

Response to reviewers' comments

We are very grateful for the reviews provided by the editors and each of the external reviewers of this manuscript. The comments are encouraging and the reviewers appear to share our judgement that this study and its results are clinically important. Please see below, in blue, our detailed response to comments. All page numbers refers to the manuscript file with tracked changes.

Our statistician made the following comments:

E.1. Reviewer comment: Please consider providing information to help readers interpret table 2A. The hazard ratios in the prior HDP group are higher (in the 32-39 age group, for example), but the conclusions suggest a more of an effect in the non-HDP group. The point being that could due to the analysis approach the authors have adopted, separate models have been fit to the groups, and thus there is a different reference group by definition, thus the hazard ratios are referring to different reference groups. So some clear guidance from the authors to help readers understand this would be very useful.

Authors' Response: To facilitate interpretation of table 2A and 2B, we have slightly reworded the table titles, stratified the reported person-time by HDP history, and included additional explanation in the legend. In addition, we also added the following sentences to the result section to clarify interpretation of the results:

Page 10-11: *“The hazard ratios presented in Table 2A and 2B convey the association between each lifestyle exposure and chronic hypertension within each category of HDP and are not suitable for estimating differences in association between categories of HDP history. In the next section, we present the results of the effect modification (i.e. interaction) analyses, which are relevant for comparing associations between women with, and without, history of HDP.”*

Importantly, our main focus is interaction on the additive risk scale. These types of interactions (i.e. those calculated in order to infer potentially different associations by HDP status) cannot easily be inferred by comparing the hazard ratios. In general, for correct inference about the implications of potentially intervening on risk factors involved in an interaction analysis, it is recommended to mainly consider interactions on the additive scale, rather than the multiplicative. [1] [2]

The editors thought it was a study with a large sample size, and the manuscript was clearly written. They also made the following comments:

E.2. Reviewer comment: Please consider specifying in the title that this study comes from the Nurses' Health Study II.

Authors' Response: We have changed the title to *“Lifestyle in the progression from hypertensive disorders of pregnancy to chronic hypertension in the Nurses' Health Study II: an observational cohort study”*

E.3. Reviewer comment: Please revise the conclusion in the abstract to avoid overly causal language.

Authors' Response: To further balance the implications of our results with the potential limitations of observational studies, we have changed “can” to “might” in the first sentence of the conclusion in the abstract.

E.4. Reviewer comment: Some editors are uncertain about the novelty of the research question as lifestyle management is an established part of hypertension prevention and treatment. Please emphasize how the research question built up on the existing evidence.

Authors' Response: We are grateful for this comment as it points to an important rationale of this study, which concerns the limits of generalization in prevention guidelines. Typically, guidelines should only be generalized across strata that are thought to be similar in aspects relevant to the guidelines. It is correct that lifestyle management is an established part of hypertension prevention and treatment. However, women with HDP are at higher risk of chronic hypertension, which debuts earlier in life and chronic

hypertension as a diagnosis does not have one single etiology, but a variety of different causes resulting – separately and synergistically - in high blood pressure. The potential for different causal pathways potentially result in different responses to lifestyle intervention. Importantly, although preeclampsia is associated with impaired vascular dysfunction post-pregnancy, [3] [4] it is unknown whether women with HDP have a different response to lifestyle interventions compared to other parous women. To effectively prevent chronic hypertension and CVD in this high risk group, it is potentially important to understand whether the association between lifestyle and chronic hypertension differs by HDP status. Though our study shows that current lifestyle advice is also relevant for women with previous HDP, it points to a greater benefit in women with HDP of maintaining normal BMI (and conversely the greater risks of not maintaining a normal BMI) in the prevention of chronic hypertension.

E.5. Reviewer comment: Although the increasing long-term risk of cardiovascular events in women with HDP is known, in many settings, it still is not something that about which doctors provide advice at the postpartum visit. The editors hope the authors could highlight the importance of their findings in affecting practice.

Authors' Response: We have clarified the clinical implications in our conclusion paragraph (page 16) and also added an additional bullet to “what this study adds” (page 19).

Page 16: “...*clinicians should especially help women with a history of HDP or gestational diabetes mellitus to attain, and keep, a healthy weight post-pregnancy. Each woman’s own reproductive plans should guide whether the main motivation of such efforts is to prepare for a healthy future pregnancy or to lower the risk of future cardiometabolic disease.*”

Page 19: “*As with women with gestational diabetes mellitus, clinicians should especially help women with a history of HDP to attain, and keep, a healthy weight post-pregnancy.*”

E.6. Reviewer comment: Please consider completing patient involvement section and describing how the findings of the research will be disseminated.

Authors' Response: No patients were involved in this particular study but patients and patient-advocacy groups are engaged in other areas of research our group is currently pursuing. The results of our research, are, and will be, disseminated in close collaboration with the Preeclampsia Foundation (a US-based patient advocacy group). Please see also response to reviewer 5 below.

Reviewer: 1

Type of reviewer: Expert reviewer

The authors investigated the association between lifestyle risk factors and chronic hypertension by history of hypertensive disorders of pregnancy (HDP: gestational hypertension and preeclampsia) and investigate the extent to which these risk factors modify the association between HDP and chronic hypertension.

This is the prospective cohort study with Nurses’ Health Study II.

The study is well conducted and the methods used are appropriate. The data is presented clearly.

This study suggests that (1) women with prior HDP age 32 to 59 years appear to have similar benefit of physical activity and adhering to dietary guidelines when compared to parous women with only normotensive pregnancies, and (2) overweight and obesity appear more detrimental in the progression to chronic hypertension in women age 32 to 59 years with a history of HDP compared to women without a history of HDP.

I have the following concerns.

1.1. Reviewer comment: I think the authors should show the definition of “HDP” and “chronic hypertension” in the study.

Authors' Response: We have clarified the definitions of HDP and chronic hypertension in the methods section (pages 6 and 7).

1.2. Reviewer comment: Although the authors suggested that overweight and obesity appear more detrimental in the progression to chronic hypertension in women age 32 to 59 years with a history of HDP compared to women without a history of HDP, they concluded that “the risk of chronic hypertension following HDP can be markedly reduced by adhering to a beneficial lifestyle. Compared to women without a history of HDP, keeping a healthy weight appears especially important”. I am not convinced the conclusions.

Authors' Response: We thank the reviewer for this comment. While we observed little difference in the association for the other lifestyle factors (i.e. they appeared to be similarly beneficial in women regardless of HDP history) our results suggest that a higher than normal BMI is more detrimental in women with history of HDP. In the abstract, we have toned down the language by substituting “can” to “might” in the first sentence of the conclusion. In the Discussion, we have rewritten the conclusion section. Please also see the response to comment E.3 above.

Reviewer: 2

Type of reviewer: Expert reviewer

In their manuscript, Timka et al. describe their investigation of lifestyle factors and previous hypertensive disorders of pregnancy on the development of chronic hypertension later in life. The authors utilized data from the Nurses' Health Study. The authors report finding that overweight and obesity are associated with an increased risk of developing chronic hypertension in women with and without a history of hypertension in pregnancy. In addition, women who were both obese and had a history of hypertension in pregnancy had a higher risk of chronic hypertension than expected based on the effect of both of these factors considered separately. Other lifestyle factors including levels of physical activity and diet had no significant effect on the association between prior hypertension in pregnancy and the development of chronic hypertension. Overall, this is an outstanding study with excellent data and prudent analysis and interpretation. This manuscript was an absolute pleasure to review, and I cannot remember the last time I reviewed a manuscript and had no substantive edits or comments.

Authors' Response: We appreciate the encouraging comments.

Reviewer: 3

Type of reviewer: Expert reviewer

3.1. Reviewer comment: This is a beautifully analysed and written paper, with an important message. I would recommend publication, after the issues below are addressed. I note in the baseline data, that women with HDP were more likely to take NSAIDs (any clues as to why?), were more likely to have gestational diabetes (was that also ascertained by self report, at a time when there was no universal screening in the US?), were more likely to be nulliparous, and interestingly, consumed less alcohol. The issue of gestational diabetes is very important, and I can't quite tell from the methods if this was included in any of the modelling. Gestational diabetes indicates a high degree of insulin resistance - insulin resistance may well be important in the development of a high weight gain trajectory, and may also be exacerbated with increasing body mass (a chicken and egg question). Insulin resistance can be influenced by factors well out of the control of the individual (fetal programming for example). Do these relationships remain when you take this marker of insulin resistance into account? Is the interaction between HDP and subsequent obesity explained by GDM? Or is GDM a factor that further strengthens this relationship? This is very important, because the pre-existing degree of insulin resistance has wide ranging effects on central mechanisms that influence appetite regulation and tolerability/desirability of exercise, and so are potentially critical in understanding the engagement of women with "healthy lifestyle advice". Sensitivity analyses around this issue might be helpful. The discussion needs to highlight the difficulty of lifestyle intervention in women who are insulin resistant, and highlight the need for additional research around this issue, as it may be quite fundamental as to why lifestyle interventions need to be so intensive to assist women in making changes? (For example

see <http://www.nature.com/nrn/journal/v15/n6/abs/nrn3745.html> - Neurobiology of food intake in health and disease, and other papers around the issues of hypothalamic regulation of appetite and movement.)

Authors' Response: We very much appreciate this helpful comment and agree that GDM (here self-reported) is of potential importance for the presented analysis. We did adjust for GDM but noted during the revision that GDM was missing from the list of confounders presented in the methods section though it was included in the legends below table 2A and 2B. This has now been corrected. However, we have also performed additional analyses in which we restrict the sample to women who do not have a history of GDM. In short, the results of these analyses were very similar to the main analysis. This suggests that our results are not driven by women with previous GDM. We have added a short summary of these results to the main text (page 12) but do not present them further, given that the results are so similar to the main analysis. However, we present a figure below to allow for transparency and easy comparison between the two analyses (Figure X).

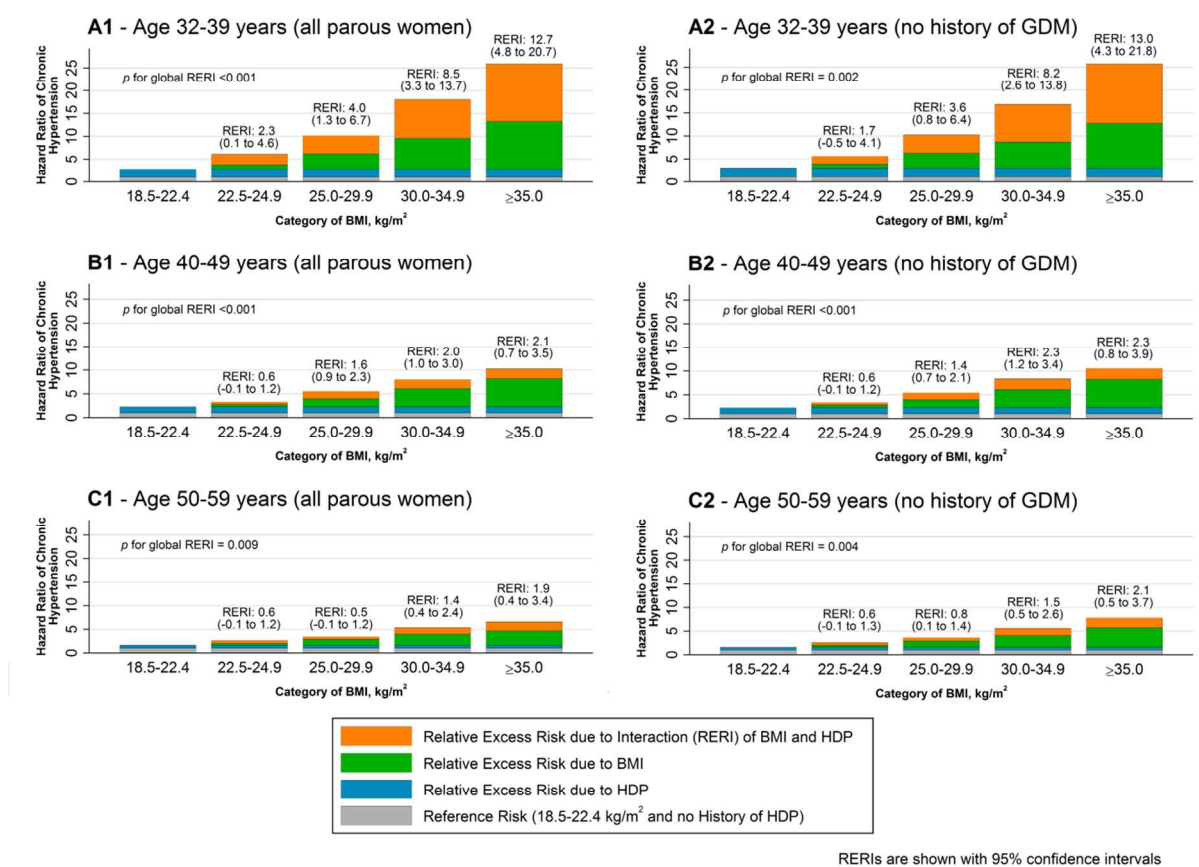


Figure X – Comparison of results for the RERI interaction analysis between HDP and BMI in the main analysis (A1-A3) and the sensitivity analysis excluding women with a history of GDM (B1-B3)

The main analysis (panel A1-A3) is also presented in Figure 2 in the manuscript. As the results of this sensitivity analysis (B1-B3), which restricted person-time to no history of GDM, is very similar we have summarized it in the results section but no additional data is shown in the paper. In women age 32-39 years, 5,110 out of 99,944 person-years (81 out of 841 events) were removed from the BMI analysis by this restriction. In women 40-49 years and 50-59 years the corresponding numbers were 17,190 out of 362,362 person-years (480 out of 7,031 events) and 8,583 out of 217,229 person-years (283 out of 6,043 events), respectively.

BMI: Body mass index, GDM: Gestational diabetes mellitus, HDP: Hypertensive disorders of pregnancy, RERI: Relative excess risk due to interaction

Authors' Response (continued): The reviewer also makes an interesting point on the difficulty of clinical lifestyle intervention in women who are insulin resistant. Consequently, we have added a comment about this potential obstacle to the main text, including the recommended reference (page 14). For a response to the comment about NSAIDs, please see our response to 3.2. below.

3.2. Reviewer comment: Some comment about the issues of NSAIDs at baseline, and across the follow up period would also be useful. Why were women with HDP using NSAIDs at a higher rate? Did this continue during follow up? Is NSAID use related to the degree of obesity (ie do higher BMI women have more aches and pains?)

Authors' Response: Speculatively, there is a previously reported association between migraine and preeclampsia [5] which might explain at least part of this association. In addition, as the reviewer points out, women with overweight and obesity might have high intake of NSAIDs because of higher prevalence of musculoskeletal pain. We have chosen not to highlight the NSAIDs in this study as this would further add to the complexity of the presentation of results.

3.3. Reviewer comment: The other medication which has been demonstrated to influence the development of chronic hypertension in women is the oral contraceptive pill -and this has not been included in these models, and I think this information is available in the Nurses Health Study. Could this be included? Does contraception contribute to weight gain, and partly explain these relationships?

Authors' Response: We appreciate the reviewer's comment and agree that OC use is potentially important. In this study, we have adjusted for OC use in a sensitivity analysis of the two younger age groups and hormones in older women (page 12). These results were not materially different.

3.4. Reviewer comment: Page 9 -analyses not shown. Could these please be included in the online supplementary material?

Authors' Response: We appreciate the opportunity to include additional results and methods and above (Figure X) present the result of an additional analysis, which is not specifically shown in the manuscript. Given that there is not much variation in the results and we have three different age strata (resulting in large tables), we would prefer not to include these results and others that are quite repetitive even in the online material. Our intention is to strike the right balance between informing all readers and overwhelming most of them with excessive information (even those who are interested enough to look in the supplement).

Reviewer: 4

Type of reviewer: Expert reviewer

The authors investigate modifiable risk factors for hypertension in women with gestational hypertension. It is already known that HPD is a risk factor for chronic hypertension, which the authors confirm with their data. This article present data about modifiable risk factors such as Na/K intake and DASH intake. This is a interesting observation with potential clinical impact.

4.1. Reviewer comment: There is al low response rate of 67%.Could this have influenced the results?

Authors' Response: We agree that it is a potential limitation that not all participants recruited in 1989 also reported their full reproductive history. However, we believe that this is slightly different compared to the standard epidemiological definition of response rate or loss-to follow up, which would be the proportion of women at baseline prospectively followed for the outcome (i.e. here chronic hypertension). While follow-up at each questionnaire cycle is 90% or higher, not all women in the cohort reported their full reproductive history, yielding this lower response rate. Nevertheless, we have clarified the potential limitation of not all women in the original cohort reporting their reproductive history.

Page 14: *“Another potential limitation is that not all participants in the original cohort did provide detailed reproductive history, which included our HDP exposure, and also that any participant had to be alive in 2009 to do so.”*

4.2. Reviewer comment: What is the rationale of a restricted follow-up to females 32-59 years old? And how many eligible women were outside this age range? How many women with a BMI <15 or >50 kg/m² were excluded? A flow diagram of the patient exclusion process would be clarifying.

Authors' Response: We thank the reviewer for these questions. Our main rationale to limit the follow-up to 32-59 years was that few women (person-time) were at risk outside these age ranges (given that women were 25-42 years in 1989 and did not contribute person time during the years around pregnancy). Furthermore, in order to meet the Cox proportional hazards assumption we limited the age-range included in each Cox model as the association between HDP and chronic hypertension declines with age. As BMI was updated during follow-up, we regard the number of *person-years* of potential follow-up lost due to BMI restriction as more relevant than the absolute number of women affected by restricting BMI. When rerunning the models without the 15-50 kg/m² restriction, 49 person-years (1 event) were added to the model for women age 32-39, 253 person-years (16 event) were added to age 40-49 years, and 142 person-years (14 events) were added to the 50-59 year strata. In order to finely control for confounding and include only relevant person-time, we allow for updating of covariates but skipping of non-relevant person-time during follow-up, e.g. during pregnancy when women are not at risk for chronic hypertension. However, we believe this methodology does not allow for the standard presentation of participants in a flow-chart as women can be excluded for different reasons during different parts of follow-up (e.g. being pregnant or being on medication with anti-hypertensive effect without being diagnosed with hypertension) and are also allowed to re-enter the analysis as long they fulfill all criteria at a later date.

4.3. Reviewer comment: Unfortunately, the data about history of preeclampsia and gestational hypertension are not assessed in the baseline table for the group without HPD. These are essential parameters for chronic hypertension later in life. The authors report that (P10 line 3) “similar results were observed when HDP was plotted separately for preeclampsia and gestational hypertension (data not shown).” These data should be provided.

Authors' Response: We use “HDP” (hypertensive disorders of pregnancy) as a summarizing term for having either a history of preeclampsia, gestational hypertension, or both. Consequently, women without HDP do not have a history of preeclampsia or gestational hypertension. We do not present stratified data on type of HDP as these results were similar and we believe that inevitable small nuances could potentially distract readers from the implications of the main interaction analysis rather to add to their understanding of its fairly complex methodology.

4.4.1. Reviewer comment: It is a prominent finding that the association between hypertension and physical activity, DASH diet and Na/K intake quartiles only in women without HPD and not in women with HPD.

Authors' Response: We disagree with this first sentence of the comment. Though for some lifestyle exposures there is evidence of associations in women without HDP history but not in those without HDP, this does not mean that there is a difference between the two groups. [6] Please also see the response to comment 4.4.3 below.

4.4.2. Reviewer comment: The lines of DASH diet and Na/K intake in figure 1 seem to be separate in women with HPD, but no p-values are provided. Are these trends significant? The authors post a unclear sentence about this: “For the other lifestyle factors, the cumulative incidence of chronic hypertension appeared to be higher in women with a history of HDP, compared to women without HDP, regardless of lifestyle.”

Authors' Response: Our intention with Figure 1 is to give a descriptive overview of the cumulative incidence of chronic hypertension over time in the sample. We do not provide any p-values for the

difference shown in Figure 1 as it is a descriptive figure of and does not harbor the complexities of the main Cox model. Our description in the main text is meant to put focus on the fact that women with HDP appear to have a higher risk of chronic hypertension regardless of lifestyle (except for BMI) compared to women without HDP, i.e. that regardless of lifestyle their risk of chronic hypertension was still higher than women without HDP history. We have slightly revised the statement to increase readability and also moved the subheading “Lifestyle factors in the development of chronic hypertension by HDP history” to after the paragraph describing Figure 1 (page 10) to better separate the descriptive section from the analytical analysis.

4.4.3. Reviewer comment: The conclusion of this data could therefore also be that women with HPD, do not have less risk of hypertension in low DASH, and low Na/K intake (table 2B). This is completely different from the main conclusions of the authors, but also a very interesting conclusion. The main conclusion and discussion however, should be rewritten.

Authors’ Response: Only about 10% of women have a history of HDP. Consequently, the power to detect an increased risk in this group is lower compared to women not exposed. Thus, it is important to acknowledge the absence of a detectable association of a similar (small) magnitude in the non-HDP group does not necessarily mean that there is a difference in the effects of the exposures between these groups. Indeed, the statistical test to determine whether such a difference exists (a multiplicative interaction term of exposure by HDP group) is not statistically significant.

4.5.1 Reviewer comment: What is the rationale of more often chronic hypertension in women with high DASH diet and Na/K intake only in women without HPD and not in women with HPD? Should women without HPD be more frequently monitored and guided with their diet? It would seem that a high Na/K intake and DASH diet would further increase the risk of chronic hypertension in women with HPD, but these data do not support that.

Authors’ Response: We do not believe that our results support a difference in association between diet and chronic hypertension by HDP history. Please also see our response to comment 4.4 above.

4.5.2 Reviewer comment: Furthermore, a high BMI seems to be interacting with the results less in women with prior HPD than women without HPD. Is that another hint that lifestyle changes (and BMI) have less influence in women with prior HPD? This should also be discussed in the conclusion and discussion session.

Authors’ Response: It is important to note that our main focus is on additive risk scale interactions and not multiplicative interactions. The clarification of tables 2A and 2B, following reviewer comment E.1 above should clarify our reasoning.

4.6. Reviewer comment: The difference of table 2B (where effect of chronic hypertension & DASH diet and Na/K intake is different between no HPD and prior HPD) and supplemental table 1B (where association of chronic hypertension & DASH diet and Na/K intake is comparable between no HPD and prior HPD) is that table 1B is less adjusted for variables. The conclusion can be made that smoking, NSAID use, history of gestational diabetes mellitus, menopausal status and parental history of chronic hypertension are the confounders, at least partially explaining the difference in chronic hypertension in patients with and without prior HPD.

Authors’ Response: We agree with the reviewer that the attenuated results in table 2B compared to table 1B may be owing to adjustment for confounding effects.

Reviewer: 5

Type of reviewer: Lay reviewer

5.1. Reviewer comment: Access to this group of nurses is an obvious opportunity to gather data, which has potential benefits to public health. While the article sets out some of these data very clearly and coherently, its value probably lies more in indicating areas for future, population based studies, as opposed

to making a substantial contribution in its own right. As the authors themselves admit, “The study population consists largely of white nurses, potentially limiting generalisability”. I would suggest that the word 'potentially' is unnecessary here.

Authors' Response: We thank the reviewer for this important comment. Studies based on groups of people that are not directly comparable to the population in general have made important contributions to public health and clinical medicine. Indeed, we know of no reason to believe that these associations would be different in other racial/ethnic or occupational groups. Given the lack of evidence for such variation, we think the word ‘potentially’ suitably expresses the uncertainty around the question of generalizability. However, please see below for our expansion to indicate that more diverse populations should be studied.

5.2. Reviewer comment: Having acknowledged this fundamental limitation, assertions such as this (in the discussion) that, “Consequently, interventions focused on weight optimisation could potentially reduce the risk of chronic hypertension to a greater extent within this group than among other parous women”, might be better phrased to include the suggestion that further research in a broader population would establish the existence and extent of this benefit.

Authors' Response: There is no strong reason to believe that the biology of female nurses are vastly different compared to other women. However, though this should not be a major concern, it is still a limitation, which we acknowledge. In addition, we have added an explicit statement regarding the need of additional studies in more diverse populations.

Page 14: *“The study population consists largely of white nurses, potentially limiting generalizability, and to further confirm our results additional studies in more diverse populations are needed.”*

5.3. Reviewer comment: It is disappointing to note that no patients were involved in the study, as this, too, limits generalisability. Whilst it is true that a pregnant woman is not a patient, per se, middle-aged and older mothers with hypertension are, and they would be able to add valuable qualitative data, which would strengthen the public health offering of such a study, as well as contributing a different perspective to the analysis of the quantitative data already gathered. If the authors are carrying out any further analysis, I hope they will include such patients from their cohort.

Authors' Response: We agree that engaging patients in the design and conduct of studies is an important aspect that is missing from many contemporary studies. Recognizing the importance of patient engagement in biomedical research, our group works closely with a patient-advocacy group (Preeclampsia Foundation – www.preeclampsia.org) and patients [7] in a related study funded by the US-based Patient-centered outcome institute (PCORI, Heart Health 4 Moms, <http://www.pcori.org/research-results/2013/heart-health-4-moms-engaging-women-history-preeclampsia-reduce-their-risk>) focusing on how to empower women following a pregnancy complicated by preeclampsia and help them make informed decisions about their lifestyle and its influence on their cardiovascular health.

5.4. Reviewer comment: Overall, it is a good article with potentially useful data, but I think it would benefit from being slightly more self-reflective of its very limited scope for generalisability.

Authors' Response: We do not feel that this limitation is likely to be significant for the reasons outlined above, but we have emphasized this potential limitation in the revised Discussion.

Reviewer: 6

6.1. Reviewer comment: I have no specific manuscript comments for the editor or authors.

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