Alzheimer's
**Drug Discovery**
Foundation

# Vitamin B6, B12 & Folic Acid (B9)

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Homocysteine is a homologue of the amino acid cysteine. High levels of homocysteine are common in people over 65 and have been linked to a wide variety of age-related problems including dementia. Several B vitamins, including vitamin B6 (pyridoxine), B9 (folic acid), and B12 (cobalamin), can reduce homocysteine levels. However, clinical trials testing the effects of homocysteine-lowering B vitamin supplementation for as long as seven years have generally shown a lack of benefit in cognitive functions, though there is some evidence to suggest that people with particularly high homocysteine levels may benefit. Vitamin B12 deficiency can lead to serious health problems including dementia if not treated.

## EVIDENCE AND POTENTIAL BENEFIT FOR BRAIN HEALTH

### Rated 3/4 based on 3/4 evidence

Large meta-analyses have concluded that supplementation with B vitamins (B6, B9, and B12) does not improve global cognitive function or memory in healthy adults but may protect from cognitive decline in people with mild cognitive impairment and high homocysteine levels.

Randomized controlled trials: A 2012 meta-analysis of 19 randomized trials reported no cognitive benefits of B vitamin supplementation irrespective of study size, study duration, or whether the participants had likely low folic acid levels because they came from countries with low folic acid status [1]. Although most of these trials were short in duration (under 2 years), longer duration trials (up to 5.4 years) were not more likely to observe benefit.

A more recent 2014 meta-analysis of 11 large trials including a total of 22,000 people concluded that while B vitamins lowered homocysteine concentrations by 26–28%, they had no significant effects on cognitive function or age-related cognitive decline [2]. When this study was published, some scientists noted that the results from the meta-analysis were not conclusive [3; 4; 5]. For example, most trials did not include people who were experiencing cognitive decline and the cognitive tests used (e.g., Mini-Mental State Examination) were not sensitive enough to detect mild cognitive changes in healthy individuals. In other words, most of the trials were not designed to detect an effect on cognitive decline. Some experts also attribute the negative findings to the likelihood that vitamin treatment may not be effective in people who already have optimum levels [4; 6].

Part of the reason for the continued interest in B vitamins is the positive results from the VitaCog studies, a two-year randomized placebo-controlled trial, which collectively suggest that B vitamins may protect from cognitive decline in select populations. The two-year treatment of high dose B vitamins (20 mg of B6, 0.5 mg of B12, and 0.8 mg of folic acid) protected against gray matter atrophy in the brains of people with mild cognitive impairment, though only in people with high homocysteine levels at baseline [7]. Moderate beneficial effects on cognitive function and memory were seen in patients with mild cognitive impairment and these positive effects were also pronounced in those with high baseline homocysteine levels [8]. The most recent publication from the VitaCog study reported that B vitamin treatment appeared to slow cognitive decline in people with mild cognitive impairment only when they had higher than average omega-3 fatty acid levels [9].

A 2014 meta-analysis corroborates some of these findings in people with mild cognitive impairment [10], concluding based on five clinical trials that B vitamin supplementation for up to two years can result in moderate beneficial effects on memory in patients with mild cognitive impairment. However, no effects were seen on general cognitive function, executive function, or attention. It is currently unknown whether B vitamins can slow or prevent the conversion from mild cognitive impairment to dementia.

Other human research: A meta-analysis of 14 cohort studies showed that the relative risk for cognitive decline was 53% higher for patients with high homocysteine levels (i.e., hyperhomocysteinemia) compared to those with normal homocysteine levels [11]. Clinical trials have consistently shown that the B vitamin complex can lower homocysteine levels.

Biology: Homocysteine is a non-protein homologue of the amino acid cysteine, derived from the metabolism of the amino acid methionine. Homocysteine can be toxic to neurons because it can act on the glutamate N-methyl-D-aspartate (NMDA) receptors, leading to excessive calcium levels and neuronal death [12]. Homocysteine can also undergo auto-oxidation, resulting in oxidative stress [13].

High levels of homocysteine are common in people over 65 and have been linked to a wide variety of age-related problems including dementia, vascular disease, stroke, depression, functional decline, and osteoporotic fractures [14]. Several distinct B vitamins including folic acid, vitamin B12 and vitamin B6 are required for homocysteine metabolism. If these age-related health issues are caused by or worsened by higher homocysteine levels, then theoretically, lowering homocysteine levels with B vitamin supplementation may be protective.

ApoE4 carriers. The evidence is mixed on whether B vitamins selectively affect ApoE4 carriers versus non-carriers. Two cross-sectional epidemiological studies reported that high homocysteine levels are associated with worse cognitive function in ApoE4 carriers, but not

non-carriers, suggesting that ApoE4 carriers are more likely to benefit from treatment with homocysteine-lowering B vitamins [15; 16]. In ApoE4 carriers with Alzheimer's disease, higher blood vitamin B12 levels were associated with larger gray matter volumes of select brain regions [17]. However, at least 3 other observational studies [18; 19; 20] report little to no interaction between ApoE genotype and vitamin B12 in terms of cognitive function or dementia risk. For more information on what the *APOE4* gene allele means for your health, read our APOE4 information page.

### For Dementia Patients

Although moderate beneficial effects on memory have been observed for patients with mild cognitive impairment, particularly in those with high baseline homocysteine levels [8; 10], no benefits have been reported with Alzheimer's disease patients [10; 21]. However, B12 deficiency is a well-known cause of damage to the nervous system [22], independent of homocysteine, that can be successfully treated if caught early enough.

Randomized controlled trials: In a meta-analysis of five clinical trials examining the effects of B vitamin supplementation for up to 2 years, no benefits of B vitamin supplementation were seen in cognitive function or behavioral measures in Alzheimer's disease patients [10].

Other human research: A meta-analysis of 68 observational studies showed that Alzheimer's disease patients had higher homocysteine, lower folic acid, and lower vitamin B12 levels compared to those who did not have dementia [23]. High homocysteine and low folic acid levels also correlated with risk of dementia occurrence. However, when only prospective observational studies are considered, high homocysteine levels are not a reliable risk factor for dementia [24]. Moreover, high homocysteine levels may be an outcome rather than a proxy measure of vulnerability, in which case reducing homocysteine with B vitamins may not help.

## SAFETY

### Rated 3/4

Vitamin B supplements are considered safe for most healthy people when taken at recommended doses, though some drug interactions are known. High folic acid intake can mask the anemia symptoms of vitamin B12 deficiency, which is concerning because a delayed diagnosis of B12 deficiency could raise the risk for serious long-term harm such as severe anemia and neurologic disturbances including ataxia (loss of control of bodily movements) and paresthesia (abnormal sensations). B12 deficiency is often caused by problems absorbing B12 from the gut so it cannot necessarily be prevented by oral B12 vitamins. However, this risk may be bypassed by directly monitoring B12 or methylmalonic acid levels [25].

A meta-analysis of 19 randomized controlled trials of B vitamin supplementation to lower homocysteine levels have generally reported neither benefit nor harm on all-cause mortality, cardiovascular-related mortality, coronary heart disease, or cardiovascular disease. However, B vitamin supplements might reduce the risk of stroke, as reported as a strong trend in one meta-analysis [26] and corroborated in a different meta-analysis [27]. In the 19 clinical trials, treatment durations ranged from 6 months to 80 months [26]. While some studies previously noted a relationship between folic acid intake and changes in cancer risk [28], a meta-analysis of randomized clinical trials over one year in duration concluded that the first five years of treatment with folic acid neither increases nor decreases cancer incidence [29].

More information on doses, side effects, and drug interactions with B vitamin supplementation can be found at the NIH Office of Dietary Supplements (vitamin B6, B12, folic acid).

## HOW TO USE

B vitamins are available over-the-counter in different formulations as pills, chewable tablets, extended release capsules, and a liquid. In clinical trials, daily supplementation with 20 mg of vitamin B6, 0.5 mg of vitamin B12, and 0.5-5.0 mg of folic acid reduced homocysteine levels [8]. However, appropriate doses depend on the individual's age, dietary intake, and baseline levels of the B vitamins. Folate in particular is often heavily fortified into grains. The ability to absorb vitamin B12 from the gut can become impaired in some people, particularly with old age [30], leading to the serious condition of B12 deficiency that must be clinically treated with injections or high dose oral B12 therapy.

Some possible interactions with B vitamins are known. For example, coffee may raise homocysteine levels [31]. Some drugs can reduce the levels of various B vitamins, including metformin, histamine H2 receptor antagonists, and proton pump inhibitors for B12 (ODS info sheet), antiepileptic medications and sulfasalazine for folic acid (ODS info sheet), and cycloserine antibiotic, antiepileptic medications, and theophylline for B6 (ODS info sheet). Also, nitrous oxide can inactivate vitamin B12 so individuals undergoing dental or surgical procedures with nitrous oxide may benefit from prior testing of B12 levels and, as necessary, supplemental injections of B12 [32].

## WHAT'S THE FUTURE?

There are no clinical trials underway to evaluate whether B vitamins may prevent cognitive decline or dementia. Some experts argue that most clinical trials on B vitamins have focused on populations that already have adequate B vitamin intake or are unlikely to decline over the duration of the clinical trial and thus unable to evaluate protection from cognitive decline. In contrast, patients with mild cognitive impairment and/or high homocysteine levels might be protected from dementia through B vitamin treatment [33],

possibly in combination with omega-3 fatty acids [9]. To our knowledge, this important question is not yet being addressed in a clinical trial.

An ongoing pilot study, supported in part by the Alzheimer's Drug Discovery Foundation, is testing whether benfotiamine, a relative of vitamin B1 (thiamine), slows cognitive decline in patients with amnestic mild cognitive impairment and Alzheimer's disease (NCT02292238). Vitamin B1 and benfotiamine do not regulate homocysteine levels so this treatment, if effective, is likely to have a distinct mechanism of action from vitamins B6, B12, and folic acid. This clinical trial is scheduled to be completed in November 2018. Another study is testing the effects of folic acid and vitamin B12 supplementation in people with type 2 diabetes (NCT02786823) and is scheduled to be completed in October 2016.

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