like to see some justification for this decision * Stepwise correction; lines 144 state age, education, oral contraceptive use (in combinations) though the supplementary table also includes SES *Results Cardiovascular health reflects a complex interplay of social and physiological factors and SES among others is an important and well recognized confounder. The results highlight the data presented on page 19 though the more honed analysis is only provided as a supplementary table. I feel that the results therefore inappropriately implicate parity in some of the outcomes although the significance of parity disappears in analysis that corrects for several confounders . This analysis seems to me to point to time as being the most significant factor contributing to changes in outcomes. This is consistent with findings in our recent longitudinal study on this topic; Long-Term Weight Gain and Risk of Overweight in Par

VERSION 1 – AUTHOR RESPONSE

Response to reviewers

Reviewer: 1

1. The sample for the entire study was derived from 40,856 responders. There is mention of 7,768 with albumin>=10mg/L and 3,394 with albumin<10mg/L or 11,162 people. It is not clear what happened to the remaining participants? I suggest amending the flow chart perhaps starting with the exclusion of men and working from there to arrive a the final sample of 4,320.

We thank the reviewer for this comment and adapted the flowchart as requested.

2. There are several variables mentioned in the statistical analysis section or table 1 that are not defined in the measurements and visits section - education, alcohol, smoking status. Please revise.

We revised the measurements section as suggested.

3. How were height and weight measured?

Height (cm) and weight (kg) have both been measured at all screening visits. Details regarding all measurements are provided by Hillege et al. (2001) in the Journal of Internal Medicine, as cited in our methods section.

4. What was the rationale for stratifying by age and why these particular groups?

Since age is an important determinant in the development of cardiovascular risk factors, we expected age to strongly influence our results. Therefore, we stratified for age in order to assess more accurately the effect of parity on cardiometabolic health.

5. How was the kilogram weight equivalence for the BMI unit change determined?

This measurement was based on the both our own data (mean length 166cm, standard deviation 7cm) and the mean length in the general population (mean length 171cm for females in the Netherlands).

6. Were there measures of waist circumference? Can the authors calculate the metabolic syndrome as a way of capturing the potentially higher burden of cardio-metabolic risk factors?

We would like to thank the reviewer for this suggestion. Unfortunately, waist circumference was not measured at the screening visits.

7. There is an extra word in line 208, page 10 - 'was'

Typo adjusted as appropriate.

8. Sentence on line 213 is worded awkwardly. I suggest revising.

Sentence revised as requested.

9. There is mention of the potentially mediating effect of weight or BMI change. Why can't this be explored in the current analyses?

We thank the author for this comment. Unfortunately, it is beyond the scope of our paper to explore the possible mediating effect. Our aim was to assess the association between parity and cardiometabolic characteristics, not to evaluate how these characteristics and changes in these characteristics influence each other. Based on literature however, it is likely that a complex interplay among these factors, including changes in weight, influence cardiometabolic health.

10. There should be further discussion of the reasons for different effects in different age groups. Is this an age, period or cohort effect?

As suggested by the reviewer, we added an section to our discussion explorating this mechanism:

Added lines: Our results indicate BMI, HDL cholesterol levels and MAP measures differed among the three age groups. Because women from all different ages were seen throughout all screening visits, we expect this to be an effect of age itself, thereby reflecting the growing influence of age on cardiometabolic health with increasing age.

11. There is mention of a sensitivity analysis in the discussion using albuminuria but this is not described in the methods. Please include.

As the data regarding this analysis is not shown, we adjusted the discussion section.

Reviewer: 2

1. Sample: Were 85 thousand invited or agreed to participate in original study? Did about 40 thousand participate (lines 105) and if so why are there only 4 thousand women available for this study before reducing this further with additional criteria. Is the information on albumin concentration (lines 105-106) relevant to this study? In general the paper requires more detail on how the sample was derived.

Answer: we thank the reviewer for this suggestion and adjusted the flowchart to clarify the way in which the sample was derived. Information regarding albumin concentration is necessary to provide, since en elevated albumin excretion mostly results in an unfavorable cardiovascular risk profile, as mentioned in the discussion of our paper.

2. Length of follow up (6 years? or 12 years?), the sentence on line 129 does not illuminate this point.

Answer: the sentence on line 129 had been changed to provide more clear information regarding the length of follow up.

3. Categories: It is interesting that women with 2+ children were placed in the same category. I would like to see some justification for this decision.

Answer: we chose this category of 2+ children since the group sizes markedly decrease when this is further spilt up in separate categories. In our opinion these are also the most relevant categories since the birth rate in Europe and North-America is mostly below 2. To explore the effects of >2 children in separate categories (3,4,5 childeren) would be interesting to confirm the effect of pregnancy on the cardiovascular system but would require larger populations in which >2 children are common.

4. Stepwise correction; lines 144 state age, education, oral contraceptive use (in combinations) though the supplementary table also includes SES

Answer: we thank the reviewer for notifying this discrepancy and adjusted the supplemental table.

5. Results: Cardiovascular health reflects a complex interplay of social and physiological factors and SES among others is an important and well recognized confounder. The results highlight the data presented on page 19 though the more honed analysis is only provided as a supplementary table. I feel that the results therefore inappropriately implicate parity in some of the outcomes although the significance of parity disappears in analysis that corrects for several confounders. This analysis seems to me to point to time as being the most significant factor contributing to changes in outcomes. This is consistent with findings in our recent longitudinal study on this topic; Long-Term Weight Gain and Risk of Overweight in Parous and Nulliparous Women.: Davis D, Brown WJ, Foureur M, Nohr EA & Xu F., Obesity, 2018.

Answer: this is a valid point and nicely illustrated in your recent paper. We acknowledge that cardiometabolic health is influenced by many factors, which have a complex interplay with each other as well. It is thereby not suprising that significance of some of our results disappear after full correction for several other factors. However, for some outcomes these results are still significant (i.e.

BMI at age 50-60 years and BMI at age >60 years). In addition, the differences among age groups are constant over the 6 year time interval, which might indicate an effect of parity itself, apart from time as being anther factor contributing to the cardiometabolic. However, our results should be interpreted with caution as is highlighted in the discussion section (e.g. lines 211-212 and lines 277-282).

VERSION 2 – REVIEW

REVIEWER	Deborah Davis University of Canberra, Australia
REVIEW RETURNED	23-Oct-2018

GENERAL COMMENTS	Thank you for the opportunity to review the revised version of this paper. The authors have attended to most of the issues raised by the reviewers however there is one remaining issue for me. I had commented that the original methods section did not mention SES as a factor adjusted for in the original supplementary table and I expected that the authors would add this factor to the list in the methods section. Rather they have removed the result adjusting for SES in a revised supplementary table. Why? You acknowledge that SES (line 216) is an attributing factor confounding the parity - BMI relationship and you have this data but no longer report on it. I feel the comments relating to the relationship between parity and BMI are therefore too strong (eg opening paragraph of discussion) and the caution to use these findings with caution is not enough. I feel the analyses presented in the supplementary table is too important not to include in the manuscript.

VERSION 2 – AUTHOR RESPONSE

Response to reviewers 2

Reviewer: 2

1. I had commented that the original methods section did not mention SES as a factor adjusted for in the original supplementary table and I expected that the authors would add this factor to the list in the methods section. Rather they have removed the result adjusting for SES in a revised supplementary table. Why?

   We apologise for the unclear response to the previous comment regarding the supplementary table. In the initial supplementary table the term SES was used incorrectly, since only information regarding education level was available. In the revised supplementary table, we adjusted for this. Unfortunately, other socio-economic parameters, such as income, were not measured in our study. Adjusting for SES was therefore not possible, although we did correct for education as stated throughout the text of the manuscript and in the supplementary table.

2. You acknowledge that SES (line 216) is an attributing factor confounding the parity - BMI relationship and you have this data but no longer report on it. I feel the comments relating to the relationship between parity and BMI are therefore too strong (eg opening paragraph of discussion) and the caution to use these findings with caution is not enough. I feel the analyses presented in the supplementary table is too important not to include in the manuscript.

We thank the reviewer for this remark. In addition to the previous mentioned adjustments, we refined the manuscript throughout the discussion to emphasize that confounding factors might play a role in this parity-BMI relationship (eg lines 216-218, 277-279 and 295-298).