Vitamin B-12 and cognition in the elderly\textsuperscript{1-4}

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ABSTRACT
Vitamin B-12 deficiency is often associated with cognitive deficits. Here we review evidence that cognition in the elderly may also be adversely affected at concentrations of vitamin B-12 above the traditional cutoffs for deficiency. By using markers such as holotranscobalamin and methylmalonic acid, it has been found that cognition is associated with vitamin B-12 status across the normal range. Possible mediators of this relation include brain atrophy and white matter damage, both of which are associated with low vitamin B-12 status. Intervention trials have not been adequately designed to test whether these associations are causal. Pending the outcome of better trials, it is suggested that the elderly in particular should be encouraged to maintain a good, rather than just an adequate, vitamin B-12 status by dietary means. \textit{Am J Clin Nutr} 2009;89(suppl):707S–11S.

INTRODUCTION

Long before it was recognized that deficiency of cobalamin (vitamin B-12) was the cause of pernicious anemia, Addison (1849) noticed that “the mind occasionally wanders” in his patients [cited by McCaddon (1)]. At the beginning of the 20th century there were several reports of mental symptoms in patients with pernicious anemia and in 1913 Barrett (2) also described histopathological changes in the cerebral cortex, notably neurodegeneration and damage to the white matter and blood vessels. While there were many subsequent confirmatory reports of cognitive deficits in pernicious anemia patients, it was not until the 1950s that dementia was first associated with low cobalamin status independently of pernicious anemia (3). Although the concept of a reversible dementia due to cobalamin deficiency became widely acknowledged, in fact there was little evidence that vitamin B-12 treatment improved cognitive status in patients with dementia, in contrast to the dramatic improvement in hematological signs after treatment of patients with pernicious anemia (4). An excellent historical account of this topic can be found in the review by McCaddon (1).

In this short survey we will focus on 3 questions:

1) What is the evidence that concentrations of vitamin B-12 within the usually accepted normal range are associated with cognitive deficit in the elderly?
2) What are the possible biological mechanisms that could mediate an effect of low cobalamin concentrations on the brain?
3) Can any of the cognitive deficits associated with low cobalamin status be reversed by treatment with vitamin B-12 and, if so, are there implications for public health policy?

LOW-NORMAL VITAMIN B-12 STATUS AND COGNITIVE IMPAIRMENT

The idea that low-normal concentrations of vitamin B-12 might be associated with cognitive impairment was raised by Bell et al (5) in 1990 and clearly expressed by Rosenberg and Miller (6) in their seminal review 2 y later, where they wrote: “For most people, including elderly people, overt vitamin deficiencies are unlikely; it is more likely that mild or ‘subclinical’ vitamin deficiencies may play a role in the pathogenesis of declining cognitive function in aging” (p 1238S). However, a recent systematic review (7) has concluded that “The evidence from longitudinal cohort and case-control studies suggests that there is no significant association between blood concentrations or the dietary intake of vitamin B-12 and cognitive test performance or Alzheimer’s disease” (p 1793). Another review found 6 prospective studies, which included 4607 subjects, that reported an inverse relation between cognitive deficit or dementia and vitamin B-12 intake or blood concentrations but also found another 10 studies, involving 7537 subjects, that found no association with vitamin B-12 status (8).

How are we to explain these discrepancies? First, we must remember that cognitive impairment is common and has many possible causes and there is no reason why it should always be associated with low vitamin B-12 status. Hence, we should look for evidence of cognitive impairment in those with low vitamin B-12 status, rather than for low vitamin B-12 status in those with cognitive impairment. Second, cognition can be assessed by many different tests and we do not know which cognitive domain(s) may be particularly associated with vitamin B-12. In their systematic review, Raman et al (7) noted that 30 different cognitive testing methods had been used in the reports that they

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examined. Third, we do not know if the association between low vitamin B-12 concentrations and cognitive deficit is linear or has a threshold; some populations might have vitamin B-12 concentrations above this threshold. Fourth, assessment of vitamin B-12 status is not straightforward because total plasma vitamin B-12 concentrations are not a good marker for the status of the vitamin in the tissues (9). Alternative approaches are to use metabolic markers reflecting the functioning of vitamin B-12, such as plasma total homocysteine (tHcy) or methylmalonic acid (MMA) (10), the blood concentration of holotranscobalamin, transcobalamin saturation (11), or the ratio of holotranscobalamin to total vitamin B-12 (12). Finally, it is becoming apparent that the association of low vitamin B-12 status with cognitive deficit may depend on the context, for example, the folate status of the population under study (13) [see also article by Selhub et al (14) in this issue]. The reviews previously cited (7, 8) have taken some of these factors into consideration. The most recent and relevant studies will be discussed below.

A case-control study of vitamin B-12 status, as assessed by plasma holotranscobalamin concentration, found that low holotranscobalamin and raised MMA and tHcy, but not total plasma vitamin B-12, were associated with pathologically confirmed Alzheimer’s disease (15). In the same study, the global cognitive test score in the control population was correlated with the plasma holotranscobalamin concentration over the entire normal range from 35 to 200 pmol/L (Figure 1). Two other studies in community-dwelling elderly found associations between raised MMA concentrations and cognitive deficit but no association of cognition with plasma vitamin B-12 (16, 17). The utility of the ratio of holotranscobalamin to total vitamin B-12 was shown in a study where only this ratio, but not total vitamin B-12 nor holotranscobalamin, was correlated with global cognitive test scores (12). A large community study, the Banbury B-12 Study, has confirmed that the newer markers, rather than plasma total vitamin B-12, are better correlated with cognition (18). In this study the authors examined 830 community-dwelling subjects $>$75 y and looked for cross-sectional associations among total plasma vitamin B-12, holotranscobalamin, MMA, tHcy, and cognitive impairment. The results, summarized in Figure 2, show that only the lowest quartile of plasma total vitamin B-12 was associated with cognitive impairment, whereas holotranscobalamin in the bottom 3 quartiles was related to impairment. High MMA (top quartile) and tHcy (top 2 quartiles) were also related to cognitive impairment. Thus, low-normal holotranscobalamin across the normal range was associated with an increased risk of cognitive impairment.

Two new prospective studies support earlier reports that vitamin B-12 status is one of the factors influencing cognitive decline. In a study from Korea, incident dementia in a population of 625 elderly subjects was not associated with baseline concentrations of vitamin B-12, but it was significantly related to the change in plasma vitamin B-12 over a 2-y follow-up period (19); this association was evident over the normal range of plasma total vitamin B-12 concentrations, with a 3-fold greater incidence of dementia in those in the lowest quintile compared with those in the top quintile. In what is probably the largest study of its kind, Clarke et al (20) examined the association between markers of vitamin B-12 status and cognitive decline over a 10-y period in 1648 community-dwelling elderly (≥65 y) in Oxford, United Kingdom. Significant cross-sectional associations were found at baseline and after 10 y between cognitive test scores and low holotranscobalamin, high MMA, or high tHcy, but not with plasma total vitamin B-12. Using a linear mixed-effects model, the authors found associations between cognitive decline from baseline to 10 y later and low baseline concentrations of holotranscobalamin and high concentrations of MMA or tHcy. No significant association was found between

![Figure 1](https://academic.oup.com/ajcn/article-abstract/89/2/707S/4596810)

**FIGURE 1.** Relation between global cognition and plasma holotranscobalamin concentration in community-dwelling elderly people (mean age: 70.5 y). The cutoff for dementia in the test used is a score of 80 (maximum possible score is 107). Linear regression is adjusted for age and sex (partial $r = 0.25$, $P = 0.04$). The dotted lines show the 95% prediction limits. Based on data reported by Refsum and Smith (15).

![Figure 2](https://academic.oup.com/ajcn/article-abstract/89/2/707S/4596810)

**FIGURE 2.** Risk of cognitive impairment [odds ratio (OR)] in 830 elderly community-dwelling subjects in relation to quartiles of plasma concentrations of markers of vitamin B-12 status. (A) Solid columns: holotranscobalamin; shaded columns: total vitamin B-12. (B) Open columns: methylmalonic acid; hatched columns: total homocysteine. In both parts, asterisks indicate when the OR was significantly different from a value of 1.0. Plotted from the data reported by Hin et al (18).
POSSIBLE BIOLOGICAL MECHANISMS

There are many possible mechanisms through which low-normal vitamin B-12 status could influence the functioning of the brain, and hence cognition, and these mechanisms are not mutually exclusive. One possibility is that the effect is mediated by homocysteine, because low vitamin B-12 status is associated with an elevation of the concentration of tHcy (21). Many mechanisms have been proposed for the effects of homocysteine on the brain, apart from an effect on the cerebral vasculature (8, 22). Alternatively, the effect of low vitamin B-12 status might be mediated by the raised concentrations of MMA, as discussed by McCracken et al (17); notably, the concentration of MMA in cerebrospinal fluid is twice that in plasma (23). Classical deficiency of vitamin B-12 is accompanied by alterations in the concentrations of cytokines, such as tumor necrosis factor-α or epidermal growth factor (24). So far, we do not know whether these cytokines are changed in subjects with low-normal vitamin B-12 status. The commonest hypothesis, however, for the neurotoxic effects of low vitamin B-12 status is that it leads to a deficiency of S-adenosylmethionine (SAM) and thereby to deficient methylation reactions in the central nervous system (25). Strikingly low levels of SAM have been found in cerebrospinal fluid (26) and in the brain (27) of patients with Alzheimer’s disease, but we are not aware of any studies of SAM in the brain in relation to low-normal vitamin B-12 status.

On a more global level, we suggest that 2 other changes associated with low-normal vitamin B-12 status might mediate the effect on cognition: atrophy of the brain and damage to the white matter. Progressive loss of brain tissue (atrophy) is well established as a factor associated with, or causing, cognitive decline and dementia (28–30), and recently it was shown that low-normal vitamin B-12 status at baseline is a predictor of whole-brain atrophy in community-dwelling elderly (31). Progressive atrophy of the brain was associated with plasma vitamin B-12 concentrations ranging from 800 to 160 pmol/L and with holotranscobalamin concentrations from 250 to 25 pmol/L. There was no obvious threshold concentration below which atrophy began (31). Subjects with plasma vitamin B-12 in the bottom tertile of plasma vitamin B-12 showed about twice the rate of atrophy (1.05%/y) as those in the other 2 tertiles (0.51%/y). Classical vitamin B-12 deficiency is associated with damage to the white matter in the spinal cord and in the brain, which has been attributed to damage to myelin as a result of deficient methylation of myelin basic protein (25, 32). There is much evidence that damage to the white matter in the brain is associated with, and may precede, cognitive decline (30, 33). It is therefore noteworthy that, in participants in the Rotterdam scan study, damage to the white matter was related to vitamin B-12 status over the normal range, as assessed by plasma total vitamin B-12, holotranscobalamin, transcobalamin saturation, and MMA (34). Previous case reports of patients with vitamin B-12 deficiency reported that changes in the white matter are reversible with treatment with vitamin B-12 (35).

We conclude that the cognitive deficit associated with low-normal vitamin B-12 status may be due in part to loss of brain tissue over many years but also to potentially reversible damage to the white matter. However, to find out whether these associations are causal requires intervention studies.

ARE COGNITIVE DEFICITS ASSOCIATED WITH LOW VITAMIN B-12 STATUS REVERSIBLE?

The findings discussed above raise key questions: Does low-normal vitamin B-12 status actually cause cognitive impairment? Or are the observed associations merely the consequence of confounding with, for example, some lifestyle factor or factors not recognized in the analyses? In clinical practice, it is found that patients with cognitive impairment associated with vitamin B-12 deficiency often, but by no means always, improve on treatment, whereas those with obvious dementia usually show no improvement (36). However, these are essentially anecdotal reports and there have been very few randomized controlled trials in which vitamin B-12 alone has been given to elderly people with cognitive impairment or dementia. The Cochrane review in 2003 (37) could find only 2 trials with acceptable methodology, which had a total of 42 patients enrolled, of whom only 36 completed the trials. Treatment periods were 1 or 5 mo. The endpoints were changes in the Mini-Mental State Examination or Alzheimer’s Disease Assessment Scale–Cognitive, which assess global cognitive abilities; no difference was found between treated and placebo groups. A recent systematic review (38) identified 6 trials that satisfied their methodologic criteria, but the wide variety of doses used and the 35 different cognitive function tests made it difficult to come to any conclusion. Notably, some of the trials reported a worsening of cognition in the vitamin B-12–treated groups compared with those receiving placebo. But in 4 of the 6 trials, the participants were normal elderly without cognitive impairment. It is clear that no conclusions can be drawn from the published trials. The trials have all been underpowered, too short in duration, and often carried out on the wrong type of subject. We strongly support the conclusions of the Cochrane reviewers: “Large randomized trials are required to evaluate the value of vitamin B-12 for improving cognitive function and preventing or retarding cognitive decline in normal and demented older people. Trials need to use established and validated diagnostic criteria and measures of cognitive function and to be long enough to detect trends” (37).

ARE THERE ANY PUBLIC HEALTH IMPLICATIONS?

It is accepted clinical and public health practice to treat people who have blood concentrations of vitamin B-12 below an established cutoff (usually 150 pmol/L) to prevent anemia, neuropathy,
and cognitive impairment. The observational studies that we have described appear to show associations between low-normal vitamin B-12 status (ie, plasma concentrations >150 pmol/L) and cognitive impairment, increased rate of brain atrophy, and damage to the white matter. The lack of evidence from interventional trials cannot be taken as evidence against a causal link because the trials were inadequate to test this hypothesis. So, in the absence of good trials, what do we do? The limited data that we have do not suggest that there is a threshold concentration of vitamin B-12 below which these effects become apparent; rather, the association seems to be continuous across most of the normal range. An unknown factor is whether prolonged exposure to low vitamin B-12 status leads to irreversible changes in the brain; there have been suggestions that there is a limited window of opportunity for reversal of cognitive changes (39, 40). Patients with genetic defects in the vitamin B-12 pathway presumably must have been exposed since birth and so it is notable that the cognitive deficits and white matter damage in a 42-year-old patient with cobalamin C disease could be reversed on treatment with a homocysteine-lowering cocktail, which included vitamin B-12 (41).

Overall, it would seem prudent to encourage people, especially the elderly, to maintain a good, rather than only a satisfactory, vitamin B-12 status by dietary means. A study on the Framingham cohort showed that the use of supplements, fortified cereal, and milk appeared to protect against lower concentrations (42). Those sections of the population that have a high preponderance of low vitamin B-12 status and those countries where vitamin B-12 deficiency is common [see article by Allen (43) in this issue] will need to draw their own conclusions from the observational data. Until we have convincing evidence from trials, we cannot recommend large-scale public health measures, such as mandatory fortification of foods with vitamin B-12 (44) [see also article by Green (45) in this issue]. Nevertheless, we suggest that the voluntary fortification of foods with vitamin B-12 (46, 47) should be encouraged, particularly in countries where mandatory fortification with folic acid has led to exposure of the elderly to increased risk of anemia and cognitive impairment (13, 48), to maintain a balance between these 2 B vitamins. (Other articles in this supplement to the Journal include references 14, 43, 45, and 49.)

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The authors are on the management committee of an ongoing trial of B vitamins (including vitamin B-12) in the elderly (ISRCTN94410159). They had no other conflicts to declare.

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