

Author's response to reviews

Title: Is Plasma Vitamin C an appropriate Biomarker of Vitamin C Intake? A Systematic Review and Meta-analysis

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Author's response to reviews: see over

Dear Editor,

“Is Plasma Vitamin C an appropriate Biomarker of Vitamin C Intake? A Systematic Review and Meta-analysis”

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On behalf of my co-author and myself, I would like to thank you for considering the above manuscript for publication in the *Nutrition Journal*. I also would like to thank the reviewers for their constructive comments.

We reviewed the manuscript for grammar check and revised it based on the comments from the reviewers and a point-by-point response is prepared for your consideration. We appreciate the opportunity to improve the quality of the manuscript based on the Reviewers' comments.

In addition, in Re to the second reviewer comment about the need for a statistical review, I would like to bring to your attention that two of the authors, NAD and LT are assistant and associate professor of biostatistics at McMaster University.

Sincerely,

Mahshid Dehghan

Reviewer No. 1

General comments:

1. The authors have not mentioned that may also account for the low-moderate correlation between dietary-assessed vitamin C and plasma vitamin C is absorption. Vitamin C may bind with other nutrient or non-nutrient components of the diet, and therefore be absorbed less: these foods are often not consumed in isolation, and there is individual variation in their absorption..

These issues are addressed on Page 11, Paragraph -2 as following:

“The literature indicates that the correlation between vitamin C intake and plasma vitamin C improves after adjusting for certain variables and it becomes evident that the diet-plasma relationship may be influenced by the presence of various confounding factors, such as body size, smoking, the use of supplements, bioavailability, multiple sources of nutrients, food processing techniques, and disease status. These factors may inhibit or enhance absorption and affect nutrient circulating concentration”.

2. Additionally, one must also take into account that (even with ‘gold standard’ dietary intake methodologies) there is significant respondent burden in being able to accurately describe what one has eaten, its preparation method and the quantity consumed. Respondents have to be numerically and verbally articulate (to quite a high level) to get good estimates of their intakes. In population-based studies not all participants have these competencies.

We agree with the reviewer on these points and we incorporated the following statements in discussion on Page 12, Paragraph -2.

An observed moderate correlation may be the consequence of uncontrollable confounding factors or due to inaccurate dietary intake measurement. Also, because of the burden of the data collection process on respondents, accurate measuring of dietary intake may be difficult. In addition, the plasma biomarker measures the amount of vitamin C in foods after storage, preparation, digestion and absorption which may also depend on various homeostatic and metabolic mechanisms.

Major Compulsory Revisions:

1. The English grammar in the manuscript needs to be corrected in several places.

We reviewed the whole manuscript for grammar check and proof reading and many changes have been made.

Reviewer No. 2

Major Compulsory Revisions:

Less attention has been paid, at least it is not described in the text, to the method of analysis of vitamin C, including the pre-analytical treatment and storage of the plasma samples. Furthermore it is important that within one study the all samples have been taken at the same hour of the day and preferably not postprandial. It is well-known that the stability of vitamin C heavily depends on the temperature and time between blood withdrawal and centrifugation and the addition of stabilizers. In addition storage condition of the plasma samples (at least $< -70\text{ C}$) are also important to maintain the stability of vitamin C.

In the criteria no attention has been paid to these conditions and possible confounders. The results of the paper will be more valuable and probably more convincing if of each study the following information will be reported in an additional Table:

the analytical method used, pre-analytical information (if available), addition of stabilizers, storage time and temperature between sampling and analysis, the average (or median) vitamin C plasma concentrations, and the time of the day (including variation) of blood withdrawal.

As suggested we included one more table (Table 3) to include the analytical method used, pre-analytical information, addition of stabilizers, storage time and temperature between sampling and analysis, the average (or median) vitamin C plasma concentrations, and the time of the day.