Author's response to reviews

Title: The association between dietary factors and gestational hypertension and preeclampsia: a systematic review and meta-analysis of observational studies

Authors:

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Author's response to reviews: see over
19 August 2014

Dear Claire Barnard,

Thank you for the opportunity to further revise our manuscript entitled “The association between dietary factors and gestational hypertension and preeclampsia: a systematic review and meta-analysis of observational studies” for potential publication in *BMC Medicine*.

As advised, we corrected minor errors in the text pointed out by the reviewer. Moreover, we have now described our findings as ‘associations’ instead of ‘relationships’ in the title and throughout the manuscript. We further described our findings in relation to RCTs that have been conducted in the prevention of pre-eclampsia, and have additionally discussed results from a recently published review and meta-analysis on dietary intervention studies and pregnancy outcomes. Detailed discussion of the non-statistically significant finding of energy intake and hypertensive disorders of pregnancy have been removed in line with the reviewer’s comment. Also, limitations and potential biases introduced by the individual studies have been discussed, acknowledging that the quality of the present review is determined by the validity of individual studies included.

Our manuscript fully adheres to the PRISMA reporting guidelines, and conforms to the journal style.

Please find below our point-by-point response to the reviewers’ comments.

Please let us know if you need any further information. We look forward to your editorial office’s decision.

On behalf of all authors

Yours sincerely,

Danielle Schoenaker
EDITORIAL COMMENTS AND AUTHORS RESPONSES:

REVIEWER 1:

Reviewer: Anne Stine Kvehaugen

In this re-submitted version of the paper, the authors have carefully addressed the concerns initially raised by all reviewers. Except a few minor essential revisions outlined below, these reviewers (Kvehaugen and Staff) do not have any major concerns with the current version of the manuscript.

The authors have done a comprehensive work. By restricting the work to include observational studies and reports written in English, the authors have systematically reviewed the existing literature on the relationship between dietary factors and hypertensive disorders of pregnancy in human populations. Moreover, meta-analyses have been performed when possible. The paper is novel, well written and the methodology is appropriate.

Minor essential revisions:

1. Newcastle-Ottawa scale: If the highest quality studies (least risk of bias) are awarded up to nine stars, then the sentence on page 6, lines 115-116, should probably read: .....”from 0 (HIGHEST degree of bias) to 9 (LOWEST degree of bias)” instead of: .....”from 0 (LOWEST degree of bias) to 9 (HIGHEST degree of bias)” ?

   Author’s reply: thank you for pointing this out. This has now been corrected to read: ...“from 0 (highest degree of bias) to 9 (lowest degree of bias).” (lines 115-116)

2. Energy intake data among preeclampsia cases: Abstract: lines 31-32 and page 9: line 195:..........."I-squared =1.9%, P=0.42.” According to Figure 2B, these are the numbers for the “overall” results, not for the preeclampsia results, and should be revised accordingly.

   Author’s reply: this has now been corrected: ...“I^2 = 23.9%, P = 0.26”. (lines 31-32 and 195)
Reviewer: Jodie Dodd

Overall, the comments raised by the reviewers have been addressed by the authors.

3. I think it is important for the authors to highlight that there are significant limitations - the data that has been meta-analysed has been drawn from case control and cohort studies all of which have significant methodological limitations. Therefore the findings can at best be associations only.

   Author’s reply: as discussed in our manuscript, causal relationships cannot be inferred from observational studies (lines 288-289). We agree that findings can at best be associations only, and have re-worded our findings: “relationship” has now been replaced by “association” in the title and throughout the manuscript (text, tables and figure legends).

4. It would be very useful for the authors to put their findings into context particularly in relation to the RCTs that have been conducted in the prevention of pre-eclampsia. While these RCTs have focussed on nutrient supplementation (vitamins C & E and calcium) rather than "whole foods" as indicated by the authors, they tend to demonstrate no effect (vitamins C&E) or modest effect at best (calcium) in prevention.

   Author’s reply: “In line with our findings, there is no compelling evidence from intervention studies for an association between maternal nutrient intake or supplementation and preeclampsia risk, with the exception of calcium supplementation in high risk populations and women with calcium deficiency (9, 10).” (Lines 357-361). In populations with calcium intake below the recommended intake, calcium was statistically significantly associated with lower calcium intake among cases compared with non-cases in our review, consistent with finding of randomized controlled trials showing reduced preeclampsia risk with calcium supplementation only in populations with low calcium intake. (lines 368-369). We have now additionally included a sentence on the agreement between our review and meta-analysis of RCTs not demonstrating an effect of reported vitamin D, C and E, and n-3 polyunsaturated fatty acids intake on preeclampsia (lines 374-377).

5. I also think it is very important that the identified associations between increased energy intake be modified - these findings are not statistically significant and the text should not focus overly on their discussion.

   Author’s reply: difference in energy intake was not statistically significant between cases and non-cases, and this has been explicitly stated in the abstract (lines 30-32) and results section (lines 193-196). We have now shortened the discussion on this finding and removed the sentence explaining in detail that higher energy intake may promote increased storage of fat that could lead to dyslipidemia and insulin resistance, which have been suggested to precede the clinical manifestation of HDP. (after line 328).

6. Overall, the validity of the review is limited, not so much in the review methodology per se, but from the inclusion of the underlying studies and their inherent bias.

   Author’s reply: we agree and have acknowledged this in our discussion section line 292: “The quality of the present review is determined by the validity of individual studies included.” We further discuss limitations and potential biases introduced by the individual studies in lines 292-324.