31 July 2018

Re: Manuscript ID BMJ.2017.042924.R1 entitled "An evaluation by meta-analysis of the diet-wide contribution to serum urate levels"

Dear Editors

Thank you for considering a revision. This letter accompanies the revised manuscript. Reviewer's comments requiring addressing are in italics below with our response underneath.

Yours faithfully

Tony Merriman and coauthors

Reviewer 1

The methods section is quite long and I wonder also if some of this detail could be placed in supplementary material, for example, the computation of each of the dietary scores. Perhaps an overview of each score is all that is required in the main text.

We have done as the reviewer suggested, with respect to moving dietary score detail to the Supplemental Material. A one-paragraph overview of the dietary score construction remains in the main text (page 9).

To shorten and simplify the methods section we have also shifted other more complex descriptions to the Supplemental Material:

1. The methodology for the diet-wide association study, with a short description remaining on page 8.
2. The methodology for the genetic risk score analysis, with a short description remaining on pages 8-9.
3. The methodology for the genome-wide heritability analysis, with a short description remaining on page 9.

In the main text I would like to see more detail on how the grouping and combining of questions was done across the dietary assessment questionnaires to come to the list of 63 food items with comparable questions, e.g. was this done by one person, multiple persons independently etc. This is important for validation and replication.

The combining of questions was primarily performed by TJM, in consultation with the other authors. New sentences have been added to this section of the methods (page 7) to include this extra detail: "…….with the aim of retaining as many food items as possible, whilst reducing the variability in questions between the five studies. (The decision on which questions were able to be combined were made by a single analyst (TJM) in consultation with the other three authors.)" We have also edited the layout of Table S3 (no content changes) so that each original question is listed on a separate line to make it more obvious which questions were combined in each cohort.

The language in the methods and in places in the results may still be beyond the average BMJ reader. For example in the DWAS section, the authors refer to 'Regression beta-values'. In lay terms, what does the beta-value represent? I would refer to this specifically in the text as the pooled effect estimate representing the 'change in….'
For the particular example referred to we had already provided the lay explanation as part of our response to the reviewer's first point. In addition we:
1. Simplified the legend to Table 1 by transferring the technical explanation of calculation of R2 to the Supplemental material (page 2).
2. Moved the technical explanation of imputation from the legend of Table 2 to the Supplemental Material (page 5).
3. Added better explanatory language in the Table 1 and Table 2 legends.

You use P_Q<0.01 to denote the presence of heterogeneity – do you not mean <0.1? This is evident throughout and table footnotes (in one instance you did not change this from the original p<0.05).
We had used a P_Q cut-off of 0.01 in the original re-submission as we were concerned that a cut-off of 0.05 or 0.10 was too strict when considering multiple-testing. However, after considering the reviewer's point regarding the reliability of Cochrane's Q-statistic to detect heterogeneity we agree that the test is known to have low power to detect heterogeneity and we agree that it would be better to take a more conservative approach. Therefore, we have re-analysed the results that previously had a $P_Q < 0.1$ and ≥ 0.01 with a random-effect meta-analysis. The new beta and p-value for these re-analysed results are highlighted in red in the supplemental tables (Tables S4-S7) with consequent changes to the data presented in Tables 1 and 2. The text throughout the manuscript has been edited to reflect these changes in results and shellfish, table sugar, and tea have been removed from Table 1 as these food items no longer have a significant association in the full, male-only, or female-only cohort.

Results – the study power section is hard to comprehend for an average BMJ reader – what does '>80% power to detect an effect size corresponding to an R2 of approximately 1% mean exactly'. Why is this even important and is this a post-hoc calculation.
Regarding the utility of this information, the power calculation (done pre-hoc after the number of separate food groups was calculated, although we acknowledge that the calculation was re-checked as the experiment-wide *P*-value for significance was adjusted when the final number of food groups changed during the re-submission) was done in the context of the multiple testing inherent in the diet-wide association study. We do appreciate the reviewer's point as to whether or not the calculation was necessary, as the detection of multiple associations, including with known urate-associated foods, indicated that power was sufficient. The calculation would have been more relevant had no associations been detected in the DWAS. Therefore, in the interests of simplifying the paper we have removed the power calculation from the manuscript.

I think the rest of the results are clear. One of the main statements made in the paper is the estimation of diet quality explaining less variability (<0.3%) than hereditary factors (23.9%) in serum urate. It's not clear in the results where this came from – should I be

seeing this result in either of Tables 1 or 2 – this needs bringing to the forefront if this is the main message.
The variance explained by diet quality scores had been presented in Table 2 and explicitly mentioned in the main text. We added a phrase to the existing sentence in the main text (1st paragraph, page 13; "Unadjusted by the genetic risk score….") to direct the reader to the correct row in Table 2. We did similar (2nd paragraph, page 13; "…, unadjusted by any dietary score,….") regarding the genetic risk score. We also bolded these numbers in Table 2.

Regarding the heritability estimate we had removed the data from Table 2 in the previous revision and reported it only in the main text. We have now added the heritability data back to Table 2.

Discussion – Paragraph 2 in the methods discusses QC procedures which resulted in a number of exclusions. In the limitations, it might be useful to explain the potential impact of these exclusions on the results.
We have added two sentences to the paragraph on page 15: "Due to the differing questionnaires between studies some food items were unable to be included. These exclusions may have resulted in this study not including some foods that have real effects on urate, however these exclusions were minimal (several items per study, and none in ARIC). Where the exclusion of a question only occurred in a single cohort (due to non-comparability of the question) it is possible that the analysis of the remaining cohorts had a reduction in power to detect an effect."

Reviewer 2
I still have one minor point, I am not clear why the authors have removed precise p-values and just have indicated <0.001. In my opinion it would be best to keep the precise p-values.
We did this to follow *BMJ* editorial policy. Note that exact *P* values are presented in the Supplementary Tables.

Reviewer 3
Abstract
1. Data-driven methods ('a posteriori' approach) empirically derive underlying dietary patterns using statistical methods such as PCA / factor analysis. Whereas, indices of overall diet quality ('a priori' approach) are typically constructed based on dietary recommendations or international dietary guidelines for the general population. "Data-driven quality score" is a confusing terminology (abstract results: line 48).
In the abstract and throughout we now refer to the data-driven score as a 'data-driven diet pattern'.

2. Since the authors have used both the data-driven and hypothesis-driven methods in this manuscript, it is recommended to mention 'dietary pattern' instead of 'diet quality' (abstract objective: line 10)
Thank-you for this suggestion, we have done this in the Abstract and throughout the revised manuscript.

3. Please correct the typo error in line 50. This should have been "raised" serum urate.
The typo has been corrected.

Materials and Methods
1. Page 30 of 2; line 44 (sub-section: diet quality scores): indicating higher adherence to the DASH diet
We have made this change. (Note that the text is now in Supplemental material, at the end of the 2nd paragraph page 3).

2. Page 31 of 52; lines 12-17 (sub-section: diet quality scores): please clarify whether sex-specific categories of alcohol consumption were considered in the construction of the Mediterranean diet score. What is the definition of moderate alcohol intake (in servings per day or week) and how did you assign the scores for moderate, heavy and no intake?
The method section (now in Supplemental Methods) had already described how alcohol consumption was incorporated into the construction of the Mediterranean diet score, done as described in reference 47 (Panagiotakos et al). Regarding definition of moderate alcohol in the Mediterranean diet there is no clear definition so we removed the word moderate from the Methods and replaced with this text (page 4 Supplemental Methods): "….as the Mediterranean diet considers alcohol intake of greater than 0 and less than 4 servings per week to be favourable." We have added a note to page 4 of the Supplemental Methods specifying that construction of the diet score was not sex-specific: "This definition of alcohol consumption categories was the same between males and females."

3. Page 31 of 52; line 21 (sub-section: diet quality scores): delete repetitive words (i.e., a larger number indicating…)
This has been corrected. (Note that the revised text is now in Supplemental material, at the end of the 1st paragraph page 4).

4. Line 21: indicating higher adherence to the Mediterranean diet.
We have made this change. (Note that the revised text is now in Supplemental material, at the end of the 1st paragraph page 4).

5. Page 31 of 52; line 51: is there are specific name for the derived dietary pattern (i.e., healthy or unhealthy dietary pattern)? What does the maximum value ('71') indicate?
We have endeavoured to minimise the use of healthy / unhealthy with respect to the various dietary patterns. Thus we have chosen to use the name 'data-driven dietary pattern' to refer to the derived dietary pattern. For this dietary pattern the maximum value indicates that the person with this value has a dietary pattern most similar to the dietary pattern defined by factor analysis. In terms of real diet these people reported consuming large amounts of non-citrus juice, soft drink, butter, white bread, pasta, beef / pork / lamb, and chips / popcorn. We have edited the final sentence of the relevant paragraph in Supplemental Methods (page 4) detailing how this diet score was constructed to include

this information: “The resultant data-driven diet score had minimum value of 0 and maximum value of 71, with a larger number indicating that an individual consumed higher amounts of the seven food items used to construct the score.”

Tables: Table 1: please simplify (especially the description of partial R-square analyses) the footnote of table 1. What is the comparison group for beer and liquor and skim milk?
We have simplified the legend in response to Reviewer 1. We are not completely sure about the reviewer’s query regarding the comparison group. We hope that the simplified legend has clarified for the reviewer, regarding the comparison to other published data. The legend now states: “β^ – β-values (μmol/L change in serum urate per weekly serve) from significantly associated analyses from published data in combined men and women: beer and liquor data were obtained from [21]; soft drink data from [50-52]; beef / pork / lamb (meat) data from [19,52]; skim milk data from [52]. Refs [19,21,50] analysed NHANES III and therefore are not independent of our study.” We hope that it is clearer that we included in the Table data from published studies.

Table S4: CARDIA study
1. Please verify the median and maximum values for coffee and tea! (For example, mean ± SD of coffee intake: 12.79 ± 20.97; whereas, the maximum value is 0).
We have corrected these errors.

2. Maximum value of diet soft drink is 184 serves / week in the female cohort. Extreme values are observed for non-citrus juice, white bread (among males), butter and etc. Are they outlier or typo error.
These extreme values are real data, as provided by each of the study cohorts. Consumption frequencies of > 70 serves / week (10 serves / day) were observed for very few participants (n = 182) spread across a wide range of food items [ARIC: food items = 2 (beer, non-citrus fruit), n = 5; CARDIA: food items = 19 (citrus juice, non-citrus juice, coffee, tea, diet soft drinks, butter, non-citrus fruit, white bread, cold cereal, nuts, peanuts, poultry, spinach, winter squash, creamer, margarine, mayonnaise, condiments, table sugar), n = 86; CHS: none; FHS: food items = 6 (non-citrus juice, diet soft drinks, cake / pie, non-citrus fruit, lettuce, table sugar), n = 15; NHANES III: food items = 10 (liquor, non-citrus juice, coffee, tea, diet soft drinks, soft drinks, ice cream, skim milk, white bread, mayonnaise), n = 76] very few participants (n = 25) reported a consumption frequency of > 140 serves / week (20 serves / day) [CARDIA: food items = 6 (coffee, tea, diet soft drinks, butter, condiments, table sugar), n = 13; NHANES III: food items = 4 (non-citrus fruit, coffee, soft drinks, skim milk), n = 12]. No data were excluded as outliers.