Author's response to reviews

Title: Vitamin B12 and folate levels in healthy swiss senior citizens

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Author's response to reviews: see over
Dear Prof. Fulop 

Thank you very much for the helpful comments of the reviewer. They helped to improve our paper substantially. We thoroughly revised the manuscript as suggested. We would be happy if you would consider our revised and resubmitted manuscript for publication. Please find below a point to point reply to the comments.

**Major compulsory revision:**

| I appreciate the corrections performed in the manuscript. However, I still consider the approach problematic. |
| Using the cut-off for holoTC (<35 pmol/L) is at best arbitrary. But it also undermines the potential that the data collected possesses. I believe that the Fedosov equation can be used to established the proportion of healthy Swiss elderly with metabolic B12 deficiency (<-0.5 wellness factor). |
| We left the approach of classifying with holoTc and now present prevalances according to Fedosov’equation, as proposed by the reviewer. |
| The equation has been shown robust to the varying cut-offs of the four single biomarkers when applied separately. If desired, this can also provide cut-offs for the individual biomarkers in the elderly. |
| We have followed this consideration and calculated the optimum decision point by ROC-analysis as originally done by Fedosov in his Metabolism 2011 paper. By this approach we further derived specific and sensitive cut-offs for the individual markers allowing to create zones, where vitamin b12 sufficiency or insufficiency is probable as well as a greyzone. This cut-offs are now given in the new |
Alternatively, the population can be used to generate a reference interval for the elderly for holoTC, just as for the other biomarkers. To my knowledge, reference intervals for holoTC for healthy elderly have not been established on such a large material before. This approach can challenge the approach commonly applied, where cut-offs from one population are mistakenly applied on other populations or population subgroups. And support the use of different reference intervals for elderly.

We calculated reference intervals for the investigated parameters elderly according to the CSLI guideline C28-A3c and now list them accordingly.

**Minor essential revisions:**

1. Background: omit second paragraph. Not relevant
   
   We have omitted this paragraph.

2. Background: the paragraph on the impact of dietary habits could be moved to the discussion
   
   We have removed this text according to the proposition of the reviewer.

3. Methods: it is not so much that assays have acceptable imprecision. It is the actual imprecision in percentage that is interesting to interpret the small numerical differences
   
   We agree. We now mention the imprecision of our assays in the methods section.

4. A discussion on the association between cognitive function in the elderly and B vitamins would be appreciated, given the recent focus on this matter
   
   We have added respective text and references.

5. The flow chart should also include the persons excluded due to medication use.
   
   We have excluded the individuals taking antidiabetic medication, proton pump inhibitors, and supplementation of Vitamin B12 and Folate and now also show this in the flow chart.

Please note that we have adjusted the author sequence.

Please note that the corresponding author to appear on a published paper will be Martin Risch, M.D.

Please note that further correspondence should follow the path used so far with urs.nydegger@risch.ch, the corresponding author during the submission process

Kind regards

Lorenz Risch, MD, senior author

Urs Nydegger, M.D. corresponding author during submission process