PEER REVIEW HISTORY

This paper was submitted to a another journal from 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.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies
AUTHORS	Ayoub-Charette, Sabrina; Liu, Qi; Khan, Tauseef; Au-Yeung, Fei; Blanco Mejia, Sonia; de Souza, Russell; Wolever, Thomas M. S.; Leiter, Lawrence; Kendall, Cyril; Sievenpiper, John L.

VERSION 1 – REVIEW

REVIEWER	Judith Sautner, consultant LK Stockerau, 2. Medical Department Lower Austrian Centre for Rheumatology Stockerau, Austria
REVIEW RETURNED	10-Jun-2018

GENERAL COMMENTS	Dear Editor, thank you for giving me the opportunity to review this paper. General remarks: The topic is interesting, the paper reads well and is written by a team that is experienced in conducting metaanalysis and has already published in this field. Up to now our knowledge concerning the impact of food sources for the development of hyperuricemia and gout mainly dates from epidemiological databases and a limited number of prospective cohort studies. Albeit only three observational studies could be chosen for the meta-analysis, this reflects the scarcity of observation and data in this field - all of which is already mentioned as limitations in the discussion by the authors. Points to consider: - page 8, line 179-181: the authors state, that they did not find prospective cohort studies reporting the association of other food sources of Fructose- containing Sugars (e.g. grain..). In this context it seems appropriate to merely mention a cross-sectional analysis including several thousand individuals also covering cereals: Zykova SN, Storhaug HM, Toft I, Chadban SJ, Jenssen TG, White SL. Nutr J. 2015 May 14;14:49 The authors's disclosure statements are impressingly comprehensive - also in this view, mentioning this paper would

	even enhance transparency. - page 8, line 194: one further Limitation that dates back to the included papers is the fact that the method chosen to diagnose gout dates from 1977 (reference 29) - meanwhile there have been published and established more accurate, appropriate instruments that can be applied without any invasive procedures with high sensitivity and specificity, like f.e. the Nijmegen Score: Kienhorst LB et al, Rheumatology (Oxford). 2015 Apr;54(4):609-14. - page 10, 1. paragraph, line 219: I cannot understand " a protective association" with an RR of 1.76, 95% CI 1.19 -2.60) - contradictory to the RR and the abstract (adverse association). - page 11, discussion, line 256: The authors write about a 207% increased risk - 2 fold increase would be more appropriate in my eyes. - page 11, line 257: ..that fruit juice intake was associated with a 14% increase in risk of incident gout. According to the abstract it should be 76% (1.76). Please clarify. - The included cohorts are caucasians (US and Canada). On page 13, line 302 the authors mention that there are case-control and cross-sectional studies that have shown a protective effect of fruit intake with gout. Both mentioned papers (40 and 41) are conducted in Asian cohorts. This comparison is questionable - and if so, should be clearly adressed in the manuscript. Best regards, JS

REVIEWER	Dr Abhishek The University of Nottingham UK
REVIEW RETURNED	22-Jun-2018

GENERAL COMMENTS	This is an excellent piece of work and should be published. I think the authors should discuss that they did not investigate studies that were not in English language. These studies may also report on dietary risk factors of gout.

REVIEWER	Adriani Nikolakopoulou Institute of Social and Preventive Medicine, University of Bern, Switzerland
REVIEW RETURNED	02-Aug-2018

GENERAL COMMENTS	This is an interesting systematic review and meta-analysis investigating the impact of food sources of sugar on incidence gout. Below are some comments for the authors. • Starting from figure 2, which I understand is the main result of this review, I think some clarifications need to be made by the authors. Most importantly, authors report a pooling summary effect at the end of the forest plot (1.29 [1.05, 1.58]). As this summary effect uses the same studies two and three times, the assumption of independence of studies in meta-analysis is not met. I would thus argue that this summary effect should be removed from the figure and not mentioned anywhere in the paper. Secondly, I do

	not find very clear the different subgroups of participants. Is the same number of cases among groups a coincidence or there is an overlap in the groups? I think this should be clarified. Moreover, if available from the studies, reporting of number of cases and total participants per group of intake in the forest plot would be preferable. Finally, at the bottom of the forest plot the two groups compared need to be mentioned, for example as “favor highest intake”, “favor lowest intake”. • Numbers on figure 1 flowchart do not agree with numbers on figure 1 legend. • What do authors mean with “lowest and highest median quantiles” in page 8, line 189? Do they mean the first and third quartiles? • In Table 1, the same studies appear as having different funding source. • In Table 1, clarify whether age is mean or median. • In page 9, line 179 number of cases with SSBs is 1,533 whereas in figure 2 it is 983. • Page 10, line 208-210: in the subgroup of ‘fruit intake on incident gout’, only two studies with opposite results exist. While authors discuss potential reasons for that in the discussion, I believe they should also comment on it here. Heterogeneity cannot be adequately estimated but it may have important implications on the interpretation of the result. • For the subgroup ‘fruit juice intake on incident gout’ I would recommend reporting also the estimation of the heterogeneity standard deviation. • Page 11, line 219: text says “protective association” but figure 2 shows “adverse association”. • Page 11, lines 234-236: results of dose response relationship are very similar for SSB intake and fruit juice intake despite the fact that the one is marginally significant and the other marginally non-significant. I believe they should not be interpreted as showing something different. • Supplementary figures 1 and 2: a) the pointwise 95% confidence intervals are not shown in the figures but mentioned in the legends b) the second part of both legends repeats the first, I believe authors meant to adjust it for the spline curve model c) please give in parenthesis in the legend the baseline reference dose you mention in the legends. • In the first part of the discussion authors interpret inaccurately their main results; 207% and 14% for SSB and fruit juicy intake respectively are not implied by figure 2.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Judith Sautner, consultant
Institution and Country: LK Stockerau, 2. Medical Department, Lower Austrian Centre for Rheumatology, Stockerau, Austria
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Dear Editor,
thank you for giving me the opportunity to review this paper.

General remarks:
The topic is interesting, the paper reads well and is written by a team that is experienced in conducting metaanalysis and has already published in this field.
Up to now our knowledge concerning the impact of food sources for the development of hyperuricemia and gout mainly dates from epidemiological databases and a limited number of prospective cohort studies. Albeit only three observational studies could be chosen for the meta-analysis, this reflects the scarcity of observation and data in this field - all of which is already mentioned as limitations in the discussion by the authors.

Many thanks for your comment.

Points to consider:

- page 8, line 179-181: the authors state, that they did not find prospective cohort studies reporting the association of other food sources of Fructose- containing Sugars (e.g. grain..). In this context it seems appropriate to merely mention a cross-sectional analysis including several thousand individuals also covering cereals:
Zykova SN, Storhaug HM, Toft I, Chadban SJ, Jenssen TG, White SL.
Nutr J. 2015 May 14;14:49
The authors's disclosure statements are impressingly comprehensive - also in this view, mentioning this paper would even enhance transparency.

We agree that, although we did not find prospective cohort studies investigating other sources of fructose containing-sugars (like grains, sweets, desserts, dairy etc.), this does not mean no other observational study exist investigating these sources. However, since we must follow our *a priori* search criteria, we have not mentioned other types of observational studies in our results not fitting our criteria. But, as the reviewer's mentioned paper is relevant to the topic, we have now discussed under the 'Findings in the context of the literature' section, which now reads: "However, cross-sectional studies suggest that cereal and yogurt may be associated with lower serum uric acid [53]." (page 14, line 332).

- page 8, line 194: one further Limitation that dates back to the included papers is the fact that the method chosen to diagnose gout dates from 1977 (reference 29) - meanwhile there have been published and established more accurate, appropriate instruments that can be applied without any invasive procedures with high sensitivity and specificity, like f.e. the Nijmegen Score:
Kienhorst LB et al, Rheumatology (Oxford). 2015 Apr;54(4):609-14.

Thank you for your comment. We agree that more accurate instruments have been developed since 1977, but this section of our results simply served to describe what the included trials did in their methods. We do not consider it as a limitation of the SRMA as the outcome assessment at the time of the studies (2010 and 2008) was considered standard.

- page 10, 1. paragraph, line 219: I cannot understand " a protective association" with an RR of 1.76, 95% CI 1.19 -2.60) - contradictory to the RR and the abstract (adverse association).

Thank you for pointing this out, it was an oversight. A change has been made. This paragraph now reads: "**Figure 2** shows the relationship between fruit juice intake and incident gout. When comparing the highest to lowest intake, an adverse association was shown for fruit juice intake on incident gout (RR 1.77, [95% CI 1.20 to 2.61]). There was no evidence of significant interstudy heterogeneity (I^2 = 0% [95% CI 0% to 90%], p = 0.54)." (Page 10, line 227).

- page 11, discussion, line 256: The authors write about a 207% increased risk - 2 fold increase would be more appropriate in my eyes.

Thank you for pointing this out. We agree that wording is an important component in knowledge translation. However, since we are also reporting a lower increase risk on fruit juice consumption (77%) in this section, we have opted to report it in percentage instead of fold increase to provide readers with comparable information for determining the increased risk from the intake of these two food sources of fructose-containing sugars.

- page 11, line 257: ..that fruit juice intake was associated with a 14% increase in risk of incident gout. According to the abstract it should be 76% (1.76). Please clarify.

Thank you for your comment. We agree that the correct value should be reported To overcome unit-of-analysis error as pointed out by another reviewer, we have updated our analysis. The corrected RR is now 77% and the change has been reflected in this section (Page 12, line 267).

- The included cohorts are caucasians (US and Canada). On page 13, line 302 the authors mention that there are case-control and cross-sectional studies that have shown a protective effect of fruit intake with gout. Both mentioned papers (40 and 41) are conducted in Asian cohorts. This comparison is questionable - and if so, should be clearly adressed in the manuscript.

Thank you, and we agree with the reviewer's comment and this should be mentioned as the relevance might be limited. The sentence has been modified and the paragraph now reads: "Furthermore, case-control and cross-sectional studies have shown a protective effect of fruit intake with gout albeit in Asian populations [40, 41]; their relevance to the included studies, conducted in a largely Caucasian population, might be limited" (Page 13, lines 310).

Reviewer: 2
Reviewer Name: Dr Abhishek
Institution and Country: The University of Nottingham, UK
Please state any competing interests or state 'None declared': no

Please leave your comments for the authors below

This is an excellent piece of work and should be published. I think the authors should discuss that they did not investigate studies that were not in English language. These studies may also report on dietary risk factors of gout.

Thank you for your kind words. Within the methods section, under the search strategy heading, we have stated that we searched for our studies with no language restriction (page 5, line 110). Our search results included papers in other languages, which we translated for the purpose of study selection and data extraction; none of these non-English studies were able to fit our inclusion criteria.

Reviewer: 3
Reviewer Name: Adriani Nikolakopoulou
Institution and Country: Institute of Social and Preventive Medicine, University of Bern, Switzerland
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is an interesting systematic review and meta-analysis investigating the impact of food sources of sugar on incidence gout.

Thank you for your comment.

Below are some comments for the authors.

- Starting from figure 2, which I understand is the main result of this review, I think some clarifications need to be made by the authors. Most importantly, authors report a pooling summary effect at the end of the forest plot (1.29 [1.05, 1.58]). As this summary effect uses the same studies two and three times, the assumption of independence of studies in meta-analysis is not met. I would thus argue that this summary effect should be removed from the figure and not mentioned anywhere in the paper.

Thank you for pointing this out. This is a valid comment. We have now modified Figure 2 per request and it does not include the summary estimate. Though, we have included an interaction term between food sources of fructose-containing sugar (page 10, line 221). This term has been calculated to overcome a unit-of-analysis error for studies appearing more than once in the same analysis. We divided participants equally among the multiple comparisons and readjusted the log-standard errors (see method section page 6, line 145). This in part overcomes the unit-of-analysis error and allows approximate investigation of heterogeneity between groups (Cochrane Handbook section 16.5.5)

Secondly, I do not find very clear the different subgroups of participants. Is the same number of cases among groups a coincidence or there is an overlap in the groups? I think this should be clarified. Moreover, if available from the studies, reporting of number of cases and total participants per group of intake in the forest plot would be preferable.

Thank you for your comment. The per-quantile cases and participants numbers are not given by all studies. However, the authors report the total cases and participants for each study and this is which we report in our forest plot. The purpose of these numbers is to inform the reader of the relative cases and participants in each study in comparison to another.

Finally, at the bottom of the forest plot the two groups compared need to be mentioned, for example as “favor highest intake”, “favor lowest intake”.

Thank you for the comment. We agree with the reviewer that a clear presentation of the two groups being compared is of utmost importance. In our methods section under statistical analyses (Page 6, lines 142) we stated that we are comparing extreme quantiles (the highest exposure versus the lowest exposure or reference group). We have considered the heading titles suggested by the reviewer; however, our current headings report the association (protective or adverse) with the intake of these food sources of fructose-containing sugars and are less prone to interpretation errors.

- Numbers on figure 1 flowchart do not agree with numbers on figure 1 legend.

Thank you for your comment. We have now made this correction. The new figure legend now reads: “**Figure 1** Summary of evidence search and selection. Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia. Of the 309 studies initially identified, 294 were excluded based on title and/or abstract. The remainder were read in full by two independent reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort studies.” to match the numbers reported in the figure.

- What do authors mean with “lowest and highest median quantiles” in page 8, line 189? Do they mean the first and third quartiles?

We agree that our statement is not clear. Quantile here meaning equal groups, each containing an equal fraction of the population. If the study reported intakes in quartiles (4 groups), these numbers refer to the medians from the first and fourth quartile. If the trial reported intakes in quintiles (5 groups), these numbers refer to the first and fifth quintile. We have changed the wording slightly to make it clearer. It now reads: “medians for the lowest and highest quantiles…” (Page 8, line 196).

- In Table 1, the same studies appear as having different funding source.

Thank you for this comment. We agree that consistency and clarity is highly valuable. We have changed the presentation of the table to avoid confusion.

- In Table 1, clarify whether age is mean or median.

Thank you for this comment. Age is reported as mean, we have added this information to Table 1.

- In page 9, line 179 number of cases with SSBs is 1,533 whereas in figure 2 it is 983.

Thank you for the comment. This has been corrected to reflect what is presented in the figure.

- Page 10, line 208-210: in the subgroup of ‘fruit intake on incident gout’, only two studies with opposite results exist. While authors discuss potential reasons for that in the discussion, I believe they should also comment on it here. Heterogeneity cannot be adequately estimated but it may have important implications on the interpretation of the result.

We agree that heterogeneity importantly impacts result interpretations. We have added the 95% confidence intervals for I^2 in the fruit juice food source only (Page 10, line 230) as this might give additional information. However, since this has already been touched upon in the discussion section, it would be redundant to mention it again in the results. As there were only 2 studies included for the SSB and fruit, we were unable to calculate 95% CI for the I^2 values.

- For the subgroup ‘fruit juice intake on incident gout’ I would recommend reporting also the estimation of the heterogeneity standard deviation.

Thank you for this comment. We agree that this may be more informative, we have now given the 95% confidence intervals for I^2 in the results (Page 10, line 230). However, because there were only 2 studies included in the other food sources, we were unable to calculate 95% CI for the I^2 values.

- Page 11, line 219: text says “protective association” but figure 2 shows “adverse association”.

Thank you for indicating this inconsistency, it was an oversight. This has been corrected.

- Page 11, lines 234-236: results of dose response relationship are very similar for SSB intake and fruit juice intake despite the fact that the one is marginally significant and the other marginally non-significant. I believe they should not be interpreted as showing something different.

Thank you for your comment. We agree that while both results appear to be similar, they are different and individually consistent with their pooled effects. The SSB result is strongly significant ($p<0.001$), while fruit juice is non-significant. Our criteria for significance was p-value<0.05.

- Supplementary figures 1 and 2: a) the pointwise 95% confidence intervals are not shown in the figures but mentioned in the legends

Thank you for your comment. This is strange, as the 95% CIs lines are in the figure. These 95% CIs are solid or dashed 'lines' above and below the estimated dose response RR lines. Perhaps, the reviewer is expecting individual CIs for each study quantile, however, the dose response analysis produces a line or a curve. Individual study RRs are given as bubbles with size accounting for the effect size. Individual CIs for each quantile were not given as it would just mirror the above information, and the graph would have too many individual lines to be interpretable.

b) the second part of both legends repeats the first, I believe authors meant to adjust it for the spline curve model c) please give in parenthesis in the legend the baseline reference dose you mention in the legends.

Thank you for your comment. The changes have been made and the legend (for supplementary figure 2) now read as follows: "Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week. Linear dose response data (solid lines) were modeled using the generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines) were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval for the fitted trend are shown above and below the solid line. Each study was centered to its own baseline reference dose when estimating increasing dose risk."

- In the first part of the discussion authors interpret inaccurately their main results; 207% and 14% for SSB and fruit juicy intake respectively are not implied by figure 2.

Thank you for your comment. We agree, it was an oversight. The corrected RR is now 77% and the changes have been reflected in this section.

VERSION 2 – REVIEW

REVIEWER	Judith Sautner LK Stockerau 2. Med. Department Lower Austrian Center for rheumatology Landstraße 18 A - 2000 Stockerau Austria
REVIEW RETURNED	11-Nov-2018

GENERAL COMMENTS	Dear editorial office, thank you for giving me the opportunity to review the manuscript again! Minor changes have been made and due to some slight changes in the statistics obviously the adverse associations have also changed slightly. Generally I think the manuscript is acceptable for publication now although I would definitely suggest a linguistic review of the paper. Best regards, Judith Sautner

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Judith Sautner
Institution and Country: LK Stockerau 2. Med. Department, Lower Austrian Center for rheumatology, Landstraße 18, A - 2000 Stockerau, Austria
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Dear editorial office,
thank you for giving me the opportunity to review the manuscript again!
Minor changes have been made and due to some slight changes in the statistics obviously the adverse associations have also changed slightly.
Generally I think the manuscript is acceptable for publication now although I would definitely suggest a linguistic review of the paper.
Best regards,
Judith Sautner

Thank you for your comment and review. We have now revised the manuscript for grammatical and linguistic edits and made minor changes to enhances clarity and readability.