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Homocysteine, B vitamins, and the risk of dementia[1,2]

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INTRODUCTION

The "homocysteine hypothesis" of Alzheimer disease was prompted by the observation in a case-control study that patients with Alzheimer disease had significantly higher serum concentrations of homocysteine, a sulfur-containing amino acid previously linked to the risk of cardiovascular disease (CVD), than did control subjects (1). More recently, however, some prospective cohort studies also reported that persons with elevated serum homocysteine concentrations have a significantly greater risk of developing dementia than do persons without elevated homocysteine (2, 3), but the results have not been entirely consistent (4). It is unclear whether low vitamin B-12 or folate status was responsible for the greater risk of dementia or cognitive decline associated with elevated serum homocysteine concentrations in those studies. In this issue of the Journal, Haan et al (5) report significant associations of dementia or cognitive impairment with elevated plasma homocysteine concentrations in a 4.5-y follow-up of a cohort study, conducted after the introduction of mandatory folic acid fortification in the United States, of 1779 Mexican Americans aged ≥60 y. The study by Haan et al found twice the risk of dementia or cognitive impairment associated with elevated homocysteine (hazard ratio: 2.39; 95% CI: 1.11, 5.16). The report also suggested a U-shaped association of dementia or cognitive impairment with plasma concentrations of vitamin B-12, but no association with red blood cell folate concentrations was found. The results of this study are important for 3 reasons. First, Haan et al provide evidence that the associations of dementia or cognitive impairment with elevated homocysteine may be explained by reduced vitamin B-12 status rather than by reduced folate status. Second, the U-shaped association of dementia and cognitive impairment with vitamin B-12 may be an artifact, but, if real, it may add to previously reported concerns about the safety of mandatory folic acid fortification in older people with vitamin B-12 deficiency. A population survey of older persons carried out in the United States after the introduction of folic acid fortification in North America found that persons with low vitamin B-12 status appeared to have a significantly more rapid deterioration in cognitive function in a setting of very high intakes of folic acid (6). Third, if Haan et al had measured plasma holotranscobalamin (the active fraction of vitamin B-12) or methylmalonic acid (specific metabolite of vitamin B-12), rather than total vitamin B-12, they may have found stronger associations of dementia or cognitive impairment with impaired vitamin B-12 status than those reported in the current study. A recent study of 1000 older persons living in the United Kingdom reported strong, independent associations of cognitive impairment with low serum concentrations of holotranscobalamin and with high concentrations of methylmalonic acid or homocysteine—associations all of which were significantly stronger than those with standard serum measurements of vitamin B-12 (7).

Because homocysteine concentrations are easily lowered by dietary supplementation with folic acid and vitamin B-12, several large-scale randomized trials in persons at high risk of CVD were initiated to test the hypothesis that lowering homocysteine with folic acid (and other B vitamins) could reduce the risk of recurrent CVD (8). Many of these trials also included some assessment of cognitive function. These homocysteine-lowering trials for prevention of CVD were designed at a time when the association of homocysteine with the risk of ischemic heart disease (IHD) and stroke was thought to be somewhat stronger than is currently believed (9). In 2002, the Homocysteine Studies Collaborative Group reported the results of a meta-analysis of prospective studies of homocysteine and risk of IHD and stroke that included 1855 IHD events and 435 stroke events (8). Among these studies, after adjustment for established IHD risk factors, a 25% lower (typically, 3 μmol/L lower) blood homocysteine concentration was associated with an 11% (95% CI: 4%, 17%) lower risk of IHD and a 19% (95% Cl: 5%, 31%) lower risk of stroke. In light of the more modest effects of homocysteine on the risks of IHD and stroke in the observational studies, the principal investigators of the homocysteine-lowering trials have agreed to participate in the B-Vitamin Treatment Trialists' Collaboration, a prospective meta-analysis of all the large-scale trials of B vitamins for the prevention of IHD and stroke.

Twelve large trials (involving a total of 52 000 participants) are currently assessing the effects of B vitamins on the risks of IHD and stroke; results have already been published for 4 of these trials (11–14), involving 14 000 participants. A meta-analysis (10) of the published results of these 4 trials found no beneficial effect of B vitamins on the risk of IHD [odds ratio (OR): 0.99; 95% CI: 0.88, 1.10] or stroke (OR: 89; 95% CI: 0.76, 1.05) or on the combined risk of IHD and stroke (OR: 0.98; 95% CI: 0.90, 1.08), but even the combined analysis of these 4 trials lacked the power to detect a 10% difference from the IHD risk predicted by the observational studies. However, the CIs around the ORs for

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the summary estimates of all 4 of these trials are compatible with a 10% difference from the risk of IHD and a 20% difference from the risk of stroke associated with a 25% lower homocysteine concentration predicted by the observational epidemiologic studies (9). Hence, a prospective meta-analysis of all 12 completed and published trials of B vitamins for the prevention of IHD and stroke involving individual patient data from ≈52 000 participants—that can adjust for the varied duration of treatment and definition of events —should ensure that reliable information emerges on the relevance of B vitamins for prevention of IHD and stroke (8).

None of the large homocysteine-lowering trials for the prevention of cardiovascular events can distinguish the independent effects of vitamin B-12 from the independent effect of folic acid. To address the management of an elderly population that has biochemical evidence of vitamin B-12 deficiency in the absence of symptoms, additional randomized evidence should be sought for the effects of daily oral dietary supplements with ≈1 mg vitamin B-12 in persons aged ≥70 y without prior vascular disease, anemia, or cognitive impairment. The results of these trials are required before recommendations can be made about the use of B vitamins for the prevention of dementia, but it may be prudent to exclude vitamin B-12 deficiency in patients with suspected dementia or cognitive impairment.

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