Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Vitamin B6, B12, and Folate

Evidence Summary

High homocysteine and low B vitamin levels are associated with increased risk of dementia, but it is unlikely B vitamin supplementation will improve cognitive function or decrease dementia risk except in cases of severe vitamin B deficiency.

Neuroprotective Benefit: Large meta-analyses have shown that supplementation with B vitamins (B6, B9, and B12) does not improve cognitive functions in healthy adults; however, some cognitive benefits are seen in people with B vitamin deficiency.

Aging and related health concerns: A large meta-analysis has shown that B vitamin supplementation has a protective effect for stroke, but no effects are seen for cardiovascular disease or all-cause mortality.

Safety: B vitamins are generally considered safe for use, though high folate supplementation can mask anemia symptoms of vitamin B12 deficiency, potentially raising the risk for neurological consequences from delayed diagnosis.

What are they? Homocysteine is a non-protein homologue of the amino acid cysteine, derived from the metabolism of the amino acid methionine. Several distinct B vitamins are required for homocysteine metabolism and vitamin supplementation may lower homocysteine levels. These B vitamins include B9 (folate), B12 (cobalamin) and B6 (pyridoxal phosphate).

High homocysteine levels associate with a higher risk of developing a variety of age-related diseases, possibly including dementia. Supplementing with vitamins B6, B9, and/or B12 can reduce homocysteine levels. However, clinical trials as long as 7 years duration have generally failed to observe either benefit or harm, with a handful of exceptions suggesting mild benefit. Longer term studies or studies targeting people with high homocysteine levels may achieve more robust effects.

Neuroprotective Benefit: Large meta-analyses have shown that supplementation with B vitamins (B6, B9, and B12) does not improve cognitive functions in healthy adults; however, some cognitive benefits are seen in people with B vitamin deficiency.

Types of evidence:

- 8 meta-analyses of numerous clinical trials examining the effects of B vitamin supplementation on cognitive function
- 4 meta-analyses of numerous observational studies examining the links between homocysteine levels, B vitamin levels, cognitive decline, and dementia
- 3 randomized controlled studies
- Numerous preclinical studies on possible mechanisms of action

A meta-analysis of 14 cohort studies showed that the pooled RR for cognitive decline was 1.53 for patients with hyperhomocysteinemia compared to those without [2]. Thus, hyperhomocysteinemia was associated with an increased risk of cognitive decline.

A 2014 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 folate levels because they came from countries with low folate status. The trials may have been too short, but longer duration trials (ranging up to 5.4 years) were not more likely to observe benefit [3]. Moreover, the rationale that high homocysteine raises the risk of dementia is not as strong as sometimes reported. Although patients with Alzheimer's disease (AD) and particularly vascular dementia have higher homocysteine levels than age-matched controls, amongst prospective

observational studies, high homocysteine is not a reliable risk factor for dementia (pooled OR 1.34, 95% CI 0.94-1.91)[4].

A meta-analysis of 11 large trials (including 22,000 people total) showed that while B vitamins lowered homocysteine concentrations by 26-28%, they had no significant effects on cognitive function or cognitive aging [5]. When this study came out, many commentaries were published noting that results from the meta-analysis were inconclusive [6; 7; 8]. Most trials did not include people who were experiencing cognitive decline and the cognitive tests used (e.g., MMSE) were not sensitive enough to detect mild cognitive changes in healthy individuals. A potential design flaw of clinical trials testing the efficacy of vitamin supplements has also been noted. Vitamin treatment may not be effective in people who already have optimum levels of the vitamins from their diet [7; 9].

B12 deficiency is a serious clinical problem, particularly common in the elderly, leading to neurological deficits and fatigue. The problem often arises from malabsorption, in which case oral supplementation may not protect and injections may be needed [1]. Vegetarians and vegans are also at higher risk.

In dementia and MCI: A meta-analysis of 68 studies showed that AD patients had higher homocysteine, lower folate, and lower vitamin B12 levels compared to controls [10]. High homocysteine and low folate levels also correlated with risk of AD occurrence.

A double-blind randomized clinical trial showed that B vitamin supplementation (0.8 mg folate, 0.5 mg B12, 20 mg B6) for 2 years lowered plasma homocysteine levels by 30% and stabilized executive function in patients with mild cognitive impairment (MCI) aged 70 years old and above [11]. In patients with high baseline homocysteine, B vitamins improved global cognition (MMSE), episodic memory, and semantic memory. B vitamins appeared to slow cognitive and clinical decline in people with MCI, particularly in those with elevated homocysteine, but it is unknown whether B vitamins will slow or prevent conversion from MCI to dementia.

In a meta-analysis of 5 clinical trials examining the effects of B vitamin supplementation (for 26 weeks to 2 years), moderate beneficial effects on memory were found in MCI patients, but no effects on general cognitive function, executive function, and attention were seen [12]. In AD patients, no benefits of B vitamin supplementation were seen in cognitive function or behavioral measures.

A combinatorial treatment of high dose B vitamins for 2 years was reported to protect against gray matter atrophy in the brains of people with MCI, though only if those people had high homocysteine

levels at baseline [13]. This study, along with occasional reports of benefit amongst a larger literature of null efficacy, suggests that supplementation longer than 5-10 years might be beneficial in people with high homocysteine levels.

ApoE4 interactions: There is inconsistent evidence. Two cross-sectional epidemiological studies reported that high homocysteine levels associate with worse cognitive function only in ApoE4 carriers, suggesting that ApoE4 carriers are more likely to benefit from treatment with homocysteine-lowering B vitamins[17; 18]. However, at least 3 other observational studies[19; 20; 21] report little to no interaction between ApoE genotype and vitamin B12 in terms of cognitive function or dementia risk. In ApoE4 carriers, but not in non-carriers, with Alzheimer's disease, there was a positive correlation between blood vitamin B12 levels and gray matter volume in select brain regions [23]. A few rodent studies have reported that ApoE null mice have different responses to high homocysteine levels for atherosclerosis, e.g. [22], but there is a need for research on the mouse models with targeted replacement or knock-in of human ApoE variants.

Aging and related health concerns: A large meta-analysis has shown that B vitamin supplementation has a protective effect for stroke, but no effects are seen for cardiovascular disease or all-cause mortality.

Types of evidence:

- 2 meta-analyses

High homocysteine levels have been implicated in a wide variety of age-related problems including vascular disease, stroke, depression, dementia, functional decline, and osteoporotic fractures [14]. High levels are much more common in people over 65 (eg. 30% vs 5-10% of the population)[14]. However, similar to the evidence for cognitive benefit, a meta-analysis of 19 RCTs of B vitamin supplementation to lower homocysteine levels have generally reported no effects on all-cause mortality, cardiovascular-related mortality, coronary heart disease, or cardiovascular disease, although a trend towards decreased stroke risk has been noted [15] and repeated in a different meta-analysis [16]. The 19 RCTs included ranged from 6 months to 80 months duration [15]. Although longer term studies might detect more benefit, the data is not encouraging.

Safety: B vitamins are generally considered safe for use, though high folate supplementation can mask anemia symptoms of vitamin B12 deficiency, potentially raising the risk for neurological consequences from delayed diagnosis.

Types of evidence:

- 1 meta-analysis of randomized controlled trials
- 1 review

High folate supplementation can mask the anemia symptoms of vitamin B12 deficiency, delaying when deficiency may be detected and treated, thus raising the risk for neurological consequences. However, this concern may be bypassed by directly monitoring B12 or methylmalonic acid levels. For cancer risk, folate intake has a complex relationship with various studies suggesting protection against common cancers and colorectal cancer while other studies suggesting high folate intake may promote tumorigenesis[24], but a meta-analysis of randomized trials over 1 year in duration reports that the first five years of treatment with folic acid neither increases nor decreases cancer incidence[25].

Vitamin B supplements are considered safe for most healthy people when taken at recommended doses, though some drug interactions are known. Side effects may include mild upset stomach or flushing, but are usually temporary. Detailed information on doses, side effects, and drug interactions can be found at WebMD (vitamin B6, B12, folate, B complex) and Drugs.com (vitamin B6, folate, B complex).

Dosing and Sources: A 1998 meta-analysis reported that daily supplementation with 0.5-5.0 mg of folic acid and 0.5 mg of Vitamin B 12 could reduce homocysteine by 1/4 to 1/3. Appropriate dose depends heavily on the baseline status and age of the individual as well as the dietary intake. Folate in particular is often heavily fortified into grains. There are some possible interactions; coffee may raise homocysteine levels [26]. 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). 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 [1].

Research underway: There are currently no ongoing clinical trials that are testing the potential of B vitamins in preventing or treating dementia. Some experts argue that most clinical trials, except for the

VitaCog trial, have tested the effects of B vitamins on the wrong patients and that patients with mild cognitive impairment and high homocysteine levels might be protected from dementia through B vitamin treatment, possibly in combination with omega-3 fatty acids. This important question is not yet being addressed in a clinical trial.

An ongoing pilot study is testing whether benfotiamine, a relative of vitamin B1 (thiamine), slows cognitive decline in patients with amnesic mild cognitive impairment and Alzheimer's disease dementia (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 folate and vitamin B12 supplementation in people with type 2 diabetes (NCT02786823) and is scheduled to be completed in October 2016.

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