original findings. The objection of Huang and Ahronheim that the MMSE and each of the nine measures of general health specified in the RAND Health Survey should not have been adjusted for daily vitamin supplementation because it might have narrowed the difference between the B_{12} deficient group and the normal B_{12} group, while an interesting supposition, is not supported once tested empirically because daily vitamin supplementation for our sample of older veterans did not contribute significantly to moderating the effect of B_{12} deficiency on the MMSE and on general health. Moreover, the objection of Lyons and Yaffe that the mean change in the MMSE resulting from B_{12} deficiency might be caused by an age bias is also not supported once tested empirically because the age of the veterans in our study neither contributed significantly to the prediction of MMSE nor moderated the effect of B_{12} deficiency on the MMSE. We appreciate Lyons and Yaffe's and Huang and Ahronheim's contribution to this effort. However, their concerns have not caused us to change our position regarding the basic findings from our original article.[1] Rather, we believe the additional analyses that we present here make our original findings even stronger.

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URINARY METHYLMALONIC ACID/CREATININE RATIO: A GOLD STANDARD TEST FOR TISSUE VITAMIN B_{12} DEFICIENCY

To the Editor: I read with interest the article by Bernard et al.[1] To assess the relationship of vitamin B_{12} deficiency to cognitive impairment and general health in older veterans properly, it is necessary to identify accurately individuals with tissue B_{12} deficiency. Physicians should be aware that the urinary methylmalonic acid (MMA)/creatinine ratio test is the "gold standard" for identifying true vitamin B_{12} tissue deficiency.[2,3]

Matchar et al.[4] determined that the serum B_{12} assay had only a 22% positive predictive value for a below normal serum B_{12} measurement and Sabloff et al.[5] showed by prospective evaluation that only eight of 28 individuals with below normal B_{12} were affected by treatment. Similarly, the serum B_{12} assay lacks sufficient sensitivity to identify some individuals with tissue B_{12} deficiency. Only 18 of 35 (51%) older subjects found B_{12}-deficient as a result of high urinary MMA had below normal serum B_{12} levels.[2]

The serum MMA test has not been evaluated adequately for specificity. As recently reported, false high values have been reported for individuals exhibiting conditions of renal insufficiency, thyroid disease, pregnancy, small bowel bacterial overgrowth, hemoconcentration, and for unexplained reasons.[6] In a recent evaluation for vitamin B_{12} status of two totally vegetarian (vegan) families, the serum MMA test was found to be less sensitive than the urinary MMA/creatinine ratio test.[7] The urinary MMA test identified seven of eight as having tissue deficiency, whereas the serum MMA assay showed only five of eight to be B_{12} deficient. Of particular interest and importance in this study, the only individual with neurologic manifestations (mild numbness in one hand) who responded to vitamin B_{12} therapy exhibited elevated urinary MMA but normal serum MMA and normal serum vitamin B_{12}.[7]

There is a need to evaluate vitamin B_{12} deficiency in the population accurately because millions of Americans apparently have tissue vitamin B_{12} deficiency and may respond to treatment if it is identified in time. The urinary MMA/creatinine ratio test requires only a random, spot urine specimen and provides a non-invasive means to screen and accurately identify individuals who could benefit from vitamin B_{12} therapy.

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Editors note: The above letter was referred to the authors of the original paper, and their reply follows.

In reply: We appreciate Dr. Norman's feedback on our article.[1] However, after reviewing the available evidence,[2–6] we found that there is no 'gold standard' test at this time that will identify true vitamin B_{12} tissue deficiency. The most commonly used standard is serum methylmalonic acid and/or homocysteine elevation greater than 2 standard deviations, as was utilized in our study[1] and as has been utilized in several other clinical studies.[7–10] There are limitations to these measurements, as pointed out by Dr. Norman. However, we find no evidence of consensus on a gold standard for measuring tissue vitamin B_{12} deficiency. If anything, the leaning is toward serum assessments.[11]