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
30 June 2014

Dear Claire Barnard,

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

The comments from the reviewers were very helpful. As advised, we have now extended the background section with further justification of potential etiologies for the relationship between nutrient (deficiencies) and hypertensive disorders of pregnancy, and highlighted what our systematic review and meta-analyses add to previously published reviews. Furthermore, random effects meta-analyses have now been performed separately for case-control and cohort studies. Two authors independently performed formal quality assessment according to the reviewers’ fine suggestions. Also, main findings of our review have been rephrased to take into account the limited number of studies, the significance and magnitude of the associations, and the heterogeneity of pooled findings. We further described implications of the review for clinical practice and research recommendations. Additionally, we have updated our systematic literature search to include articles published up to May 2014. Please find below our point-by-point response on the reviewers’ comments.

On behalf of all authors

Yours sincerely,

Danielle Schoenaker
EDITORIAL COMMENTS AND AUTHORS RESPONSES:

REVIEWER 1:

Reviewer: Sarah McDonald

1. The authors have undertaken a very large task, to summarize the data from observational studies on dietary factors and hypertensive disorders in pregnancy. Unfortunately, there are a number of major concerns with this manuscript as outlined below: firstly, there should be better justification included in the background section on why nutrients/ deficiencies are potential etiologies of hypertension during pregnancy. Without this, the reader might suppose that these are just associations.

Author’s reply: thank you for pointing this out. We have now extended the background section on the potential etiologies through which nutrients may influence hypertensive disorders of pregnancy (page 4, line 56-65): “Even though the etiology of gestational hypertension and preeclampsia remains largely unclear, evidence suggests that diet may play a role. HDP are characterized by metabolic disturbances similar to those found in cardiovascular diseases and type 2 diabetes mellitus including endothelial dysfunction, inflammation, oxidative stress, insulin resistance and dyslipidemia [1, 2]. Diet is a well-known risk factor for cardiovascular disease and type 2 diabetes [7, 8]. Furthermore, serum nutrient levels (such as elevated polyunsaturated fatty acids, and decreased vitamin C and E, zinc, and iron) have been associated with increased inflammation, oxidative stress, and dyslipidemia [9, 10]. Nutrient status has also been directly linked with increased risk of preeclampsia, including increased serum triglyceride and fatty acids and reduced levels of serum calcium, vitamin D, magnesium and zinc [9].”

More detailed explanations of potential pathways for energy, magnesium and calcium and hypertensive disorders of pregnancy have been described in the discussion section.

There are major methodological concerns including:

2. There did not appear to be any justification for why randomized controlled trials were excluded. There have been a number of key randomized controlled trials in this area which have formed the basis for recommendations by many obstetrical societies for example for calcium supplementation to decrease the risk of preeclampsia during pregnancy.

Author’s reply: Randomized controlled trials have been performed with dietary supplements, focusing on single nutrients (for example see systematic reviews by De Regil LM, 2012; Imhoff-Kunsch, 2012; Conde-Agudelo A, 2011; Makrides M, 2001; Duley L, 2005). We have not included RCTs because we were primarily interested in dietary factors, representing habitual food intake of women. From a public health perspective, evidence on the relationship between dietary factors including nutrients, foods, and overall diet and hypertensive disorders of pregnancy can inform practical dietary guidelines. (page 4 and 5, line 65-76; and page 13, line 280-283).
Moreover, the lack of definition of included study types was noted. 
Author’s reply: we agree that we were not completely clear on the study types included. This has now been clarified on page 5, line 90-91: “Criteria for inclusion in this systematic review were: observational studies including case-control and cross-sectional, retrospective, and prospective cohort studies among women of reproductive age reporting…”

3. There was a general lack of definition throughout the method section which is very atypical of systematic reviews. For example, there was no comment in the methods section about whether adjusted data or unadjusted data would be focused upon.

Author’s reply: we have now made this more clear on page 6, line 105-107: “For each individual dietary exposure, unadjusted and adjusted dietary intake data for cases and non-cases as well as effect estimates for the association between dietary factors and gestational hypertension and/or preeclampsia were extracted.” Using the available data we could perform meta-analysis of unadjusted mean differences, and adjusted effect estimates (page 7, line 125-132).

Unadjusted and adjusted results were described in separate paragraphs in the results section for each nutrient exposure (page 9-11).

4. There was no formal quality assessment done, and this is a key part of any systematic review, but particularly of observational studies.

Author’s reply: this is a valid point and two authors have now independently performed formal quality assessment using the Newcastle-Ottawa Scale (page 6, line 113-116). Quality scoring results are shown in Additional Table 4 and described on page 8-9, line 171-181.

5. The methods are mixed in with the results and should be maintained separate. For instance, on page 6, much of it consists of results which should be moved to the actual results section.

Author’s reply: we agree and have moved results described in the methods to the results section (page 8, line 148-154)

6. Undertaking a meta-analysis with an exposure such as dietary factors does pose challenges when it comes to combining data due to differences in units in the original studies. However, it is possible to do this by standardizing the units. For example, please see the following meta-analysis which dealt with a similar challenge, significantly increasing the proportion of studies that could be pooled. Anglin R, BJJPsych 2013, Vitamin D deficiency and depression: systematic review and meta-analysis

Author’s reply: units of dietary exposure were indeed different in the original studies. Units were converted to the most commonly used as described in our manuscript on page 7, line 121-124: “Dietary intake data were converted into uniform units when inconsistently reported across studies (kcal/day for total energy intake, mg/day for calcium, vitamin C and sodium, g/day for n-3 fatty acids and mcg/day for vitamin D).”
7. The data from the cohort study should be analyzed separately from the case-control studies, due to methodologic concerns with case-control studies such as recall bias, etc.

Author’s reply: this is a good point and case-control and cohort studies have now been meta-analyzed separately (page 6, line 120). Conclusions remained similar as previously reported.

8. It would be helpful to understand the number of women included in the cohort study separate from the case-control studies.(Page 7)

Author’s reply: number of women in case-control and cohort studies has now been described separately in the results section on page 8, line 161-163: “Number of pregnant women ranged from 92 to 928 in case-control studies and from 65 to 63,226 in cohort studies.”

9. A lack of two reviewers at the title and abstract stage was concerning.

Author’s reply: titles and abstracts identified for systematic review were reviewed by one reviewer, which we do recognize as a limitation of our study. Bibliographies of potentially relevant articles as well as reviews were manually screened for additional relevant studies. Two reviewers then independently reviewed full text articles based on inclusion criteria and also independently performed quality assessment.

10. It would be helpful for the authors to highlight what is new in their study compared to previous systematic reviews.

Author’s reply: previous systematic reviews have synthesized evidence from intervention trials on supplementation of single nutrients and preeclampsia. To our knowledge, findings on the relationship between a wide range of maternal dietary factors (nutrients, foods, overall diet) and both gestational hypertension and preeclampsia from observational studies have not been systematically reviewed or meta-analyzed. (page 4-5, line 65-76)
Reviewer: Anne Stine Kvehaugen

In the paper by Danielle AJM Schoenaker and colleges, data from observational studies in reproductive-aged women on the relationship between dietary factors and gestational hypertension and preeclampsia, published up to January 2014, has been systematically reviewed, and a meta-analysis has been conducted. Only a few narrative reviews have previously been published on this topic, and an update is very much appreciated. The paper is well written, the aim of the study is well defined and methods are appropriate and sufficiently described. Although the discussion is well balanced, some additional comments should be made, see below. Moreover, because significant between-study heterogeneity was clearly present in many cases, and number of reviewed studies was limited, the results may have been somewhat overstated/over interpreted.

Discretionary revisions:

11. Differences in dietary assessment tools: Although the studies included in the meta-analysis reported on the same exposure, such as total energy intake in kcal, different dietary assessment tools were used in the different studies. Limitations associated with self-reported dietary intake, as well as potential bias resulting from the assessment of dietary intake at different time points, are nicely discussed. However, a comment should also be made on how different dietary assessment tools could have contributed to heterogeneity between studies. Although FFQ were frequently used, the same FFQ was likely not used in all studies, and information obtained from a FFQ may differ from that obtained by a 24- or 48-hour dietary recall.

Author’s reply: indeed different dietary assessment methods were used across studies, which could have introduced heterogeneity in the pooled results. This has now been described as a limitation in the discussion section on page 13, line 298-302: “Additionally, dietary assessment methods differed between studies (FFQs, dietary interviews, recalls or records). A dietary recall may more accurately assess actual nutrient intake compared with an FFQ, however, possible heterogeneity in pooled results due to different dietary assessment methods used could not be formally tested due to limited number of studies.”

12. The rationale and implications of removing the large MoBa study in additional meta-analyses of total energy intake and calcium intake should be briefly discussed. In the result section describing results for total energy-intake, it is stated that the difference in total energy-intake between HDP cases and non-cases became larger and statistically significant after excluding the MoBa-study. This finding may be unimportant as substantial between-study heterogeneity was still present for the overall pooled result of HDP cases (all preeclampsia and gestational hypertension studies) compared to non-cases. However, by highlighting this finding without further discussion, this could potentially lead the reader to think that this large MoBa study was considerably different from the other studies, and that inclusion of this study precludes a significant association. However, between-study heterogeneity was not present for the total energy-intake data in the preeclampsia group only. This could have been mentioned. Although the magnitude of difference between cases and non-cases increased slightly in the pooled result after excluding this MoBa study, so did the uncertainty of the estimates (larger
95% CIs). In general, large studies increase statistical power to detect an association and increase the precision/accuracy of estimates. Results from large (population-based) studies are therefore usually considered superior to results from smaller studies, and will also be given more weight in meta-analyses, and thereby dominate over smaller studies. From the reviewers’ point of view, what is essential to communicate to the reader is that when excluding this large MoBa-study, pooled results from the remaining studies were similar to results from the larger study (and pooled results including the larger study), both for the total energy intake data and the calcium intake data.

Author’s reply: it is correct that in-or exclusion of the large MoBa-study did not alter the conclusions for energy intake data. This has now been described in the results section on page 9/10, line 196-201 to read: “Since the result for preeclampsia was dominated (weight 69%) by findings from a large prospective cohort, the Norwegian Mother and Child Cohort Study (MoBa) [20], we additionally present the forest plot excluding this study (Additional Figure 1). The difference in total energy intake between preeclampsia cases and non-cases became slightly larger and statistically significant (87 kcal/day, 95% CI 5.99, 168.11; I² = 0.0%, P = 0.45). Exclusion of the MoBa study did not alter the overall non-significant result for HDP.”

Meta-analysis excluding the MoBa-study for the relationship between calcium and HDP was no longer performed as the study did not extremely dominate the pooled results from cohort studies (weight 25%) (Figure 4B).

Minor essential revisions:
13. Table 1 6th column: According to the column heading, age in years should be presented as mean and SD. However, this is not always the case.

Author’s reply: age in years was presented as mean and SD in most studies, the heading was therefore retained. When age in years was reported differently, the unit has now been added to Table 1 and explained in a footnote: “age reported as mean (SD) unless indicated”.

14. For some studies, age is given separately for HDP cases and non-cases. Did the remaining studies not present maternal age separately for cases and non-cases? A comment could be made in the manuscript text on whether or not cases and non-cases in general were comparable with respect to maternal age.

Author’s reply: if reported, age has now been described for cases and non-cases separately in Table 1. Maternal age was comparable between cases and non-cases even in non-matched case-control studies (Additional Table 2). (page 8, line 157-158)

If information on other relevant characteristics, such as gestational age at delivery and maternal BMI also were available from the individual studies, this information could also be included in text or table.

Author’s reply: we have now created additional Table 2 to describe more characteristics of cases and non-cases. We included: body mass index, nulliparity, gestational age at delivery and infant birth weight. “In studies comparing characteristics of cases and non-cases, BMI and the
proportion of nulliparous women were consistently higher, and gestational age at delivery and infant birth weight were consistently lower, among HDP cases compared with non-cases (Additional Table 2).” (page 8, line 158-161)

15. In Table 1, the 3rd row following the subheading; “Case-control studies,” describes the study by Duvekot EJ (2002). Information presented here is somewhat misleading, as the dietary assessment method is a questionnaire on milk consumption and calcium supplements, while “source” is claimed to be “diet only” (not with supplements).

Author’s reply: thank you for pointing this out, this has now been corrected to “diet with supplements”. (page 30)

16. In Table 4, year of publication for reference 40: Atkinson JO, differs from year of publication given in the reference list. This should be corrected.

Author’s reply: the year of publication for the publication by Atkinson et al. was incorrect in Table 4, this has now been corrected to “Atkinson JO, 1998”.

17. Figure 5. The figure legend of Figure 5 states that five studies from three articles are included in the meta-analysis of adjusted calcium intake. However, in the forest plot showing odds ratios for highest versus lowest category of calcium intake, seven studies (four references) are presented; of which four studies report results for preeclampsia and three studies also report on results for gestational hypertension. This needs clarification.

Author’s reply: the figure legend has now been corrected and updated according to meta-analysis for case-control studies only. 5 study results, 3 for gestational hypertension and 2 for preeclampsia, reported in 3 articles were included. (page 27)

18. Additional Table 2: According to Table 1 and Figure 4, the paper by Geraldo Lopes Ramos J (reference 25), includes both preeclampsia and gestational hypertension cases. However, the definition of gestational hypertension is lacking for this study in Additional Table 2. As results presented from this same study is also separated into “severe” and “mild” preeclampsia, a definition of these sub-types of preeclampsia should likewise be given in Additional Table 2. This also applies to Table 2 footnote a), Table 4 footnote c) and Additional Figure 2 footnotes a) and b). The number of cases classified as “severe” and “mild” preeclampsia respectively should also be given in Table 1.

Author’s reply: definitions of preeclampsia and severe preeclampsia in the 4 studies reporting on both conditions separately (Geraldo Lopes Ramos J, 2006; Wei S-Q, 2009; Brantsaeter AL, 2011; Klemmensen, 2009) have now been added to Additional Table 3 (previously Additional Table 2). This table has been referenced in Table 2 and 4 and Figure 4B footnotes. The number of cases classified as severe and mild preeclampsia have now also been given in Table 1 for all 4 studies if reported.
19. Footnote c) in additional Table 2 seems to include a typing error: ..”but not of they developed”....

*Author’s reply:* this has now been corrected to read “..but not if they developed..” (Additional Table 3)

20. In the discussion section, the 2nd sentence of the 3rd paragraph reads: “Firstly, diet was assessed using a validated FFQ in 16 of 35 studies”..... This number (35), differ from the number given in the method section, describing 37 included studies. This should be corrected.

*Author’s reply:* the total number of studies included in the review was 37, this is now 38 after updating the search until May 2014, this has now been corrected. (page 13, line 293)

21. Discussion section, 3rd paragraph: The following sentence seems incomplete: “Five studies examining subtypes suggest a more pronounced risk for severe or early onset compared to mild and late onset preeclampsia (12, 18, 25, 30, 47)”. Which exposure increased the risk of severe/early onset preeclampsia?

*Author’s reply:* the more pronounced risk for severe preeclampsia was found for lower intake of calcium, vitamin C and probiotics and higher consumption of tea in studies examining subtypes. This has now been described: “Four studies examining subtypes suggest a more pronounced risk for severe compared with mild preeclampsia for lower intake of calcium [35], vitamin C [26], and probiotics [20] and higher consumption of tea [36]. Clausen et al. found a significant trend towards increasing intake of energy and sucrose across categories without preeclampsia, late-onset preeclampsia, and early-onset preeclampsia [41].” (page 14, line 309-313)

**Major essential revisions:**

22. Findings may have been overstated. Although limitations of the study, including the presence of heterogeneity, are acknowledged in the discussion, a more balanced presentation of findings should be made in the abstract (such as describing between-study heterogeneity along with the results) and a more careful interpretation of results should be made in the conclusion (....e.g.: “data suggest that....” rather than: “are associated with...”).

*Author’s reply:* We agree that our findings may have been overstated and have now rephrased our conclusion: “Based on cohort studies included in this review, maternal dietary intake of total energy was higher among preeclampsia cases compared with non-cases, even though not statistically significant.” and “Furthermore, data suggest that higher calcium and magnesium intake and a diet rich in fruit and vegetables may be beneficial for HDP.” (page 17, line 382-387)

It could also be questioned whether the reported differences between HDP cases and non-cases, such as a difference in 20 kcal/day, is clinically relevant? Nevertheless, the findings are interesting in light of previous reports on an association between BMI and preeclampsia.

*Author’s reply:* we agree that differences in total energy, calcium and magnesium intake reported in studies between gestational hypertension and preeclampsia cases and non-cases were small, but that our results are interesting in light of previous studies on the association between BMI
and hypertensive disorders of pregnancy. We have acknowledged the small differences between cases and non-cases in the discussion section on page 16, line 354-358.

23. Fruit and vegetable intake and association to preeclampsia: The result subsection “Fruit and vegetables” reads: “A total of five case-control [13, 15, 35, 39, 40] and four cohort studies [18, 26, 30, 41] examined the association between fruit and/or vegetable consumption and preeclampsia (Table 4). Two case-control [13, 39] and two cohort studies [18, 26] all adjusting for confounding factors (Additional Table 3) consistently indicated a beneficial effect of higher fruit and/or vegetable consumption on preeclampsia”. However, according to Table 4, reference 18 did not show a significant association between fruit and/or vegetable consumption and lower risk of preeclampsia. Moreover, from Table 1 it seems that the two case-control studies showing an association between total fruit and vegetable intake (reference 13 and 39) are based on the same study population, although with a somewhat larger sample size in reference 13 (women delivering between 1998-2001 versus women delivering between 1998-2000 in reference 39). This needs to be discussed. Thus, from the above text the reviewers are not convinced that “Systematic review of studies examining foods and dietary patterns showed consistent findings for a beneficial effect of a diet rich in fruit and vegetables on preeclampsia” (cited from the discussion section, last sentence of first paragraph).

Author’s reply: this is a valid point and sections describing findings on fruit and vegetable consumption and hypertensive disorders of pregnancy have now been rephrased to more accurately synthesize study results:

Abstract: “Few studies examining foods and dietary patterns suggested a beneficial effect of a diet rich in fruit and vegetables on preeclampsia, even though results were not all statistically significant.” (line 36-38)

Results section page 11/12, line 247-250: “Two case-control studies (based on one study population) [21, 47] and two cohort studies [26, 36] all adjusting for confounding factors (Additional Table 5) suggested a beneficial effect of higher fruit and/or vegetable consumption on preeclampsia, although not all statistically significant.”

Discussion section last sentence of first paragraph on page 13, line 275-276: “Systematic review of a few studies examining foods and dietary patterns suggests a beneficial effect of a diet rich in fruit and vegetables on preeclampsia.”

24. Discussion section, 8th paragraph reads: “Apart from intake of total energy, magnesium, calcium and fruit and vegetables, consumption of other nutrients and foods were not associated with HDP. This may be due to studying low risk populations where nutrient deficiencies are rare and women regularly take multivitamin supplements [55], or due to lack of heterogeneity of intake in most well-nourished populations reducing the ability to detect an association with HDP [32]. Further studies in different populations are needed to examine a range of nutrients and foods in relation with HDP.” Does this mean that the reported calcium intake in the reviewed studies in general was adequate as well? Or could differences in intake between study populations perhaps explain some of the between-study heterogeneity? This
could have been useful information with respect to previous findings of lower risk of preeclampsia with calcium supplementation in low-intake groups.

Author’s reply: thank you for pointing this out. Even though we could not formally test for between-study heterogeneity by difference in intake between study populations, we have now extended our discussion and indicated that based on findings from our review the association between calcium intake and hypertensive disorders of pregnancy may be larger in populations with lower calcium intake. (page 16, line 363-374)

25. “Severe versus mild preeclampsia”: Along with the difficulties in assessing dietary intake, the heterogeneity of HDP (types and sub-types), represent perhaps the main challenge of studying the relationship between dietary intake and HDP. For the total calcium intake meta-analysis, one study (Geraldo Lopes Ramos) made a distinction between “severe” and “mild” preeclampsia, while none of the other studies made such a distinction. Inclusion of this study in the meta-analysis is not wrong, but it deserves a comment in the discussion (i.e. could this have affected between-study heterogeneity and/or significance of finding?).

Author’s reply: exclusion of the study result for severe preeclampsia reduced between-study heterogeneity. Although we could not formally test for heterogeneity using subgroup analysis or meta-regression, this suggests that the finding for severe preeclampsia may have affected between-study heterogeneity and we have now commented on this in the discussion: “In meta-analysis of cohort studies on difference in calcium intake between HDP cases and non-cases only the study by Geraldo Lopes Ramos et al. reported on mild and severe preeclampsia separately, showing a stronger and statistically significant association of lower calcium intake with severe preeclampsia compared with mild preeclampsia [35]. Exclusion of the result on severe preeclampsia from meta-analysis reduced the significant between-study heterogeneity for preeclampsia and HDP as well as the statistically significant overall results of lower calcium intake among HDP cases compared with non-cases.” (page 14, line 315-321).

26. Publication bias: Why was publication bias only assessed for the adjusted calcium intake data?

Author’s reply: publication bias has now been assessed via a funnel plot for all meta-analyses including at least five study results. Interpretation of the funnel plots for the association between energy, magnesium and calcium and HDP showed no suggestion of publication bias (P-values for Egger's test for small-study effects all >0.05, figures not shown). (page 11, line 237-239)

27. In the conclusion, it is stated that pregnant women should be advised to maintain energy balance. This statement could be questioned. Although excessive weight gain should be avoided, a slightly positive energy balance is needed during pregnancy to ensure growth of the baby and maternal tissues.

Author’s reply: this statement has now been rephrased to read: “In line with existing guidelines, pregnant women should be advised to avoid too high energy intake and excessive weight gain during their pregnancy.” (page 17, line 384-386)
Also, the authors state that “... pregnant women should be advised to......increase their intake of calcium and magnesium, by increasing intake of low-fat dairy and fruit and vegetables”. The present meta-analysis cannot support this advice, however rational it may seem. No RCT has been performed to support that an advice of increasing calcium supplementation or magnesium would decrease the risk of hypertensive pregnancy disorders across all populations. In particular, there is no evidence if this recommendation has any value in populations without economical restrictions for a balanced diet in pregnancy. The text should be revised accordingly.

Author’s reply: to find causal associations indeed intervention studies are needed. Our findings could inform such trials, indicating potential dietary factors of interest. We have now rephrased the implications of our review more carefully on page 17, line 386-391: “...Furthermore, data suggest that higher calcium and magnesium intake and a diet rich in fruit and vegetables may be beneficial for HDP. Adequate calcium and magnesium intake may be achieved by increasing intake of low-fat dairy and fruit and vegetables. There is a need for well-powered prospective cohort studies and intervention trials in a range of populations assessing nutrition prior to and during pregnancy examining the association with the different subtypes of HDP.”
Reviewer: Shakila Thangaratinam
The authors have addressed a clinically relevant area of interest by systematically reviewing the association between dietary factors and pre-eclampsia and gestational hypertension. The authors have undertaken a comprehensive search strategy (although restricted to English) and the methodology is mostly appropriate.

Major revisions

Methods:

28. Case control and cohort studies will need to be meta-analysed separately and should not be combined.

*Author’s reply:* case-control and cohort studies have now been meta-analyzed separately, see page 6, line 120. Conclusions remained similar as previously reported.

29. MOOSE is reporting criteria and not for quality assessment. Other alternative methods such as Newcastle Ottawa Scale may be more appropriate for quality assessment

*Author’s reply:* two authors have now independently performed formal quality assessment using the Newcastle-Ottawa Scale (page 6, line 112-116). Quality scoring results are shown in Additional Table 4 and described on page 8/9, line 171-181.

30. Random effects may be more appropriate than fixed effects model for the meta-analysis, especially given the heterogeneity observed.

*Author’s reply:* we agree and have redone our analysis using random effects models (page 7, line 134).

31. The difference in energy intake is not statistically significant between the two groups, and this needs to be explicitly stated in the abstract and Results section

*Author’s reply:* this is a good point. To accentuate the non-significant result we made changes in the abstract and results:

Abstract: “Based on meta-analyses of cohort studies, unadjusted total energy intake was higher among preeclampsia cases (WMD 46kcal/day, 95% CI -13.80, 106.23; I² = 1.9%, P = 0.42), even though not statistically significant.” (line 30-32)

Results section: “Findings from cohort studies indicated that preeclampsia cases reported a higher energy intake of 46 kcal/day compared with women without preeclampsia (95% CI -13.80, 106.23; I² = 1.9%, P = 0.42), even though this was not statistically significant.” (page 9, line 193-196)
Minor essential revision

32. Some additional information in the Introduction, on the rationale for this review, given current evidence and recommendations will be helpful

Author’s reply: current recommendations include calcium supplementation for prevention of preeclampsia in women with low dietary calcium intake and for those at high risk. This is based on evidence from systematic reviews and meta-analyses of intervention trials on supplementation of single nutrients. Evidence for other nutrients remains inconsistent. To our knowledge, findings on the relationship between a wide range of maternal dietary factors (nutrients, foods and overall diet) and both gestational hypertension and preeclampsia from observational studies have not been systematically reviewed. Such findings could inform further intervention trials and contribute to development of dietary guidelines for pregnant women. We have now further described this on page 4/5, line 60-76.

33. Similarly in the discussion, some more elaboration on the added value of this study for clinical practice and research recommendations is needed.

Author’s reply: we have now extended our discussion on the added value of our review for clinical practice and research recommendations on page 17, line 384-390: “In line with existing guidelines, pregnant women should be advised to avoid too high energy intake and excessive weight gain during their pregnancy. Furthermore, data suggests that higher calcium and magnesium intake and a diet rich in fruit and vegetables may be beneficial for HDP. Adequate calcium and magnesium intake may be achieved by increasing intake of low-fat dairy and fruit and vegetables. There is a need for well-powered prospective cohort studies and intervention trials in a range of populations assessing nutrition prior to and during pregnancy examining the association with the different subtypes of HDP.”

ADDITIONAL REVISIONS:

The systematic literature search using MEDLINE and EMBASE databases was updated to include studies published up to May 2014. The study by Richards et al. published in February 2014 was additionally included in the systematic review. The flow diagram, results and tables have been updated accordingly.