

BMJ - Decision on  
Manuscript ID  
BMJ.2017.042924

**Body:**

23-Feb-2018

Dear Dr. Merriman

Manuscript ID BMJ.2017.042924 entitled "An evaluation of the diet-wide contribution to serum urate levels"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Tiago Villanueva  
Associate Editor  
tvillanueva@bmj.com

\*\*\* PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. \*\*\*

[https://mc.manuscriptcentral.com/bmj?URL\\_MASK=9a1ca68ec64344c08b5b1cd8663c14b0](https://mc.manuscriptcentral.com/bmj?URL_MASK=9a1ca68ec64344c08b5b1cd8663c14b0)

**\*\*Report from The BMJ's manuscript committee meeting\*\***

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Jose Merino (chair), Jamie Kirkham (statistician), Elizabeth Loder, Tiago Villanueva, Wim Weber, John Fletcher

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:

This is a secondary analysis of 5 cohorts of data which could be combined once certain 'matching' criteria was taken into account.

I suspect that the description of the methods and the presentation of the results might be a bit tricky for the average BMJ reader. The methods seem appropriate but would benefit from being simplified. Even I was failing to see where some of the results from the text were appearing in the tables (although there was a lot of cross referencing to sup material).

The message in the abstract however seems mostly clear.

-One editor said the message is clear, but the methods are hard to follow, esp. the DWAS.

One also wonders how many gout patients with a diet are in these cohorts. He appreciated the message of the paper, but this is, of course, in unselected populations, and dietary advice in patients with gout might still be clinically relevant.

- Another editor said the paper was a comprehensive effort and will be of interest to patients but felt the paper requires an improved presentation. For instance, he added the table of beta coefficients isn't very friendly for assessing the role of each food item in explaining uric acid.

Moreover, it is pretty common knowledge already that diet plays only a minor role in altering uric acid levels. Dehydration and diuretics seem to account for far more clinically. While genetics may play a much bigger role, you can't alter your genes but you can change your diet. So despite the small impact, beyond attention to medication review and considering allopurinol, dietary advice is still worth giving.

- Another editor did not have strong feelings about the paper. This editor added the message is unlikely to change what is done already, since dietary advice is already given and is probably still worth giving even if the contribution is small.

- Another editor said there is no PI statement or acknowledgment. Since patients are your focus it would be good for you to get their feedback about dissemination materials. e.g. how do they share this message with the real world?

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

Major et al. examined the association of Serum Urate Level (SUL) with individual dietary component in a diet-wide association study (DWAS) and quantified the relevant contribution of overall diet and common genome wide SNPs in determining SUL.

In general, this interesting article adds more information about the influential factors in SUL.

Straight: Well written paper. Decent sample size through combination of five cohorts. Availability of Food Frequency Questionnaires across cohorts. Availability of Genome-Wide Association data.

Critiques:

While overall information about the participants provided by authors, it is not clear how many participants included in final model of each analysis. Since additional exclusion mentioned for each test, is important to show not excluded participants are missed in random. Perhaps a chart that shows flow of participants for each analysis will help.

Authors applied GWAS methodology used for the DWAS, it is fine, yet I do not understand what is the point of correcting for population stratifications in diet data?

For genetic analysis 30 top hit GWAS was selected and a weighted genetic risk score constructed for analysis. It is helpful to explain why authors did not directly use a relatively small panel of SNPs (28 SNP, 30 excluding 2 that did not meet HWE criteria) and instead used an aggregated score.

Authors provided information about the genetic and diet main effect, was there any interaction dietary and genetic componants?

Additional Questions:

Please enter your name: Morteza Bashash

Job Title: Assistant Professor

Institution: Dalla Lana School of Public Health, University of Toronto

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A

HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check-lists/declaration-competing-interests'target='\_new'> (please see BMJ policy)

</a>please declare them here:

Reviewer: 2

Recommendation:

Comments:

Title: An evaluation of the diet-wide contribution to serum urate levels

Reviewer: Nithya Neelakantan  
National University of Singapore

Review comments:

The topic of research is very interesting and the manuscript is well written. I have listed minor revisions (/suggestions) to improve the quality of the article. Also, I have a few queries that require further clarification.

Abstract:

It was stated that the objective was to evaluate the percent variance in serum urate explained by a 'healthy' diet. In fact, the authors have quantified the relative contributions of overall diet quality and genetic variants in determining serum urate levels. Could this be addressed in the abstract?

Materials and Methods:

Page 5: Dietary Assessment

- 1) Each study cohort administered a slightly different food frequency questionnaire, with a differing number of questions and a slightly different list of food items within each question. Did the authors consider portion size into account while converting servings per week? If yes, how were they standardised?
- 2) What is the rationale for creating individual foods and food groups in servings/week instead of servings per day (as the food pyramid or dietary guidelines recommends intakes per day)?

Page 8: Diet Quality Scores

- 1) It is not clear why these two indices were selected for this study among the various indices in the literature (e.g. In a study by Kontogianni et al. 2012, adherence to the Mediterranean diet is associated with lower serum UA levels).
- 2) How did the authors prioritize the foods for inclusion into different levels? For example, alcohol is considered as a strongest risk factor for elevated serum urate. This was included in level 2 along with dairy products. Also, it is not clear whether the authors have distinguished low vs. high fat dairy products.
- 3) Please clarify whether unfavourable foods (for serum urate) such as tomatoes and preserved vegetables (due to high sodium content) were excluded in the most favourable level 4 category?
- 4) Harvard pyramid and healthy eating plate emphasis on inclusion of healthier fats/oils in daily dietary intake. Why was this not considered in the construction of the 'Healthy-Eating' score?
- 5) Lines 41-52: The terminology "minimized" is somewhat confusing. Perhaps, another terminology such as 'unfavourable' can be used to avoid confusion. So, can this be rephrased for better understanding of DASH scoring criteria?

Results:

- 1) It is not clear whether the authors have checked the linearity assumptions for the dietary variables (e.g. alcohol intake has been associated with increased serum urate levels or risk of hyperuricemia in a dose-dependent manner).
- 2) I am not sure why important confounders such as smoking, physical activity, level of education, socio-economic status, and supplement use (e.g. vitamin C) were not accounted for in the multivariate analyses.
- 3) Page 12: line 33: '-3' should be in superscript.
- 4) The DASH score does not include a separate component for alcohol. Therefore, it is recommended to adjust for alcohol intake in the models that involve the DASH score.

Tables and Figures:

Table S4:

- 1) It will be useful to report median (IQR) or (minimum, maximum) for the highly skewed food items.
- 2) CARDIA study: intake distribution of food items seem to be rather low for this cohort as compared with other cohorts. Could you please clarify this?
- 3) Indicate gram or oz equivalent of each serve in the table footnote.
- 4) Indicate number of participants (male & female) in each cohort.
- 5) Include '\*' for candy, peanuts, becon and table sugar

Table S3:

Please clarify whether 'nut' category is missing in the CHS cohort. If not, define the "nut" category. Also, include '\*' for candy as this item was found to be missing in one cohort.

Figure S1:

Please avoid using '-' sign and simply report the number of participants meeting each exclusion criterion

Additional Questions:

Please enter your name: Nithya Neelakantan

Job Title: Postdoctoral fellow

Institution: National University of Singapore

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A

HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check-lists/declaration-competing-interests'target='\_new'> (please see BMJ policy)  
</a>please declare them here:

Reviewer: 3

Recommendation:

Comments:

The paper aims at understanding the impact of food consumption on urate levels. In particular it uses a very large number of samples to test numerous specific food items and two different dietary quality scores to determine if any are responsible for differences in urate levels.

The paper is interesting especially in the comparison of the relative contribution between the genetic factors and the dietary ones.

There are however some major points which should be addressed.

1) The underlying assumption of the paper is that food consumption is a non-heritable trait and that genes are not involved in its determination. This is actually not true as shown in heritability studies and several GWAS especially on Coffee, Alcohol but also food consumption. The introduction and discussion should consider this point. Also, it should be considered that the heritability of food consumption may contribute to the heritability of uric acid and thus the polygenic risk score and dietary measures should be tested together to assess the relative contribution.

2) The authors have analysed the effect of either extremely specific foods or the effects of two general dietary quality measures, however it would be important to analyse also groups in between the two. It would be useful to understand if there is an effect of macronutrient consumption (ie protein or fat) or of food groups (ie fruit, meat, vegetables).

3) Continuing from the previous point, the authors have used a two dietary quality scores as summary of dietary patterns, however these are based on what we think people should be eating and do not reflect actual dietary patterns. Given that the authors were able to derive a correlation matrix between the items, it would be useful to get a data driven measure of true dietary pattern using for example PCA or factor analysis to test more realistic dietary patterns.

4) As in other "WAS" studies independent replication of the results would be needed to give credibility to the findings. These do not necessarily need to come from other cohorts but possibly from previous independent studies. For example the associations with alcohol and sea food have been previously reported, however the one with peanuts have not and it should be replicated before being claimed. It would also be interesting to see a comparison between previously reported effect sizes and the observed ones.

Additional Questions:

Please enter your name: Nicola Pirastu

Job Title: Chancellor's Fellow

Institution: Usher Institute PHSI - University of Edinburgh

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A  
HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check  
lists/declaration-competing-interests'target='\_new'> (please see BMJ policy)  
</a>please declare them here: