Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline

Dear Sir:

Walker et al (1) recently reported that that long-term daily supplementation of folic acid and vitamin B-12 promotes performance on immediate and delayed memory but not processing speed among community-dwelling older adults with elevated psychological distress (1). The authors argued that folic acid + vitamin B-12 supplementation may have a greater effect on processes within the hippocampus and its functions than on other processes or areas that are more connected to processing speed, and the relations may explain their trial findings.

I would like to propose that the coexistence of positive and negative findings from this trial can be explained by the differential effects of folate and homocysteine on the brain and the changes in folate and homocysteine concentration during the intervention period. Folate and vitamin B-12 influence the brain with their roles in one-carbon metabolism, whereas homocysteine exerts direct detrimental effects to the brain through vascular and neurotoxic mechanisms (2). In older adults, it has been reported that blood concentrations of folate and homocysteine are associated with different domains of cognitive function (3). For folate, higher concentrations are associated with better memory, whereas for homocysteine, higher concentrations are associated with slower processing speed (3). Interestingly, this pattern coincides with findings from the study by Walker et al (1).

Walker et al (1) found that the concentrations of folate and vitamin B-12 increased after intervention but supplementation of B vitamins failed to lower plasma homocysteine concentrations. On the contrary, homocysteine concentrations increased from 9.6 to 10.4 μmol/L. Because homocysteine was not lowered in the intervention group, the negative finding on processing speed is not unexpected.

Given the above, I would suggest that the authors conduct a stratified analysis based on baseline homocysteine concentrations: B vitamins may lower homocysteine and improve processing speed only among trial participants with suboptimal homocysteine status at baseline. Furthermore, given the existing evidence on micronutrient and gene interaction (4, 5), the authors may wish to conduct further analyses to examine potential influences of the apolipoprotein E (APOE) genotype.

The study by Walker et al (1) adds important evidence to the literature on the value of B vitamin supplementation in prevention of cognitive decline. The use of high-dose B vitamin supplements did not slow cognitive decline in patients with Alzheimer disease (6), and contradicting results were reported from 2 randomized controlled trials that were conducted in healthy older adults (7, 8). More recently, Smith et al (9) showed that the accelerated rate of brain atrophy among elderly persons with mild cognitive impairment can be slowed by treatment with homocysteine-lowering B vitamins. Because of methodologic differences in study designs and in selection criteria of trial participants, it is impossible to compare previous trials directly and no definite conclusion could be drawn.

Folate as a supplement is cheap, safe, and likely to be accepted by patients as a preventive measure. Evidence-based folate supplementation in routine clinical practice and prevention programs will have enormous potential impact for health care savings and societal welfare. More research in this area is needed.

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Reply to L Feng

Dear Sir:

I am writing on behalf of the authors of Walker et al (1) in response to Feng’s letter. We followed Feng’s suggestion and conducted a basic stratified analysis according to baseline homocysteine concentrations, classifying participants as having low or high (≥10.4 μmol/L in women and ≥11.4 μmol/L in men) homocysteine concentrations based on the criteria identified by Selhub et al (2). In our randomized controlled trial in 900 community-dwelling adults aged 60–74 y with elevated psychological distress, 225 (25%) met criteria for high homocysteine concentrations, including 108 (24.2%) in the folic acid and vitamin B-12 (FA + vitamin B-12) condition and 117 (25.8%) in the placebo condition. The outcomes investigated were the Telephone Interview for Cognitive Status–Modified (TICS-M; 3), the Brief Test of Adult Cognition by Telephone (BTACT, a measure of processing speed; 4), and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; 5). The following subscales of the TICS-M were also examined: orientation, immediate recall, delayed recall, and attention/calculation.

Results indicate that in the group with high homocysteine concentrations, FA + vitamin B-12 supplementation was significantly associated with subsequent performance on the TICS-M total (F2, 179.6 = 5.46, P = 0.005), the TICS-M immediate recall (F2, 187.0 = 3.67, P = 0.027), and the TICS-M attention/calculation (F2, 194.6 = 5.16, P = 0.007). Specifically, TICS-M total and TICS-M immediate recall were significantly higher for the FA + vitamin B-12 supplementation group at 24 mo (total: t180.0 = 2.70, P = 0.008; immediate: t184.1 = 2.14, P = 0.033) but not at 12 mo (total: t198.7 = −0.72, P = 0.470; immediate: t202.4 = −0.53, P = 0.598) compared with the placebo condition. However, TICS-M attention/calculation scores were significantly lower for the FA + vitamin B-12 supplementation group at 12 mo (t205.1 = −2.0, P < 0.050) but not at 24 mo (t186.7 = 1.82, P = 0.071) compared with the placebo condition.

There were no significant effects of FA + vitamin B-12 supplementation in the low-homocysteine group. The effect on TICS-M delayed recall in the full sample was not replicated in either of the homocysteine subgroups, which may have been attributable to the reduced power in the smaller subsamples. There were no other significant effects of FA + vitamin B-12 supplementation in the stratified analyses, including TICS-M orientation, BTACT, or IQCODE. The poorer performance in attention/calculation scores in the high-homocysteine group who received B vitamin supplementation may warrant further investigation, although there was no difference in performance at 24 mo.

Unfortunately, we did not conduct genetic testing as part of the trial, so we cannot examine interactions with apolipoprotein E genotype in this sample. However, these additional findings provide some evidence that the effects of B vitamin supplementation may indeed be specific to those who initially have suboptimal homocysteine status. Yet, the pattern of findings failed to confirm the specific hypothesis of Feng that processing speed would be poorer for those with elevated homocysteine concentrations. Further research in population-based and clinical samples and reviews of existing studies in this area may provide additional insight into the circumstances in which B vitamin supplementation is most effective. In particular, research examining mediators and moderators of folate response is needed to identify subgroups who stand to benefit most from folate supplementation.

Finally, in interpreting our results it should be noted that the units for serum vitamin B-12 on page 198 and in Table 1 of our article should be pmol/L not nmol/L (ie, picomole/L not nanomole/L).

The author did not declare any conflicts of interest.

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Are nonsignificant differences between SFAs and oleic acid truly indicative of equality or masked by methodologic errors?

Dear Sir:

Voon et al (1) in their article that appeared in a recent issue of the Journal suggested similarities in outcomes of diets enriched with palmitic or lauric + myristic fatty acids compared with an oleic acid–rich diet and concluded that SFA-rich diets do not alter postprandial or fasting plasma homocysteine and inflammatory markers. Their findings suggest that SFAs do not contribute to the inflammatory milieu of risk associated with cardiovascular disease. We believe that some of these conclusions are not supported by data that they provided.

There appears to be confusion throughout their article in reporting plasma “apo A-100” and “apo B-1” outcomes. We suggest that the authors are referring to apo A-I and apo B-100 because these