

PEER REVIEW HISTORY

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This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reduced risk of preeclampsia with organic vegetable consumption; results from the prospective Norwegian Mother and Child Cohort Study
AUTHORS	Torjusen, Hanne; Brantsaeter, Anne-Lise; Haugen, Margaretha; Alexander, Jan; Bakketeig, Leiv Sigmund; Lieblein, Geir; Stigum, Hein; Næs, Tormod; Swartz, Jackie; Holmboe-Ottesen, Gerd; Roos, Gun; Meltzer, Helle Margrete

VERSION 1 - REVIEW

REVIEWER	ODENT, Michel Primal health research centre, Preventive Medicine
REVIEW RETURNED	17-May-2014

GENERAL COMMENTS	<p>This study is not a repeat of previous studies. It is highly original. It has a high scientific value. I hope that its publication in BMJ will inspire similar studies in countries that do not share the particularities of Norway (different possible associated factors). It is worth keeping in mind some particularities of Norwegian lifestyle. One of the particularities of Norway is easy access to the seafood chain. Furthermore the Norwegian health authorities officially recommend the consumption of fish. Yet there is no mention of seafood in this article. It is plausible that Norwegian women who consume organic vegetables are also, more than others, fish eaters. It is probable that sea food consumption can influence the risks of preeclampsia by providing iodine (thyroid hormones alterations in preeclampsia are well documented), and also vitamin D and preformed very long chain polyunsaturated fatty acids of the omega 3 family (effects on the system of prostaglandins and inflammatory processes).</p> <p>Another particularity of Norway is a comparatively low consumption of alcohol. Wine, spirits and strong beer are only sold at "vinmonopolet". Yes the word alcohol only appears once, discreetly, in a table (yes/no). The effect of alcohol consumption on the risks of preeclampsia is enigmatic and therefore an important topic for research. There are even studies suggesting that alcohol consumption is protective regarding preeclampsia. None of these studies have dissociated the effects of wine, beer, and spirits. It is plausible that Norwegian women consuming organic vegetables have a tendency to consume their alcohol as organic red wine (?) .</p>
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REVIEWER	Payne, Beth University of British Columbia
REVIEW RETURNED	31-May-2014

GENERAL COMMENTS	<p>Thank you for giving me the opportunity to review this manuscript in which authors describe a possible association between organic food consumption and reduced risk of pre-eclampsia. The authors present an interesting argument for the health benefits of organic food consumption in general. Using available data from a large cross-sectional survey of pregnant women conducted as part of the broader prospective Norwegian Mother and Cohort Study they are able to assess impact of eating organic food and healthy lifestyle on the risk of pre-eclampsia with some limitations.</p> <p>Although I found this article well written overall and think the authors present an interesting argument I have several concerns with the methods and interpretation of results. My specific comments regarding methods used and results presented are below.</p> <ol style="list-style-type: none"> 1. The title of the study describes it as a prospective cohort but data used seems to be from a cross-sectional survey of food intake. This is in reality a secondary analysis of a small component of the larger prospective cohort study. The title should reflect this. 2. In the introduction and summary of known information on the topic the authors focus on epidemiological data that has indicated association between nutritional factors and pre-eclampsia. Although this is an area I believe requires further investigation as evidence does suggest there may be nutritional interventions that could impact the incidence of the disorder it would be useful to point out that in RCTs of dietary interventions and supplementation with Vitamin E, Vitamin C, salt-restriction; or protein intake increases no impact on incidence of HDP has been demonstrated. In the case of Vitamin C and E supplementation may have a negative effect on fetal development. Calcium supplementation has also been widely studied with mixed results only showing an effect when supplementation was given to women with poor nutrient status prior to conception. The authors introduction may be misleading to readers without presenting the whole picture. 3. Authors state that studies have shown little difference in nutrient content between organic and inorganic foods, so would this not mean that any effect of eating organic foods seen should focus on differences related to non-nutrient content of organic foods? Again this argues as to the appropriateness of the statements in the introduction stating support for nutritional interventions. 4. One concern regarding data used is that MoBA questionnaire assesses dietary intake during pregnancy but does not establish pre-pregnancy nutritional status. Studies on the effect of calcium intake on pre-eclampsia have highlighted the importance of pre-pregnancy health status on incidence of pre-eclampsia. A further limitation of this study that requires discussion is that the data available do not allow assessment of impact of pre-pregnancy nutritional status as that may be a confounder of the relationship shown. It seems reasonable that the women who chose to eat organically would have started out at a healthier status prior to conception. 5. It would be useful to add further explanation as to how the sum index was developed and validated. The scale of 0 to 18 depending on number of food types in which organic food consumption was indicated as "mostly" implies an additive scale of effect of eating the various organic food types (the more types eaten mostly organically the higher the score) but interpretation of the index is based solely
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	<p>on eating one or more food type “mostly” organically. This interpretation seems to defeat the purpose of developing an additive sum index. Could the authors further explain how they determined the method of applying this index to the analysis and further justify its use as a confounder?</p> <p>6. I would also like a better description in this manuscript of the principal component analysis used to develop the healthy food pattern ranking. How were tertiles defined and how did they differ? The primary conclusion of this study is that organic vegetable consumption is associated with lower risk of pre-eclampsia independent of a healthy food pattern. It is extremely difficult to tease out the effect of organic food consumption over the general differences found in healthy lifestyle behaviours in women who chose to eat organically. With the description provided of how the healthy food pattern is defined I am left with doubts as to whether the conclusion the organic vegetable consumption independently effects risk. I assume other readers will be unconvinced that residual confounding is not greatly at play in this analysis as well, so further description and justification would be helpful. It is noted that the authors state it is impossible to rule out residual confounding but it is given as a minor point. This should be addressed more thoroughly.</p> <p>7. Some discussion about excluded potential confounders would be useful in how this study compares to others, for example, in this study dietary supplementation with Vitamin D was not found to be associated with either exposure or outcome (this data is not presented so I am not sure which) and was not included in the final analysis. Does this imply some difference in the cohort under study to other large cohorts where an association was found? Further to this, presenting results of all univariate and multivariate assessment of confounders would be helpful to interpretation of results by readers. In the limitations of the study it would also be helpful to point out known risk factors and confounders for pre-eclampsia that were not measured in the study such as pre-existing renal or metabolic disorders.</p> <p>8. Finally the sub-group analysis failed to show any maintenance of effect found. This is particularly relevant to analysis of late vs. early onset pre-eclampsia. How do the authors feel this lack of effect in either group alone impacts interpretation of results? This should be addressed in the discussion.</p> <p>9. In the description of data it is stated that time of diagnosis is not known but an analysis of time of onset based on gestational age is presented. What time of diagnosis is being referred to in line 49?</p> <p>10. I greatly enjoyed the description of possible causal mechanisms for the association found. Focus on the impact of aspects of organic food consumption on what are known to be underlying mechanisms of the maternal syndrome of pre-eclampsia, namely oxidative stress and inflammation is well thought through. These arguments could be strengthened by some discussion of how the mechanisms described could affect placental development and function and not just the downstream consequence of the maternal syndrome that manifests as endothelial dysfunction.</p> <p>I hope these comments are useful to the authors.</p>
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewer: 1

Comments:

This study is not a repeat of previous studies. It is highly original. It has a high scientific value. I hope that its publication in BMJ will inspire similar studies in countries that do not share the particularities of Norway (different possible associated factors). It is worth keeping in mind some particularities of Norwegian lifestyle.

- 1) One of the particularities of Norway is easy access to the seafood chain. Furthermore the Norwegian health authorities officially recommend the consumption of fish. Yet there is no mention of seafood in this article. It is plausible that Norwegian women who consume organic vegetables are also, more than others, fish eaters. It is probable that sea food consumption can influence the risks of preeclampsia by providing iodine (thyroid hormones alterations in preeclampsia are well documented), and also vitamin D and preformed very long chain polyunsaturated fatty acids of the omega 3 family (effects on the system of prostaglandins and inflammatory processes).

RESPONSE:

We agree that food intakes, e.g. seafood, and nutrients, e.g. iodine and calcium, are interesting aspects to take into consideration. Fish (and seafood) was among the food groups included in the analysis of dietary patterns associated with consumption of organic food during pregnancy, reported in Torjusen et al. (2012). However, since seafood intake was not significantly different in women reporting frequent consumption of organic food (all food groups or Sum Index) than in those with no or low organic food consumption, it was not highlighted in the paper. (It can be observed in the figure included in supplemental material in Torjusen et al, 2012). We have earlier studied iodine intake in the same cohort and found that the main food source is milk, followed by seafood (Brantsaeter et al., 2013). Milk is also an important source of calcium, another nutrient shown to be associated with preeclampsia. Thanks to the reviewer comments we have explored the data even closer than before and found that women with high consumption of organic vegetables did in fact have higher intakes of seafood, milk, iodine, calcium and several other foods and nutrients than those with no or low organic vegetable consumption. However, no food or nutrient intake attenuated the association of interest. Adjusting for single food groups, e.g. fish or milk, or for specific nutrients, e.g. iodine or calcium, did not change the association between consumption of organic vegetables and preeclampsia. The analyses indicated independent associations between some nutrients, e.g. calcium or iodine and preeclampsia (data not shown in this paper). The associations between these nutrients and preeclampsia were however, attenuated when simultaneously adjusted for the dietary pattern. Therefore, adjustment for the overall dietary pattern was done to correct for differences in food intakes and for differences in nutrient intakes contributed by foods.

Associations between organic food consumption and the dietary pattern have been reported in detail in (Torjusen et al., 2012), and the associations between dietary patterns and preeclampsia have been reported in (Brantsaeter et al., 2009).

In the revised manuscript we have included a new paragraph related to specific foods and nutrients both in the results section (page 11) as well as in the discussion (page 15).

- 2) Another particularity of Norway is a comparatively low consumption of alcohol. Wine, spirits and strong beer are only sold at "vinmonopolet". Yes the word alcohol only appears once, discreetly, in a table (yes/no). The effect of alcohol consumption on the risks of preeclampsia is enigmatic and therefore an important topic for research. There are even studies suggesting that alcohol consumption is protective regarding preeclampsia. None of these studies have dissociated the effects of wine, beer, and spirits. It is plausible that Norwegian women consuming organic vegetables have a tendency to consume their alcohol as organic red wine (?).

RESPONSE:

The level of alcohol consumption is indeed low in the present cohort. When asked about pregnancy-related changes in consumption of food and beverages, 10% were abstainers before pregnancy and nearly 80% answered that they had stopped due to pregnancy (Meltzer et al., 2008). However, in our previous study we found that alcohol consumption was fact slightly higher among women with frequent organic food consumption (Torjusen et al. 2010, n=63,808). The data showed that particularly the wine category was slightly higher, and it may indeed be due to consumption of organic wine. In the present study sample (comprising only nulliparous women,

n=28,192), we found no difference in alcohol consumption between women who reported high organic vegetable intake and those who did not, and this is only briefly mentioned in the paper. Adjusting for alcohol consumption did not influence the association between high use of organic vegetables and preeclampsia and no association between alcohol and preeclampsia was indicated. Hence, we find that there is no rationale for additional text related to alcohol consumption in this paper.

Additional Questions:

Please enter your name: Michel Odent

Job Title: Director

Institution: Primal Health Research Centre. London NW3 2JR

Response to reviewer: 2

Recommendation:

Comments:

Thank you for giving me the opportunity to review this manuscript in which authors describe a possible association between organic food consumption and reduced risk of pre-eclampsia. The authors present an interesting argument for the health benefits of organic food consumption in general. Using available data from a large cross-sectional survey of pregnant women conducted as part of the broader prospective Norwegian Mother and Cohort Study they are able to assess impact of eating organic food and healthy lifestyle on the risk of pre-eclampsia with some limitations. Although I found this article well written overall and think the authors present an interesting argument I have several concerns with the methods and interpretation of results. My specific comments regarding methods used and results presented are below.

1. The title of the study describes it as a prospective cohort but data used seems to be from a cross-sectional survey of food intake. This is in reality a secondary analysis of a small component of the larger prospective cohort study. The title should reflect this.

RESPONSE:

This comment surprises us. We do consider this to be a prospective cohort study, similar to a number of other studies with a similar set-up from the Norwegian Mother and Child Cohort study which previously have been published as such. The enrollment, background information and dietary exposure assessment took place and were gathered well ahead of the outcome, which complies with the classical definition of a prospective study. (The methods section tells that information about food intake and use of organic food was assessed in mid-pregnancy, while information about the preeclampsia outcome was obtained from the Medical Birth Registry of Norway).

2. In the introduction and summary of known information on the topic the authors focus on epidemiological data that has indicated association between nutritional factors and pre-eclampsia. Although this is an area I believe requires further investigation as evidence does suggest there may be nutritional interventions that could impact the incidence of the disorder it would be useful to point out that in RCTs of dietary interventions and supplementation with Vitamin E, Vitamin C, salt-restriction; or protein intake increases no impact on incidence of HDP has been demonstrated. In the case of Vitamin C and E supplementation may have a negative effect on fetal development. Calcium supplementation has also been widely studied with mixed results only showing an effect when supplementation was given to women with poor nutrient status prior to conception. The authors introduction may be misleading to readers without presenting the whole picture.

RESPONSE:

We appreciate this comment and have added a new section in the introduction to supplement our account of previous studies.

3. Authors state that studies have shown little difference in nutrient content between organic and inorganic foods, so would this not mean that any effect of eating organic foods seen should focus on differences related to non-nutrient content of organic foods? Again this argues as to the appropriateness of the statements in the introduction stating support for nutritional interventions.

RESPONSE:

The text in the introduction is meant to give a short presentation of previous studies on associations between dietary factors and the risk of preeclampsia. As far as we know, there are no studies specifically on non-nutrients. As mentioned above, a new paragraph has been added to the introduction. Furthermore, in the revised manuscript we have also included new paragraphs to elucidate that the association between organic vegetables and preeclampsia was independent of the association between overall diet and preeclampsia – supporting that the association seen for organic vegetables is not likely explained by nutrients, but rather by the amount or composition of non-nutrients in organic foods. See also our response to comment 1 from Reviewer 1.

4. One concern regarding data used is that MoBA questionnaire assesses dietary intake during pregnancy but does not establish pre-pregnancy nutritional status. Studies on the effect of calcium intake on pre-eclampsia have highlighted the importance of pre-pregnancy health status on incidence of pre-eclampsia. A further limitation of this study that requires discussion is that the data available do not allow assessment of impact of pre-pregnancy nutritional status as that may be a confounder of the relationship shown. It seems reasonable that the women who chose to eat organically would have started out at a healthier status prior to conception.

RESPONSE:

It is correct that there is no information about pre-pregnancy nutritional status in this dataset. Possible effect modifying by differences in pre-pregnancy nutritional status can therefore not be accounted for and has been added to the discussion related to limitations of our study.

5. It would be useful to add further explanation as to how the sum index was developed and validated. The scale of 0 to 18 depending on number of food types in which organic food consumption was indicated as “mostly” implies an additive scale of effect of eating the various organic food types (the more types eaten mostly organically the higher the score) but interpretation of the index is based solely on eating one or more food type “mostly” organically. This interpretation seems to defeat the purpose of developing an additive sum index. Could the authors further explain how they determined the method of applying this index to the analysis and further justify its use as a confounder?

RESPONSE:

An in-depth explanation as to how the sum index was developed has been published previously ([Torjusén et al., 2010](#), [Torjusén et al., 2012](#)). The aim of these studies was to identify background and dietary characteristics associated with organic food consumption and for that purpose the sum index was useful. However, we agree that the index is not equally relevant for examining the association between organic food use and health outcomes because different types of organic food are likely to reflect different aspects of organic farming methods.

This current study is explorative, and we aimed at investigating the use of organic food using several different approaches. The additive sum index developed for the previous studies was therefore a first attempt to explore possible effects of any organically grown food, as there was little previous evidence to go by. However, we acknowledged the limitations of the index and consequently explored the separate organic food groups.

The rationale for using the sum index as a confounder was that organic users tend to eat organic food from more than one food group. We are aware that this could overspecify the model, but was included in order to examine whether consumption of organic vegetables was an expression of the total organic food consumption, or if it was something 'over and above' this.

6. I would also like a better description in this manuscript of the principal component analysis used to develop the healthy food pattern ranking. How were tertiles defined and how did they differ? The primary conclusion of this study is that organic vegetable consumption is associated with lower risk of pre-eclampsia independent of a healthy food pattern. It is extremely difficult to tease out the effect of organic food consumption over the general differences found in healthy lifestyle behaviours in women who chose to eat organically. With the description provided of how the healthy food pattern is defined I am left with doubts as to whether the conclusion the organic vegetable consumption independently effects risk. I assume other readers will be unconvinced that residual confounding is not greatly at play in this analysis as well, so further description and justification would be helpful. It is noted that the authors state it is impossible to rule out residual confounding but it is given as a minor point. This should be addressed more thoroughly.

RESPONSE:

Principal component analysis has been fully described in the previous publication ([Torjusen et al., 2012](#)), and only a short description is appropriate in the current paper. The principal component analysis, which was used to identify the dietary pattern, is based on the intake of all food consumed and assigns a score to all subjects. A high score reflects higher intake of foods correlated with the pattern and a low score reflects lower intake. The tertiles were defined by ranking the food score variable (i.e. into three equally large groups).

We agree that it is difficult to tease out the specific effects of organic food consumption over other possible differences between the women who eat vs. do not eat organic food. However, the Norwegian Mother and Child Cohort Study provide information about a broad spectrum of variables which may be of interest in this respect.

We fully accept the possibility that there may be residual confounding, but have done the best we could to take account for all relevant variables available in the data-set.

7. Some discussion about excluded potential confounders would be useful in how this study compares to others, for example, in this study dietary supplementation with Vitamin D was not found to be associated with either exposure or outcome (this data is not presented so I am not sure which) and was not included in the final analysis. Does this imply some difference in the cohort under study to other large cohorts where an association was found? Further to this, presenting results of all univariate and multivariate assessment of confounders would be helpful to interpretation of results by readers. In the limitations of the study it would also be helpful to point out known risk factors and confounders for pre-eclampsia that were not measured in the study such as pre-existing renal or metabolic disorders.

RESPONSE:

A higher dietary intake of vitamin D among women with frequent organic food consumption has been reported in ([Torjusen et al., 2012](#)). An earlier sub-study in the Norwegian Mother and Child Cohort study showed an inverse association between the total intake of vitamin D (diet + supplements) and preeclampsia ([Haugen et al., 2009](#)). However, this association was not apparent when use of food supplements with vitamin D was modelled alone (see Table 3 in Haugen et al. 2009). In the present paper, we used the dietary supplement variable with three categories: i) non supplement users, ii) supplements without vitamin D, and ii) supplements with vitamin-D. This variable was not associated with preeclampsia, and did not influence the association between organic vegetables and preeclampsia. Thus it was not included in the final analysis. Dietary intake of vitamin D was accounted for by the inclusion of the dietary pattern score.

We agree with the reviewer that careful presentation of the issue of confounding is important. However, we are not allowed to report the association between all potential confounders and the outcome in this manuscript because the MoBa Scientific Management Group has a restrictive policy when it comes to publishing direct effects of putative confounding variables on the outcomes. This is in order to avoid infringement on other manuscripts of these outcomes. This is not uncommon in large multi-outcome cohorts involving many investigators.

There is no available information in the scientific literature indicating that these disorders should be associated with the intake of organic food. However, data about pre-existing renal disease, diabetes, heart-condition and asthma is available among variables recorded in the MBRN. Because of this reviewer's comment, we checked it out, and for your information, adjusting for these conditions did not influence the association between use of organic vegetables and preeclampsia.

8. Finally the sub-group analysis failed to show any maintenance of effect found. This is particularly relevant to analysis of late vs. early onset pre-eclampsia. How do the authors feel this lack of effect in either group alone impacts interpretation of results? This should be addressed in the discussion.

RESPONSE:

We believe this to be the effect of smaller groups and therefore less statistical power in these sub-analyses. The tendency remains, although no longer statistically significant, and we consider this relevant. This has been addressed in the discussion as a limitation.

9. In the description of data it is stated that time of diagnosis is not known but an analysis of time of onset based on gestational age is presented. What time of diagnosis is being referred to in line 49?

RESPONSE:

We acknowledge that the statement in the description may be confusing as we do have information on whether preeclampsia was diagnosed before week 34 (early preeclampsia). We have therefore deleted this statement.

10. I greatly enjoyed the description of possible causal mechanisms for the association found. Focus on the impact of aspects of organic food consumption on what are known to be underlying mechanisms of the maternal syndrome of pre-eclampsia, namely oxidative stress and inflammation is well thought through. These arguments could be strengthened by some discussion of how the mechanisms described could affect placental development and function and not just the downstream consequence of the maternal syndrome that manifests as endothelial dysfunction.

RESPONSE:

Thank you for this comment. We have considered elaborating the discussion to include additional information of how oxidative stress and inflammation could affect placental development and function. However, we acknowledge that the discussion of possible explanations of our findings is speculative, and considered a further discussion of how oxidative stress and inflammation could affect placental development beyond the scope of this paper.

I hope these comments are useful to the authors.

Additional Questions:

Please enter your name: Beth Payne

Job Title: PhD Candidate

Institution: University of British Columbia

References

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