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Dietary Supplements for Brain Health

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In Reply Dr Smith and colleagues take issue with a statement in our Viewpoint,¹ suggesting that in select patient groups, cognitive decline may be prevented or slowed with supplements. The authors cite data from the VITACOG trial, which found that participants with mild cognitive impairment and higher Hcy levels who received supplemental B vitamins showed slower brain atrophy in regions affected by Alzheimer disease compared with patients who received a placebo. Secondary analyses suggested links between neuroimaging findings and clinical and cognitive outcomes.² While we encourage the rigorous approach of the VITACOG study, there are study design limitations to consider when interpreting these data as supporting supplement use to prevent or slow cognitive decline.

The VITACOG study used gray matter loss as a primary outcome, stating that neuropsychological testing “is subject to short-term fluctuations, practice effects and intra-/ interrater variability.”² Objective, comprehensive measures of cognitive and functional decline represent the standard by which such interventions should be judged. Drug trials in patients with Alzheimer disease, including the recently terminated aducanumab phase 3 studies, have repeatedly demonstrated the risk of extrapolating effects on surrogate outcomes, such as neuroimaging measures, as proof of efficacy.³ Furthermore, atrophy in the noted brain regions is not specific to Alzheimer disease and can be seen in other neurologic conditions. It is also unclear how participant demographics and baseline plasma measures may have influenced the neuroimaging findings because these measures were not reported within the treatment subgroups by Hcy levels.² Also, VITACOG participants were clinically heterogeneous, with diagnoses of mild cognitive impairment possibly deriving from a spectrum of causes. Mild cognitive impairment was determined through telephone-based cognitive screening scores compared with local normative data that were not apparently corrected for education level rather than formal neuropsychological testing in a controlled setting. Participants were not excluded for confounding medical conditions or reversible causes of cognitive change. Participants with low-normal B₁₂ levels were included, which

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can cause symptoms and raise Hcy levels.^{2,4} Participant selection did not aim for a common underlying neuropathology of Alzheimer disease based on neuropsychological testing profiles and/or biomarker confirmation.¹

We agree with Smith and colleagues that nutrition is important to cognitive functioning. Symptomatic patients with a documented vitamin B₁₂ deficiency or low-normal levels may benefit from supplementation by a licensed clinician; this is the standard of care for patients with cognitive issues.⁴ However, the efficacy of supplements without a nutritional deficiency remains questionable. A review of the effectiveness of over-the-counter supplements for brain health concluded that the “evidence is insufficient” at this time to show the benefit of combined B vitamins in patients with mild cognitive impairment based on limited study data.⁵ Further research is needed to replicate and build on the VITACOG work. Such well-designed studies on claimed brain health supplements are needed, and contrast with the unknown data quality substantiating many direct-to-consumer–marketed supplements. Supplement manufacturers are not legally required to provide efficacy data to the US Food and Drug Administration, and a US Department of Health and Human Services report determined supplement claims were often “inconsistent with FDA guidance” for “competent and reliable scientific evidence.”⁶

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