24-Apr-2017

Dear Dr. Timpka

Manuscript ID BMJ.2017.037875 entitled "The role of lifestyle in the progression from hypertensive disorders of pregnancy to chronic hypertension: an observational cohort study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Daoxin Yin
dyin@bmj.com

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**Report from The BMJ’s manuscript committee meeting**

Members of the committee were:
Elizabeth Loder (chair), Gary Collins (stats), Wim Weber, Georg Rogglia, Jose Merino, Tiago Villanueva, Rubin Minhas, Daoxin Yin, John Fletcher, Sophie Cook.
Decision: Put points.

The committee was interested in the topic of your research. The following concerns were mentioned, which we would like you to take into account in preparing a revision:

Our statistician made the following comments:
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.

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

- Please consider specifying in the title that this study comes from the Nurses' Health Study II.
- Please revise the conclusion in the abstract to avoid overly causal language.
- 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.
- 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.
- Please consider completing patient involvement section and describing how the findings of the research will be disseminated.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
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. I think the authors should show the definition of “HDP” and “chronic hypertension” in the study.
2. 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.

Additional Questions:
Please enter your name: Takumi Kurabayashi

Job Title: MD

Institution: OB/GYN, Niigata City General Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
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.

Additional Questions:
Please enter your name: Robert Powers

Job Title: Associate Professor

Institution: University of Pittsburgh

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:
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.)

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?)

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?

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

I hope these are useful and thought provoking comments.

Leonie Callaway
Obstetric Physician
Professor of Medicine

Additional Questions:
Please enter your name: Leonie Callaway

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Institution: Royal Brisbane and Women's Hospital.

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

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Recipient of research funds from the Royal Brisbane and Women's Hospital Foundation, the National Health and Medical Research Council of Australia, and the Diabetes Australia Research Program of Australia.

No commercial research funds. None of this has a conflict of interest with the present paper.

Reviewer: 4

Recommendation:

Comments:
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 an interesting observation with potential clinical impact.

There is a low response rate of 67%. Could this have influenced the results?

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.

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.

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. 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.” 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.

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. 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.

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.

Additional Questions:
Please enter your name: Amber Otten and Jan Paul Ottervanger

Job Title: MD, PhD

Institution: Isala klinieken

Reimbursement for attending a symposium?: No

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Reviewer: 5

Recommendation:

Comments:
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.

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.

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.

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.

Additional Questions:
Reviewer: 6

Recommendation:

Comments:
I have no specific manuscript comments for the editor or authors.

Additional Questions:
Please enter your name: Erica Lake

Job Title: Associate Librarian

Institution: Spencer S. Eccles health Sciences Library

Reimbursement for attending a symposium?: No
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