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B vitamins and cognitive function: do we need more and larger trials?[1,2]

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The failure to directly translate promising observational associations between disease and intakes or blood concentrations of vitamins into effective chemoprevention or clinical treatment modalities is not new. The first major disappointment came a decade ago after studies of β-carotene and lung cancer (1). Contrary to expectations, the large Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and Carotene and Retinol Efficacy Trial showed that this provitamin may increase lung cancer rates and all-cause mortality. Also, a recent meta-analysis of cardiovascular disease trials showed that high doses of vitamin E could increase all-cause mortality (2).

There is a clear association between total homocysteine (tHcy) concentrations and cardiovascular disease, and a series of large randomized clinical trials in patients with coronary heart disease or stroke are ongoing and a few studies have been completed. In these trials, the effects of treatment with folic acid in combination with vitamin B-6 and vitamin B-12 were compared with those of placebo. A large study of stroke patients in the United States showed no beneficial effect of B vitamins (3). In patients undergoing coronary angioplasty, one trial showed a clear reduction in restenosis (4), whereas another trial showed an increase in restenosis (5) with B vitamin therapy.

On the positive side, solid evidence from randomized trials and intervention studies has shown that folic acid prevents neural tube defects (6). This knowledge provides the basis for recommendations that women take folic acid if they plan to become pregnant and early in pregnancy and is why food-fortification programs have been implemented in several countries in North and South America.

Observational studies, including a recent investigation in 2871 subjects (7), have consistently reported that an elevated concentration of tHcy in serum or plasma is a risk factor for dementia and impaired cognitive function (8). This association has been explained by neurotoxic effects of homocysteine or the ability of elevated homocysteine to cause vascular lesions. Alternatively, the effects are mediated by the impaired function of the B vitamins involved in homocysteine metabolism, including vitamin B-12, folate, and vitamin B-6. Impaired vitamin B-12 status is known to be prevalent among the elderly, and vitamin B-12 deficiency may cause severe myelopathy and also prominent mental symptoms and memory loss (9). Poor folate status has been associated with depression and dementia in the elderly, and folate metabolism is linked to a variety of neurochemical processes (10). Vitamin B-6 status declines with age, and low blood concentrations of vitamin B-6 have been associated with impaired cognitive function and Alzheimer disease. Such associations could be explained by the involvement of vitamin B-6 in the synthesis of several neurotransmitters (11).

However, recent Cochrane Library reviews of randomized trials with folic acid, vitamin B-12, and vitamin B-6 provide no evidence of any improvement of cognition or dementia (11–13). The Cochrane reviewers, however, concluded that the current evidence was based on small trials and that the research question was sufficiently important to motivate more randomized trials.

In an elegant study from Sweden in this issue of the Journal, Lewerin et al (14) failed to show any effect of a combination treatment with folic acid, vitamin B-6, and vitamin B-12 on cognitive function or movement performance tests among elderly community-dwelling men and women. They conducted a double-blind, placebo-controlled randomized trial with 126 subjects allocated to the intervention and 69 subjects allocated to placebo. Their study also had an observational component, which showed strong relations of plasma tHcy and serum methylmalonic acid (MMA) with movement and cognitive performance tests.

The Swedish authors used an impressive panel of tests that assessed movement and cognitive performance in elderly subjects. The authors noted different associations between tHcy and MMA and different aspects of movement and cognitive performance. However, multiple comparisons of independent variables in a limited number of subjects may produce chance findings. Therefore, one should be cautious when interpreting the data and associations in terms of specific biological mechanisms.

The authors discuss their results relative to those of the now retired professor Ranjiit Kumar Chandra (15). Their failure to reproduce Chandra's results is not surprising in light of the recent controversy surrounding his research, which has received considerable attention both in the media (16) and in prominent medical journals (17).

When should we stop pursuing a treatment option with more randomized trials? Neither previous meta-analyses nor the single trial published in this issue of the Journal found evidence that B

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vitamin treatment improves cognitive function and dementia. Before we conclude that this treatment option should be abandoned, several other issues need to be addressed.

First, is the observational and mechanistic evidence sufficient to justify further trials? The rationale for the studies that have been conducted is solid. Strong associations have been established between tHcy, Alzheimer disease risk, and cognitive dysfunction in several high-quality epidemiologic studies (8). The suggested mechanisms are biologically plausible, as indicated above.

Second, were the previous trials adequately powered to study the effects of vitamins on the study outcomes? The Swedish investigators did not provide information on how their sample size was determined. Calculations of sample size are routinely carried out before a trial is conducted, and it is recommended that such calculations be reported together with the study results (18). Only large trials can show important but smaller therapeutic gains relative to placebo. It is to be anticipated that much larger trials than those published so far are needed to establish or dismiss the role of B vitamin therapy in this area.

Third, were the doses and duration of the vitamin supplementation adequate? In terms of metabolite response, the doses used in the Swedish study seemed adequate. However, the doses required to normalize central nervous functions may be different from those that reduce concentrations of tHcy or MMA in blood and could be related to both the duration of therapy and the extent of vitamin depletion. A short-term trial may fail to show both efficacy and side effects. We suggest that future trials consider treatment over several years. Ideally, treatments should be tested as preventive measures and in persons with various degrees of functional impairment.

Fourth, designing the trial as a 2×2 or higher-order factorial trial might allow the investigators to gain additional information on the treatment efficacy of other vitamins or drugs without increasing cost. Such a design also allows the use of a commercial arm and a noncommercial (vitamin) arm and cofunding with industry. With scarce public resources and little commercial incentive to pursue research on vitamins, such a strategy—which has been used successfully in studies such as the Heart Protection Study (19)—might be the only way to fund needed future large vitamin trials.

Finally, because safety issues concerning the use of folic acid have been raised recently (20, 21), we suggest that future trials involving treatment over several years include monitoring of cancer outcomes.

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