

BMJ -  
Decision on  
Manuscript  
ID  
BMJ-2018-  
048332

**Body:** 24-Jan-2019

Dear Dr. Qi

Manuscript ID BMJ-2018-048332 entitled "Habitual glucosamine use is associated with a reduced risk of cardiovascular disease, a prospective study in the UK Biobank"

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.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

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**\*\*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: Sophie Cook (chair), Rafael Perera (statistical advisor), Kamran Abbasi, John Fletcher, Elizabeth Loder, José Merino, Wim Weber, Daoxin Yin.

Decision: Put points

Detailed comments from the meeting:

We thought your study addressed an interesting and important research question. We had the following concerns.

The reviewers point out that the results seem over interpreted. People who take glucosamine are likely to be different to those who don't maybe more health conscious, more likely to exercise etc. Difficult to disentangle this from the glucosamine intake. You did do multiple adjustments and this does seem well done, but we don't know how much glucosamine or for how long these people took this, so it's hard to know what to take away clinically. The main message seems to be "we need a trial to test this hypothesis" rather than "we need more cohorts and trials to confirm this".

We would have liked a longer description of potential side effects associated with glucosamine. We think this might be important to evaluate the impact of the findings.

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.

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:

Overall, this is an interesting study and well-written manuscript, which examined the prospective association between glucosamine use and CVD risk, using data from the large UK Biobank. The authors found a reduced risk for several cardiovascular outcomes associated with regular glucosamine use, after adjustment for a number of potential confounders.

While these results are attractive, I would suggest caution in the interpretation of these findings in terms of potential causation. We have observed several disappointing results from clinical trials of nutritional supplements and chronic disease prevention, despite consistent observational evidence. Hence, I would not over-interpret these results as suggestive of causal effect, but simply as observational associations. Specific suggestions for the authors:

- 1) Please provide sex-stratified analyses, given the large sample size and the need to examine potential sex differences.
- 2) Glucosamine use might represent an overall marker for a healthy lifestyle, so please address this possibility in your discussion.
- 3) Please rule out potential selection bias in your study population, given the large number of excluded participants.
- 4) A major limitation of this study is the lack of detailed information on duration and dose of glucosamine use, which does not allow to explore the nature of this potential association with CVD risk.
- 5) I would suggest to attenuate the interpretation of results, as simple observational findings, thus refraining from any statement suggesting causation.

Additional Questions:

Please enter your name: Saverio Stranges

Job Title: Professor & Chair

Institution: Western University, London, Ontario, Canada

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

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If you have any competing interests <A

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

Reviewer: 2

Recommendation:

Comments:

In this manuscript, Ma et al examined associations of habitual glucosamine use and risk of CVD in the UK Biobank. By involving 466,039 participants, the authors found that habitual use of glucosamine supplement was associated with significantly reduced risks of CVD events. This is a very interesting analysis, nicely conducted and clearly written. I only have some minor comments.

1. This is an observational study and the authro used "reduced risk of CVD". I would suggest to change reduced to lower risk of CVD, as reduce indicates causality.

2. How did the author test interactions for smoking given that smoking had three categories?

Also, given that no interaction for stroke was found, there is pausibility that the interaction for smoking is due to chance. I would suggest downplay this finding by not mentioning it in the abstract.

3. Did the author test the interaction between genetic scores and glucosamine use?

4. The author mentioned that "we could not exclude the possibility of residual confounding or unmeasured biological and social factors". What social factors? A healthy lifestyle might be an important confounder between glucosamine use and risk of CVD, and the author might want to specify it.

Additional Questions:

Please enter your name: Ming Ding

Job Title: Research Associate

Institution: Harvard T.H. Chan School of Public Health

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

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