

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effects of Dietary Sodium and the DASH Diet on the Occurrence of Headaches: Results from Randomized Multicenter DASH-Sodium Clinical Trial
<b>AUTHORS</b>	Amer, Muhammad; Woodward, Mark; Appel, Lawrence

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Dr Yannan Jiang The University of Auckland New Zealand
<b>REVIEW RETURNED</b>	05-Oct-2014

<b>GENERAL COMMENTS</b>	<p>In this study, a post-hoc analyses of the DASH-Sodium trial was conducted to investigate the effects on the occurrence of headaches of three levels of dietary sodium intake and two diet patterns. The main study design incorporated a parallel, two-group comparison of diet (DASH vs. control) together with a three-period crossover of the three levels of dietary sodium intake. The primary outcome was systolic blood pressure at the end of each 30-day period of dietary intervention. Headache was collected as one of the side effects via self-administered questionnaires during the last seven days of each feeding period.</p> <p>1. Abstract: As indicated in Figure 1, a total of 412 participants were randomized to the DASH or control diet. The 390 participants who completed symptoms questionnaires in all 3 periods were included in this analysis. The information was not presented clearly, however, in the Participants section.</p> <p>2. Methods: With a randomized crossover design, was there any wash-out period between each of the 30-day sodium feeding periods? Were carryover effects from the previous period expected and therefore included/tested in the GEE model?</p> <p>As a post-hoc analysis of the main trial, was the study powered to detect a clinically significant difference on the occurrence of headaches between sodium levels and diet patterns? Note that all small p-values were close to the nominal level of 5%. Similar issues may also apply to the subgroup analyses.</p> <p>What non-parametric test was used for trends in the frequency of headache by sodium intake? Also, further details are required on the GEE models, e.g. how fixed and random effects were fitted; were adjusted covariates measured at baseline?</p>
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	<p>3. Results: Figure 3 presents the ORs between low and high sodium levels by subgroups in each diet. A value of greater than 1 indicates higher odds of headache with high sodium intake. However, the title says "Odds of headache (low vs high sodium)..." with the estimates of OR all above 1. Is this correct? Note that the ORs presented in Table 3 are in opposite direction.</p> <p>There was no Supplement attached for self-administered symptoms questionnaires, as referred on Page 9.</p> <p>The paper is well written and nicely presented.</p>
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<b>REVIEWER</b>	Teresa Fung Simmons College, USA
<b>REVIEW RETURNED</b>	03-Nov-2014

<b>GENERAL COMMENTS</b>	<p>For many of the questions above, although I selected "yes", it is really "somewhat", which I further explain in my comments to the authors.</p> <p>Interesting study, but there are a number of obvious limitations, which the authors have pointed out.</p> <p>Specific comments: P6, L7 -- to miss work due to headaches, it has to be severe or persistent headaches. Would be more informative if the authors can be more clear about it. At L28, at what range of BP?</p> <p>P9 -- stratified analysis is useful, but do you really have enough power to perform them?</p> <p>Results, first sentence -- the counts are more suitable to be placed at Methods.</p> <p>Results -- when mentioning table 1, please highlight the most interesting results there.</p> <p>P11, L10 -- The urinary sodium and potassium seems to be more relevant in terms of indicating compliance to intervention. Perhaps table 2 can be put as an online supplemental table and mention the results in the text.</p> <p>P11, middle paragraph -- The last sentence is not necessary since there is no association with diet pattern and no interaction with sodium level.</p> <p>Table 1 -- if physical activity data is available, please add to table 1.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

In this study, a post-hoc analyses of the DASH-Sodium trial was conducted to investigate the effects on the occurrence of headaches of three levels of dietary sodium intake and two diet patterns. The main study design incorporated a parallel, two-group comparison of diet (DASH vs. control) together with a three-period crossover of the three levels of dietary sodium intake. The primary outcome was systolic blood pressure at the end of each 30-day period of dietary intervention. Headache was collected as one of the side effects via self-administered questionnaires during the last seven days of each feeding period.

### 1. Abstract:

As indicated in Figure 1, a total of 412 participants were randomized to the DASH or control diet. The 390 participants who completed symptoms questionnaires in all 3 periods were included in this analysis. The information was not presented clearly, however, in the Participants section.

Response: Figure -1 (flow diagram) reflect details of the enrollment, allocation and outcomes with exclusion and inclusion criterion of the trial. The Participants section in the abstract was worded to reflect final number of participants included in the trial.

### 2. Methods:

With a randomized crossover design, was there any wash-out period between each of the 30-day sodium feeding periods? Were carryover effects from the previous period expected and therefore included/tested in the GEE model?

Response: There was no “wash out” period between the 30-day sodium feeding periods.

The Sodium feeding periods were separated by feeding breaks of up to 5 days in duration, which were not intended as “washout” periods.

The potential for carryover effects was unavoidable in this trial, however, since the experimental agent was one’s diet and participants must eat something during these intervals. Hence, statistical (GEE) models were adjusted for carry-over effects from the previous periods.

As a post-hoc analysis of the main trial, was the study powered to detect a clinically significant difference on the occurrence of headaches between sodium levels and diet patterns? Note that all small p-values were close to the nominal level of 5%. Similar issues may also apply to the subgroup analyses.

Response: Since headaches were not the main outcome of the trial, power calculations were not done to detect a clinically significant difference on the occurrence of headaches between sodium levels and diet patterns in the post hoc analysis.

The mean effects as shown in the Table 3 (Odds ratio of headaches by diet and sodium sequence), were consistent despite small/borderline significance.

What non-parametric test was used for trends in the frequency of headache by sodium intake? Also, further details are required on the GEE models, e.g. how fixed and random effects were fitted; were adjusted covariates measured at baseline?

Response: nptrend; an extension of the Wilcoxon rank-sum test (STATA) was used for trends in the frequency of headache by sodium intake. The adjusted covariates used in this analysis were measured at baseline.

### 3. Results:

Figure 3 presents the ORs between low and high sodium levels by subgroups in each diet. A value of greater than 1 indicates higher odds of headache with high sodium intake. However, the title says "Odds of headache (low vs high sodium)..." with the estimates of OR all above 1. Is this correct? Note that the ORs presented in Table 3 are in opposite direction.

Response: Figure 3 and Table 3 are not similar.

Figure 3 NOT only represents the OR's between low and high sodium levels by diet and sodium sequence. Within each diet, the Sodium sequence listed first, is the reference level.

Table 3; is a subgroup analysis showing differences in headache comparing low to high sodium ALONE, within subgroups, in each diet.

There was no Supplement attached for self-administered symptoms questionnaires, as referred on Page 9.

Response: Rightly noted. Uploaded at the BMJ open manuscriptcentral page with revised draft.

The paper is well written and nicely presented.

Reviewer: 2

Interesting study, but there are a number of obvious limitations, which the authors have pointed out.

Specific comments:

P6, L7 -- to miss work due to headaches, it has to be severe or persistent headaches. Would be more informative if the authors can be more clear about it. At L28, at what range of BP?

Response: Indeed. However, the frequency is what hampers the quality of life as mentioned with references.

Literature supports mild to moderate essential hypertension, unrealistic to mention specific BP range.

P9 -- stratified analysis is useful, but do you really have enough power to perform them?

Response: No.

The subgroup analysis were conducted to assess qualitative consistency and benefit-hazard profiles between participants. The results were not the highlight of the manuscript, anyway.

Results, first sentence -- the counts are more suitable to be placed at Methods.

Response: Right. We did mentioned counts in the method section as well. The counts in the results section provide further details not mentioned/desired in methods section.

Results -- when mentioning table 1, please highlight the most interesting results there.

Response: Agreed. However, the basic characteristics were uniquely similar between two diet groups.

P11, L10 -- The urinary sodium and potassium seems to be more relevant in terms of indicating compliance to intervention. Perhaps table 2 can be put as an online supplemental table and mention the results in the text.

Response: Agreed. However, a general reader can question the compliance to intervention and may not be able to browse for additional link.

The authors, agreed to keep table 2 in the manuscript for a quick eye ball check of compliance to interventions.

P11, middle paragraph -- The last sentence is not necessary since there is no association with diet pattern and no interaction with sodium level.

Response: Given numerous comparison groups, mentioned paragraph was added to clarify and correlate results between Table 3 and Figure 2 for ease of read and interpretation.

Table 1 -- if physical activity data is available, please add to table 1.  
Response: Unfortunately, no data was available on physical activity.