Author's response to reviews

Title: Association between intake of B vitamins and cognitive function in elderly Koreans with cognitive impairment

Authors:

Hyesook Kim (khs7882@hanmail.net)
Ggotpin Kim (bloomk1109@gmail.com)
Won Jang (jangwon1011@naver.com)
Seong Yoon Kim (sykim@amc.seoul.kr)
Namsoo Chang (nschang@ewha.ac.kr)

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Author's response to reviews: see over
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Dear Sir/Madam:

Thank you very much for inviting us to resubmit a new version of the above manuscript (MS 1623147809139371) to your journal. The authors appreciate the valuable comments from the editor and reviewers aimed at improving our manuscript. We have made modifications to the manuscript according to the reviewer’s suggestions. Detailed information regarding the revision is provided in the attached document entitled “Authors’ Responses.”

We hope that we have adequately addressed the reviewer’s concerns and that the resubmitted manuscript is now acceptable for publication in The Nutrition Journal. We look forward to hearing from you regarding the journal’s decision.

Yours sincerely,

Namsoo Chang, Ph. D

Professor
Department of Nutritional Science and Food Management, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul, 120-750, Korea
Cell Phone: 82-10-6513-3468, Office: 82-2-3277-3468, FAX: 82-2-3277-2862
E-mail: nschang@ewha.ac.kr
This is a useful study relating B vitamin intake to various measures of cognitive status in the elderly. Its strengths are that it considers three groups of elderly, normal, those with MCI and those with AD. Furthermore, estimates are made of the intake of 4 different B vitamins: folate, B6, B12 and B2. Minor revision is needed to deal with several issues.

We thank you for your very valuable comments.

1. Throughout the manuscript – including the title - please change ‘vitamin B’ to B vitamins since there is no such thing as ‘vitamin B’

   This has been corrected.

2. Throughout the manuscript, including Tables, change the units for B12 intake to µg/day from mg/day. This is a serious and surprising error.

   This has been corrected.


   As the reviewer suggested, we have added this reference in this section. (Page 4, line 40)


   As the reviewer suggested, we have added this reference in this section. (Page 4, line 40)


   As the reviewer suggested, we have added this reference in this section. (Page 4, line 44)

6. Line 63: replace ‘are’ by ‘have’

   This has been corrected. (Page 5, line 63)

7. Line 112: reference 10 is not correct; I suppose reference 17 was intended

   This has been corrected. (Page 7, line 125)

8. Line 121: split the words ‘ashypertension’
This has been corrected. (Page 7, line 134)

9. Line 125: It is essential here that the paper (ref 17) reporting the plasma vitamin concentrations is referred to here.
   As the reviewer suggested, we have reported our previous paper in this section. (Page 8, line 139)

10. Lines 131-2: It is not clear what is meant here. Should it read "No significant correlation was found between plasma vitamin B12 and intake of any or all of the B vitamins"?
   This has been corrected. (Page 8, line 149)

11. Lines 140-164: It is not necessary to repeat in the text the correlation coefficients and p values since these are all given in Table 3.
   According to another reviewer's suggestion, that under the section of "Correlation between dietary vitamin B intake and plasma concentrations of folate, vitamin B12, and Hcy": please provide the magnitudes of correlation, we have revised this section. (Page 8, lines 139-146)

12. Line 170: remove the second B’
   This has been corrected. (Page 9, line 187)

13. Lines 189-90: The meaning of the sentence 'Excluding a significant difference in plasma Hcy level, no differences in dietary intake of vitamin B2, vitamin B6, vitamin B12 and folate were observed among diagnostic groups.' is obscure. Please rewrite.
   We revised this sentence. (Page 10, lines 206-207)

14. Line 190: It was a UK study, not US
   This has been corrected. (Page 10, line 208)

15. Line 203: add to the citations here the study by Aisen et al. JAMA (2008) 300:1774, which showed that in mild AD treatment with B vitamins did slow cognitive decline, whereas in moderate AD it did not.
   As the reviewer suggested, we have added this reference in this section. (Page 11, lines 221-223)

16. Line 212: In reference 39 the subjects were not stratified for baseline homocysteine, possibly explaining the negative result.
   As the reviewer suggested, we have revised this section. (Page 11, lines 232-233)

17. Line 221: delete the first occurrence of [46-48]
   This sentence has been removed. (Page 11, line 241)

18. Lines 232-243: This whole paragraph should be deleted as it refers to unpublished data and anyway is not relevant to this study.
   As the reviewer suggested, we have deleted this paragraph. (Page 12, line 250)
19. Lines 244-249: This paragraph is superfluous and anyway mentions unpublished data. To clarify this confusion, we have deleted this paragraph. (Page 12, line 250)
AUTHORS' RESPONSES

Reviewer # 2 Bo Qin (Comments to the Author)

The paper describes the association between several B vitamins intake and cognitive function in elderly Koreans. The research question posed by the authors is important since modifiable lifestyle changes e.g. dietary interventions may be effective in postponing the onset of pathological cognitive decline. Results from observational studies on this topic have been inconsistent.

Thank you for your critical comments and helpful suggestions. Please see the response below for the detailed comments.

Major Compulsory Revisions

Regarding the clarity of the research question

1. Please indicate clearly if the B vitamins intake was from diet, or both diet and supplement sources in the methods part and throughout the paper. For example, you can use ‘total folic acid intake’ when referring both sources, or ‘dietary B vitamins’ when only referring dietary sources.

This has been corrected.

2. Separating the analysis by food vs. supplementary sources is necessary. Such information would be helpful for the design of clinical trials and dietary guidelines.

As the reviewer suggested, we presented the additional result by food(diet only) in Table 1~Table 3. (Page 8, lines 158-166; Table 1&2&3)

Methods

3. Please provide brief rationale for the covariates selected to be adjusted in the model. How they were measured should be described in Methods.

As the reviewer suggested, we presented brief rationale for the covariates selected to be adjusted in the model, and we described that how they were measured in method section. (Page 7, lines 108-115; Page 5, lines 77-83)

4. In addition to total energy intake, I did not find other dietary covariates considered in the model. Higher B vitamins intake may represent an overall healthy eating behavior, or may associate with other antioxidants or vitamin intake that may benefit cognitive function. That is to say, the observed association may not be due to B vitamins, but other food/nutrients intake that associate with B vitamins intake. Please address this issue.

We fully agree with this comment by the reviewer that the higher B vitamins intake may represent an overall healthy eating behavior, or may associate with other antioxidants or vitamin intake that may benefit cognitive function. Unfortunately, because the present study data does not include the parameters needed to catch the overall healthy eating behavior, we could not consider this point. However, we performed a further analysis, to eliminate the possible obscuring effects of other factors such as antioxidant nutrient consumption. When we additionally adjusted for intakes of antioxidant nutrient such as vitamin C, vitamin E and b-carotene, the positive association between B vitamins intake and cognitive function still existed. A stronger association was shown in patients with AD compared to normal and MCI subjects. This suggests that the positive association between B vitamins intake and cognitive
function in our study was not likely due to an increased B vitamins intake in these elderly whose antioxidant nutrient consumption was high compared with their counterparts.

5. What was the range of energy intake? Consider to remove outliers if there is any in the sensitivity analysis.
   In our subjects, the range of energy intake was 541.9~2807.6 kcal/d, and the outlier for energy intake does not exist. Therefore, we did not remove the outlier.

Discussion
6. It may be too early to state "supplementation for groups with MCI and AD may be necessary" considering the current analysis did not evaluate the supplementary sources alone, and the cross-sectional nature of the study.
   We fully agree with this comment by the reviewer. To clarify this confusion, we have deleted this paragraph. (Page 12, line 250)

7. Due to the observational nature, please acknowledge residual confounding is possible.
   As the reviewer suggested, we acknowledged residual confounding is possible due to the observational nature. (Page 12, lines 251-254)

8. The authors mentioned that the causal inference was hard to achieve with the current data, which is good, but please spend few sentences to elaborate more: Is reverse causation a potential big concern? e.g. is it possible that patients who were suffering from MCI or AD were more likely to give the advice to take more B vitamin supplements which contributes to the observed association?
   As the reviewer suggested, we revised this section. (Page 12, lines 251-254)

Tables
9. Please provide the mean (SD) value of each test scores in Table 3 to help readers interpret the beta coefficients.
   We fully agree with this comment by the reviewer. To help readers interpret the beta coefficients, we have provided the mean (SD) value of each test scores in Table 3 and Table 4.

Minor Essential Revisions
10. Under the section of "Correlation between dietary vitamin B intake and plasma concentrations of folate, vitamin B12, and Hcy": please provide the magnitudes of correlation.
    As the reviewer suggested, we have provided the magnitudes of correlation. (Page 8, lines 140-146)