

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Systematic review of the association between dietary acid load, alkaline water, and cancer
<b>AUTHORS</b>	Fenton, Tanis; Huang, Tian

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Marialena Trivella University of Oxford, UK
<b>REVIEW RETURNED</b>	12-Dec-2015

<b>GENERAL COMMENTS</b>	<p>I very much enjoyed reviewing this work. It is well written and conducted and in an uncomplicated manner it responds sensibly to a seemingly growing but essentially unfounded dietary promotion.</p> <p>Although I am not knowledgeable in the scientific intricacies of the field of diet and nutrition, I am knowledgeable in the area of systematic reviews, and from the methodological point of view I am satisfied that the authors have been meticulous and objective.</p> <p>There are however, some minor suggestions and issues I would like to highlight.</p> <p>Abstract: The abstract is usually the first impression of a paper and currently the description of the review inaccurately implies that the conduct of the work may not be methodologically sound and that it is clinically very broad to be of use. In particular combining randomised interventions and observational studies within the same analysis would not be appropriate and although it is clear from reading the review that the authors had no such intentions, the brevity of the abstract points otherwise. Maybe adding the word 'separate' reviews for randomised and observational studies would clarify this.</p> <p>Also, the list of outcomes in the abstract lists 'any outcome of cancer treatment' which would be almost impossible to assess in any systematic review that had a sizeable yield in included studies.</p> <p>In the abstract results section, it would be helpful to have information on how many studies the search yielded, before the one included was selected, the number of participants in that included study, and brief info on the quality of evidence.</p> <p>Lastly, the abstract conclusion section, mentions that the review "revealed a lack of evidence for an association...", where in fact there is just a lack of evidence, in that, despite the promotion of alkaline diet by the media, there is no actual research to either support or disprove it. This is different to claiming that there is no evidence of association.</p> <p>The same comment above applies to the 'Conclusions' section of the main text.</p> <p>In page 5 – Description of results – The information given for the</p>
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	<p>systematic review found and the narrative studies is somewhat limited. If there is another systematic review out there, how different is it to this one? Where the same outcomes examined? How many studies did it include? What did the narrative reviews explore, and what they concluded?</p> <p>The results section is dominated by details of the one included study, and of course this is inevitable as there is only one study in the review. However, if there were more studies in the review, it would not be possible to describe them all in such detail; in fact the dominance of these details in my view diverts the attention from the essence of the paper. The point of the review, as I see it, is to summarise existing evidence, and if no evidence is found – as is the case here – to highlight the lack of evidence and the discrepancy between the wide promotion of alkaline diet and the lack of research supporting that claim.</p> <p>In summary, although the manuscript is methodologically sound, I feel that it needs minor adjustments on the emphasis and extend some of the methods, results, and conclusions are described, so that there is better balance in the paper.</p> <p>Some other details:</p> <ul style="list-style-type: none"> <li>- Page 4 – line 55: I would not classify the Cochrane register as grey literature.</li> <li>- Page 5-line 32: "... controlled for or &gt; 5.0 ...", is it meant to be an OR (odds ratio?). Not clear what that sentence means</li> <li>- Page 5 – line 46 and line 52: the same reference is quoted (ref 25). Probably a typo as ref 25 doesn't refer to a systematic review, and is in fact the only included study. It is not also clear whether references 26 and 27 are reviews as is implied in the text.</li> <li>- Page 7: There is no caption for table 1</li> <li>- Page 10 – lines 41 to 48. I feel that it is not necessary to refer in particular to one factor (smoking) for one cancer (bladder), in one of the studies considered in discussion.</li> </ul>
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<b>REVIEWER</b>	Shamima Akter Department of Epidemiology and Prevention National Center for Global Health and Medicine Tokyo, Japan
<b>REVIEW RETURNED</b>	10-Jan-2016

<b>GENERAL COMMENTS</b>	<p>The author Fenton et al. conducted a systematic review to evaluate the association between dietary/alkaline water and cancer. The author found only one prospective study that assesses the association between urinary pH and bladder cancer risk. The authors concluded that there is lacking of evidence to say that there is an association between diet acid load or alkaline water and cancer risk. This research is very important to formulate dietary guidelines as explained by authors in the introduction. The manuscript itself is well written and I have only some minor suggestions to improve.</p> <p>In the introduction and other parts of the discussion, the author only mentioned the contribution of vegetables and fruits or mineral component of foods that may make the body acidic, or alkaline, or neutral. But the dietary acid-base balance formulation was also getting emphasized on low protein intake. Thus, I will suggest adding this information both in introduction and discussion.</p> <p>I am wondering that a number of studies conducted so far to assess the association between dietary acid-base load and type 2 diabetes</p>
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	<p>or hypertension, but only one study is on cancer. Although there was no meta-analysis, some good quality prospective studies suggest a relation between dietary acid-base load and type 2 diabetes or hypertension. The author can link these studies somewhere in discussion and also give some future study directions in conclusion.</p> <p>In the discussion, it may not important to explain smoking as a risk factor of bladder cancer rather than acid-base diet because smoking is already recognized as a risk factor for many sites of cancer.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Marialena Trivella

I very much enjoyed reviewing this work. It is well written and conducted and in an uncomplicated manner it responds sensibly to a seemingly growing but essentially unfounded dietary promotion.

Response: Thank you for your careful assessment of this work.

Although I am not knowledgeable in the scientific intricacies of the field of diet and nutrition, I am knowledgeable in the area of systematic reviews, and from the methodological point of view I am satisfied that the authors have been meticulous and objective. There are however, some minor suggestions and issues I would like to highlight.

Abstract: The abstract is usually the first impression of a paper and currently the description of the review inaccurately implies that the conduct of the work may not be methodologically sound and that it is clinically very broad to be of use. In particular combining randomised interventions and observational studies within the same analysis would not be appropriate and although it is clear from reading the review that the authors had no such intentions, the brevity of the abstract points otherwise. Maybe adding the word 'separate' reviews for randomised and observational studies would clarify this. Response: Done

Also, the list of outcomes in the abstract lists 'any outcome of cancer treatment' which would be almost impossible to assess in any systematic review that had a sizeable yield in included studies.

Response: "any" removed

In the abstract results section, it would be helpful to have information on how many studies the search yielded, before the one included was selected, the number of participants in that included study, and brief info on the quality of evidence.

Response: Good suggestion, thank you.

Lastly, the abstract conclusion section, mentions that the review "revealed a lack of evidence for an association...", where in fact there is just a lack of evidence, in that, despite the promotion of alkaline diet by the media, there is no actual research to either support or disprove it. This is different to claiming that there is no evidence of association.

The same comment above applies to the 'Conclusions' section of the main text.

Response: Done

In page 5 – Description of results – The information given for the systematic review found and the narrative studies is somewhat limited. If there is another systematic review out there, how different is it to this one? Where the same outcomes examined? How many studies did it include? What did the narrative reviews explore, and what they concluded?

Response: We have included a description of what the narrative reviews explored and concluded.

The results section is dominated by details of the one included study, and of course this is inevitable

as there is only one study in the review. However, if there were more studies in the review, it would not be possible to describe them all in such detail; in fact the dominance of these details in my view diverts the attention from the essence of the paper. The point of the review, as I see it, is to summarise existing evidence, and if no evidence is found – as is the case here – to highlight the lack of evidence and the discrepancy between the wide promotion of alkaline diet and the lack of research supporting that claim.

Response: Thank you, we agree and reduced the discussion of this one study.

In summary, although the manuscript is methodologically sound, I feel that it needs minor adjustments on the emphasis and extend some of the methods, results, and conclusions are described, so that there is better balance in the paper.

Some other details:

- Page 4 – line 55: I would not classify the Cochrane register as grey literature.
- Page 5-line 32: "... controlled for or > 5.0 ...", is it meant to be an OR (odds ratio?). Not clear what that sentence means
- Page 5 – line 46 and line 52: the same reference is quoted (ref 25). Probably a typo as ref 25 doesn't refer to a systematic review, and is in fact the only included study. It is not also clear whether references 26 and 27 are reviews as is implied in the text.
- Page 7: There is no caption for table 1
- Page 10 – lines 41 to 48. I feel that it is not necessary to refer in particular to one factor (smoking) for one cancer (bladder), in one of the studies considered in discussion.

Response: Thank you, we acted on each of your suggestions as directed.

Reviewer Name: Shamima Akter

The author Fenton et al. conducted a systematic review to evaluate the association between dietary/alkaline water and cancer. The author found only one prospective study that assesses the association between urinary pH and bladder cancer risk. The authors concluded that there is lacking of evidence to say that there is an association between diet acid load or alkaline water and cancer risk. This research is very important to formulate dietary guidelines as explained by authors in the introduction. The manuscript itself is well written and I have only some minor suggestions to improve.

Response: Thank you for your careful assessment of this work

In the introduction and other parts of the discussion, the author only mentioned the contribution of vegetables and fruits or mineral component of foods that may make the body acidic, or alkaline, or neutral. But the dietary acid-base balance formulation was also getting emphasized on low protein intake. Thus, I will suggest adding this information both in introduction and discussion.

Response: We have added a thorough description of the diet in the introduction and discussion, which we hope meets the need you see.

I am wondering that a number of studies conducted so far to assess the association between dietary acid-base load and type 2 diabetes or hypertension, but only one study is on cancer. Although there was no meta-analysis, some good quality prospective studies suggest a relation between dietary acid-base load and type 2 diabetes or hypertension. The author can link these studies somewhere in discussion and also give some future study directions in conclusion.

Response: Thank you for this suggestion. We located 6 prospective studies on relation between dietary acid-base load and type 2 diabetes or hypertension and included a paragraph about them in the discussion.

In the discussion, it may not important to explain smoking as a risk factor of bladder cancer rather than acid-base diet because smoking is already recognized as a risk factor for many sites of cancer.

Response: Removed

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Marialena Trivella University of Oxford, UK
<b>REVIEW RETURNED</b>	22-Feb-2016

<b>GENERAL COMMENTS</b>	I am satisfied that all requested changes have been made. However, there are some typos and occasional errors, and the manuscript would benefit from a fresh read. Also, the second sentence in the objectives of the abstract seems out of place. The sentence describing the outcomes measures, again in the abstract, could be made clearer.
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<b>REVIEWER</b>	Shamima Akter Department of Epidemiology and Prevention National Center for Global Health and Medicine Tokyo, Japan
<b>REVIEW RETURNED</b>	07-Mar-2016

<b>GENERAL COMMENTS</b>	The author Fenton et al. has well revised the paper based on my previous comments. I have only some very minor comments to consider. In abstract, The sentence “ the alkaline diet is also promoted for conditions including diabetes and hypertension” may not well fit in here, because this is not an objective of this study. In the introduction, the authors separated many small paragraphs. You may consider combining the small paragraphs based on the topics covered.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Marialena Trivella

Institution and Country: University of Oxford, UK

Competing Interests: None declared

I am satisfied that all requested changes have been made.

However, there are some typos and occasional errors, and the manuscript would benefit from a fresh read.

Also, the second sentence in the objectives of the abstract seems out of place. The sentence describing the outcomes measures, again in the abstract, could be made clearer.

Response: Thank you very much for your second helpful review. We omitted the sentence that seemed out of place and revised the outcome measures to make them clearer.

Reviewer: 2

Reviewer Name: Shamima Akter

Institution and Country: Department of Epidemiology and Prevention, National Center for Global Health and Medicine, Tokyo, Japan

Competing Interests: None declared

The author Fenton et al. has well revised the paper based on my previous comments. I have only

some very minor comments to consider.

In abstract, The sentence “ the alkaline diet is also promoted for conditions including diabetes and hypertension” may not well fit in here, because this is not an objective of this study.

In the introduction, the authors separated many small paragraphs. You may consider combining the small paragraphs based on the topics covered.

Response: Thank you very much for your second helpful review. We omitted the abstract sentence that did not fit in well, and changed 7 paragraphs in the introduction into 5 paragraphs.