Effect of vitamin intake on cognitive decline: Evaluation of the evidence

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April 2014
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Glossary

25OHD; 25-hydroxyvitamin D
AD; Alzheimer’s Disease
ADAS-cog; Alzheimer’s Disease Assessment Scale-Cognitive Subscale
AIBL; Australian Imaging, Biomarkers and Lifestyle
APOE; apolipoprotein E
CAMCOG; Cambridge Cognitive Examination
CHAP; Chicago Healthy Aging Project
CDR; Clinical Dementia Rating Scale
CI; Confidence interval
CSF; Cerebrospinal fluid
DARE: Database of review of effects
FFQ; Food frequency questionnaire
HC; Healthy control
holoTC; holotranscobalamin
IOM; Institute of Medicine
JBI; Joanna Briggs Institute
MCI; Mild cognitive impairment
MMA; methyl malonic acid
MMSE; Mini-Mental State Examination
NHMRC; National Health and Medical Research Council
NHS EED; National Health Service Economic Evaluation Database
OR; Odds ratio
PIB-PET; Pittsburgh compound B  Positron Emission Tomography
PLP; pyridoxal phosphate
RCT; Randomised controlled trial
TICS; Telephone Interview of Cognitive Status
RR; Relative risk
SMD; Standardised mean difference
UVB; ultraviolet B
VITACOG; Homocysteine and B vitamins in cognitive impairment RCT study
WMD; Weighted mean difference
Executive summary

The objective of this review was to evaluate the evidence from human studies on the intake of vitamins, either as monotherapies or in combination with other vitamins, as neuroprotective agents that may delay the onset of cognitive decline. Evidence-based methodologies were used to capture and evaluate the highest levels of evidence (systematic reviews). If systematic reviews were not available, well-designed randomised clinical trials or lower levels of evidence were included. The current evidence available showed no association for cognitive benefits of vitamins B6 or B12 as a monotherapy, and recent systematic reviews provide no clear evidence that supplementation with vitamin B6, B12 and/or folic acid improves dementia outcomes or slows cognitive decline, even though it may normalise homocysteine levels. However, imaging studies reporting slower rates of brain atrophy in mild cognitive impaired (MCI) participants with high homocysteine levels taking vitamin B supplements appears promising. Meta-analyses from systematic reviews have shown an association between low vitamin D levels and diminished cognitive function, although causality cannot be confirmed from the available evidence. There is no convincing evidence for an association of vitamin C and vitamin E either as a monotherapy or in combination with other antioxidant vitamins such as vitamin C, A and β-carotene and the prevention of cognitive decline. Evaluation of the totality of the current available evidence indicates that intake of the above vitamins, either as a monotherapy, or in combination with other vitamins, has no clinically-relevant effect on delaying cognitive decline or delaying the onset of dementia.
1 INTRODUCTION

The term ‘dementia’ is used to describe the symptoms of a large group of illnesses which cause a progressive decline in a person’s cognitive functioning. It is a broad term used to describe a loss of memory, intellect, rationality, social skills and normal emotional reactions. There are many different forms of dementia and each has its own cause. Neurodegenerative diseases such as Alzheimer’s Disease (AD) are the most common cause of dementia, thought to be responsible for up to 70% of cases. The major risk factor for AD is age, with the prevalence doubling every 5 years after the age of 65. Other terms associated with dementia are mild cognitive impairment (MCI) and subjective memory complainers. MCI is a clinical syndrome characterized by reduced cognitive performance (often involving memory), which represents a high risk state for the development of AD (1, 2).

Lower plasma levels of some vitamins in AD patients compared to cognitively healthy elderly, even in the absence of malnourishment (3) have led to investigations on the role of vitamins in the prevention of cognitive decline and the onset of AD. It has been reported that deficiencies in B group vitamins, particularly vitamin B1 (thiamine), B6, B9 (folic acid) and B12 may contribute to age-associated cognitive impairment (4, 5) and that low serum vitamin B levels may lead to elevated homocysteine levels which is a modifiable risk factor for AD (5).

While low plasma vitamin C has been reported in some AD patients despite an adequate diet (6), other studies (7) have evaluated intake and functional levels of vitamin C in AD and normal subjects and found them to be similar in both groups.

Vitamin E refers to a group of eight fat-soluble compounds that include both tocopherols and tocotrienols. α-Tocopherol is the most abundant form of vitamin E in the human body and has been extensively investigated in clinical trials for its possible role in the prevention of AD (8).
Some studies have suggested a link between vitamin D deficiency and cognitive impairment and dementia, particularly in the elderly (9, 10). Vitamin D, also known as calciferol, is a steroid hormone that can be obtained from dietary sources as both vitamin D2 and D3. However, most of the vitamin D is obtained in the form of vitamin D3, synthesized through the action of ultraviolet B (UVB) radiation on 7-dehydrocholesterol in the skin (11). While synthetic vitamin D3 and vitamin D2 are available commercially, vitamin D3 is generally the major supplemental form available.

Research on the potential of nutritional interventions to prevent or delay cognitive impairment and the development of AD is rapidly gaining momentum, with numerous clinical trials recently being completed and others underway. The aim of this evidence-based review was to evaluate the effect(s) of vitamin intake, both as a monotherapy, or in combination with other vitamins as neuroprotective agents that may delay cognitive decline and the onset of AD.
2 METHODS

2.1 Search Strategy

Literature searches were undertaken on vitamin A, vitamin B complex components (B1, B2, B3, B6, B7, B9, B12), vitamin C, vitamin D and vitamin E and their effect on cognitive decline using a two-step process. Once search terms were established, the following databases were searched: Medline on PubMed, Web of Science, Cochrane Central (Database of Systematic Reviews and Cochrane Collaboration Central Register of Controlled Trials), Centre for Reviews and Dissemination Databases (Database of Reviews of Effects (DARE)), National Health Service Economic Evaluation Database (NHS EED) and Health Technology Assessment Database), Joanna Briggs Institute (JBI) Library of Systematic Reviews and the Agency for Healthcare Research and Quality (US Department of Health and Human Services). Searches covered to December 2013, without language or date restriction.

Ongoing clinical trials and as-yet-unpublished trials that may have yielded data were identified using the following databases: ISRCTN International metaRegister of Current Controlled Trials and all its sub-files, the Alzheimer’s Society register of projects, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal and all of its nation-based sub-files, which includes among others, the US National Institutes of Health database via Clinical trials.gov and clinical trials registries of Australia/New Zealand, China, India, Germany, Japan and the Netherlands.

2.1.1 INCLUSION AND EXCLUSION CRITERIA

Population

This review considered studies of adult humans without AD at baseline, including those who reported difficulties with memory (memory complainers) and/or with mild cognitive impairment (MCI) as a result of the ageing process, but not cognitive impairment due to brain injury. To increase the homogeneity of studies on the effect of dietary interventions to delay the onset of cognitive decline, the review did not include studies of patients with established AD, as it is believed that even so-called “early clinical stages” of AD reflect advanced-stage
brain failure that may be impossible to reverse (12). The review did not include studies using animal models.

**Types of interventions / phenomena of interest**

This review considered quantitative studies that evaluated the effects of vitamins as neuroprotective agents. Vitamins included in the review were vitamin A (including β-carotene), B group vitamins (vitamin B1, vitamin B3, vitamin B6, vitamin B7, vitamin B9 (folate), vitamin B12), vitamin C, vitamin D and vitamin E. The review did not consider studies of multivitamin supplements or studies that combined drugs with vitamins or supplements.

**Types of outcomes**

The review considered studies that included outcome measures from a range of cognitive function tests diagnostic of MCI and AD including but not limited to; Alzheimer’s Disease Assessment Subscale (ADAS-Cog), Clinical Dementia Rating Scale (CDR), Cambridge Cognitive Examination (CAMCOG), Mini Mental State Examination (MMSE), Telephone Interview of Cognitive Status (TICS). The review also considered outcome measures from brain imaging techniques including, volumetric cranial magnetic resonance imaging (MRI) scan, uptake of the radioligand $^{11}$C-Pittsburgh compound B (PIB, which binds to fibrillar β-amyloid (Aβ) deposits in the brain), by positron emission tomography (PIB-PET), blood biomarkers of MCI and AD risk (e.g. plasma Aβ$_{42}$, plasma Aβ$_{40}$, tau protein) and markers of vitamin status such as the biomarkers, methyl malonic acid (MMA) and holotranscobalamin (holoTC) and 25-hydroxyvitamin D (25OHD).

**Types of studies**

The review considered published systematic reviews and randomized controlled trials (RCTs) on the listed vitamins. In the absence of systematic reviews or RCTs, other research designs, such as non-randomized controlled trials and other human cohort studies, were considered for inclusion to enable the identification of current highest levels of evidence on the effects of vitamins that have the potential to delay cognitive decline.

**Data extraction and synthesis**

Studies selected for retrieval were assessed for methodological quality prior to inclusion in the review. Data extracted from papers included details about the populations, interventions, study methods and outcomes of significance to the review question and specific objectives. The data were extracted and listed by intervention and by levels of evidence, using the National Health and Medical Research Council (NHMRC, Australia)
criteria (13). The NHMRC criteria for the levels of evidence define Level I evidence as: Evidence obtained from a systematic review of all relevant RCTs, while Level II evidence is defined as: Evidence obtained from at least 1 properly-designed RCT. Meta-analyses were not undertaken due to the heterogeneity of the study designs, confounding factors that were not controlled for and due to subjective measures of some end-point determinations.
3 RESULTS

3.1 B Group Vitamins

B group vitamins have been studied either as monotherapies or in combination in human trials to evaluate their effects on cognitive decline.

3.1.1 B-GROUP VITAMINS AS MONOTHERAPIES

A summary of the studies evaluated and outcomes is shown in Table 1. No studies have been identified for vitamin B1, vitamin B3, vitamin B7 or vitamin B9 as monotherapies that met the inclusion criteria, however a series of studies including Cochrane reviews and other systematic reviews have evaluated the levels of evidence for vitamin B6 and vitamin B12 intake and their potential effects on cognitive decline. Malouf and Grimley Evans (14) evaluated the efficacy of vitamin B6 supplementation in reducing the risk of developing cognitive impairment by healthy older people, or improving cognitive functioning of people with cognitive decline and dementia, whether or not vitamin B6 deficiency was diagnosed. This review was undertaken in late 2003 and last assessed as up-to-date in 2008 and found no evidence for short-term benefit from vitamin B6 in improving mood (depression, fatigue and tension symptoms) or cognitive functions of people, >65 years in age with normal vitamin B6 status or with vitamin B6 deficiency. Oral vitamin B6 supplements were found to improve biochemical indices of vitamin B6 status in one of the two trials included in the review, but potential effects on blood homocysteine levels were not assessed in either study. The reviewers found evidence for increasing some biochemical indices of vitamin B6 status among a group of healthy men aged 70-79 years following daily oral supplementation of 20mg vitamin B6 for 12 weeks, however, there was inadequate evidence for any effects of B6 supplementation on cognition in healthy older people or those with cognitive impairment or dementia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Vitamin Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malouf, 2003 et al (updated 2008) (14)</td>
<td>Systematic review (Cochrane)</td>
<td>X</td>
<td>Two RCTs found no evidence for the short-term benefit of supplementation on cognition regardless of vitamin B6 status</td>
</tr>
<tr>
<td>Malouf et al, 2003 (updated 2006) (15)</td>
<td>Systematic review (Cochrane)</td>
<td>X</td>
<td>Three RCTs found no evidence of effect on cognition in healthy elderly</td>
</tr>
<tr>
<td>Doets et al, 2012 (16)</td>
<td>Systematic review with meta-analysis</td>
<td>X</td>
<td>Critical appraisal of 25 studies of 122 -3,634 participants, 60 -101 years of age and study duration /follow up of 4 weeks -9 years. Separate meta-analyses using at least 3 cohort studies showed serum/plasma B12 (50pmol/L) was not associated with dementia, global cognition z scores or memory z scores. B12 markers showed significant association with risk of dementia, AD and global cognition</td>
</tr>
<tr>
<td>O'Leary et al 2012(17)</td>
<td>Systematic review</td>
<td>X</td>
<td>Critical appraisal of 35 prospective cohort studies of 24 -1,405 participants, 47-101 years of age and study duration/ follow up of 0.5-35 years found no association between serum B12 and cognitive decline or dementia. B12 markers showed association between poor B12 status and increased risk of cognitive decline or dementia.</td>
</tr>
<tr>
<td>Moore et al 2012(18)</td>
<td>Literature review</td>
<td>X</td>
<td>Critical review of 43 studies found that B12 therapy did not improve cognition in patients without pre-existing deficiency</td>
</tr>
<tr>
<td>McCracken, 2010(19)</td>
<td>Literature review</td>
<td>X</td>
<td>Narrative review found no evidence of effect on cognition</td>
</tr>
<tr>
<td>Lildballe et al, 2011(20)</td>
<td>Cross-sectional study</td>
<td>X</td>
<td>Cohort of 839 participants, ≥75 years found that B12 markers showed an association between poor B12 status, high homocysteine levels and cognitive impairment</td>
</tr>
</tbody>
</table>
As a monotherapy, vitamin B12 has been studied more extensively than other B vitamins in relation to cognition. A Cochrane review examining the effect of vitamin B12 supplementation on cognitive function of elderly healthy people in terms of preventing the onset or progression of cognitive impairment or dementia was published in 2003 (15), and last assessed as up-to-date in 2006, concluded that there was no evidence for any efficacy of vitamin B12 in improving the cognitive function of healthy elderly people.

More recently, there have been a number of reviews (18, 19) but higher levels of evidence are provided by two recent systematic reviews (16, 17) that have examined the potential effect of vitamin B12 on cognitive decline. The systematic review of Doets and colleagues included 25 RCT and cohort studies and evaluated the dose-response relationship between vitamin B12 intake or status and cognitive function with a view to developing recommendations for vitamin B12 on cognition (16). The results of a meta-analysis of three prospective cohort studies showed no association between vitamin B12 intake and incidence of AD. The relationship between B12 status and cognition was assessed through a series of meta-analyses using 50pmol/L serum / plasma vitamin B12 as a measure of association. The results showed no association with risk of dementia (from 4 cohort studies), memory z-scores (4 cohort studies) or global cognition z-scores (4 cohort studies). A systematic review (17) of 35 prospective cohort studies, assessing several of the same studies found no association between serum B12 levels and cognitive decline. It was also noted that four of the studies using the biomarkers, methyl malonic acid (MMA) and holotranscobalamin (holoTC) to measure B12 status, showed consistent significant associations between lower vitamin B12 status and the increased risk of cognitive decline, AD and dementia (16, 17). This observation was consistent with a cross-sectional study of 839 people aged 75 years and over where serum vitamin B12 and associated markers were compared to the Mini-Mental State Examination (MMSE) scores (20).

### 3.1.2 B GROUP VITAMIN COMBINATIONS

A summary of the studies evaluating B group vitamin combinations and outcomes is shown in Table 2.
### Table 2: Studies of B group vitamins combinations on cognitive decline

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Vitamin Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malouf et al, 2008(21)</td>
<td>Systematic review (Cochrane)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ford et al, 2012(22)</td>
<td>Systematic review with meta-analysis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wald et al, 2010(23)</td>
<td>Systematic review with meta-analysis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Jia et al, 2008(24)</td>
<td>Systematic review with meta-analysis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Williams et al, 2010(25)</td>
<td>Systematic review</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dangour et al, 2010(26)</td>
<td>Systematic review</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>Vitamin Intervention</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------</td>
<td>----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Balk et al, 2007(27)</td>
<td>Systematic review</td>
<td>X X X</td>
<td>Critical appraisal of 14 RCTs of 7-249 adult participants with a study duration of 4 weeks–2 years found no adequate evidence for the effect of B vitamins alone or in combination on the healthy or cognitively impaired.</td>
</tr>
<tr>
<td>Raman et al, 2007(28)</td>
<td>Systematic review</td>
<td>X X X</td>
<td>Critical appraisal of 24 longitudinal and case control studies of 30-1,092 participants ≥60 years of age and study duration / follow up 2 -8 years (longitudinal studies) found limited evidence for any effect on cognition.</td>
</tr>
<tr>
<td>Hinterberger and Fischer 2013(29)</td>
<td>Literature review</td>
<td>X X X</td>
<td>Review of 7 RCT studies of 140-2,009 participants, mean age 60-79, with study duration / follow up of 2-8 years and 14 longitudinal studies of 213-3,634 participants, mean age 45-81 years and a study duration of 4-9 years. Trend in RCT’s for cognitive benefits from B vitamin supplements for subjects with high homocysteine or low folate at baseline.</td>
</tr>
<tr>
<td>Van de Rest et al 2012(5)</td>
<td>Literature review</td>
<td>X X X</td>
<td>Narrative review found insufficient evidence of effect on cognition.</td>
</tr>
<tr>
<td>Buhr et al, 2010(30)</td>
<td>Literature review</td>
<td>X X X</td>
<td>Narrative review found insufficient evidence of effect on cognition.</td>
</tr>
<tr>
<td>Bhat et al, 2009(31)</td>
<td>Literature review</td>
<td>X X X</td>
<td>Narrative review found no evidence for effect on cognition.</td>
</tr>
<tr>
<td>Vogel et al, 2009(32)</td>
<td>Literature review</td>
<td>X X</td>
<td>Review found no evidence for effect of folic acid and/or B12 on cognition, even though it may normalise homocysteine levels.</td>
</tr>
<tr>
<td>Smith et al, 2010(33)</td>
<td>RCT</td>
<td>X X X</td>
<td>Participants (all MCI) of the VITACOG RCT study (n= 271, ≥70 years of age) taking vitamin B supplements showed a much slower rate of brain atrophy compared to the placebo group over a 2 year follow up.</td>
</tr>
<tr>
<td>Douaud et al, 2013(34)</td>
<td>RCT</td>
<td>X X X</td>
<td>Voxel modelling, showed that B vitamins slowed the rate of brain atrophy in participants with high homocysteine levels (above median 11μmol/L) in the VITACOG study.</td>
</tr>
</tbody>
</table>

Abbreviations: AD; Alzheimer’s disease MCI; Mild cognitive impairment, RCT, randomised controlled trial
Folate and vitamin 12
The effects of folic acid supplementation, with or without vitamin B12, in preventing cognitive impairment or retarding its progress was examined in a Cochrane review (21) and a narrative review (32). Both reviews came to similar conclusions, that there is no evidence that folic acid, with or without vitamin B12, improves cognitive function of unselected elderly people, with or without dementia, and that long-term supplementation may benefit cognitive function of healthy older people with high homocysteine levels.

Folate, vitamin B6 and vitamin B12
There have been a series of reviews (5, 29-31) and systematic reviews (22-28), evaluating the association of B vitamins, particularly folate, vitamin B6, vitamin B12 and cognitive function, mainly in elderly populations, although the meta-analysis of Jia et al (24) included a study using vitamin B1 as an intervention and the review by Williams et al (25) included a vitamin B3 study. While the evidence in earlier systematic reviews (27, 28) was limited by a sparsity of studies, small sample sizes, heterogeneity in outcomes, including cognition assessment methodology and threshold levels for categorising low B-vitamin status, further RCTs have enabled more recent systematic reviews (22-24) to pool data to provide a summary of effect measures. The most recent of these (22) included most of the studies previously analysed and investigated the efficacy of treatment with folate, vitamin B6 or B12 in slowing cognitive impairment among adults ≥ 50 years with and without cognitive impairment. The meta-analysis showed that supplementation of vitamin B6, B12 and folate, either alone or in combination, did not improve the cognitive function in individuals with existing cognitive impairment or in individuals without cognitive impairment. Due to the wide range of cognitive tests applied across the 19 studies, the authors classified each cognitive test into one of six cognitive categories of; tests of general cognitive functioning (e.g. MMSE), memory, speed of processing and attention tasks, language, executive function and visuo-spatial tasks to enable a quantitative comparison across cognitive domains. As some tests are not highly specific to one domain, they explored reclassifying tests from one domain to another and found that it did not result in any substantial change in effect. Neither the standard mean difference of all the cognitive scores combined, nor the specific cognitive domains investigated, showed any significant effects for older adults either with or without existing cognitive impairment. Further sub-group analysis showed that vitamin supplementation of at least six months duration had no impact on cognitive
status, nor did the folate availability (low/medium/high) of the country where the trials were conducted.

The effect of supplementation of B group vitamins on cognition has also been studied indirectly by brain imaging techniques, such as serial volumetric MRI scans (33) using a subset of 186 participants aged 70 years and over from the Homocysteine and B vitamins in cognitive impairment (VITACOG) RCT study. Participants with similar homocysteine levels at baseline, taking a vitamin B supplement (folic acid 0.8mg/d, vitamin B12 0.5mg/d, vitamin B6 20mg/d) showed a significantly slower rate of brain atrophy compared to the placebo group over two years. The rate of brain atrophy in the placebo group was higher in participants with higher baseline homocysteine levels. The authors noted that the homocysteine lowering effect was likely to be from folate and vitamin B12 rather than from vitamin B6, as cystathione, a marker of B6, was unchanged between treatment and placebo groups. Although not part of the study, a strong association was observed between atrophy rate and cognition (35). The same group subsequently reported that B vitamin supplementation could slow the atrophy of specific regions of the brain that are associated with cognitive decline (34). Furthermore, it was observed that the beneficial effect of B vitamins was confined to participants with high homocysteine (above the median of 11µmol/L) but of no benefit to participants with low homocysteine levels, as there were no differences in gray matter atrophy between participants with low and high homocysteine levels taking B vitamins for two years.
3.2 Vitamin C

A summary of studies of vitamin C, either as a monotherapy or in combination with other antioxidants such as vitamin E and vitamin A or β-carotene on cognitive decline, is shown in Table 3.

A recent review of the role of vitamin C in AD (36) has highlighted that high intake of a supplement or food rich in vitamin C does not necessarily translate to adequate vitamin C levels in blood plasma, as the ability of the body to transport vitamin C from the intestines to the blood is limited by the sodium-dependent vitamin C (SVCT1) transporters into the gut, consequently vitamin C levels transposed from food frequency surveys may not reflect blood plasma levels. Further recent reviews (37, 38) have highlighted a need for future studies to determine whether there is an association of vitamin C in plasma and cerebrospinal fluid (CSF) with rates of cognitive decline.
Table 3: Studies of vitamins A, C and E, either as monotherapies or in combination, on cognitive decline

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Vitamin Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>Heo et al, 2013 (37)</td>
<td>Literature review</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bowman, 2012 (38)</td>
<td>Literature review</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Harrison, 2012 (36)</td>
<td>Literature review</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Farina et al, 2012 (39)</td>
<td>Systematic review (Cochrane)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Li et al 2012 (40)</td>
<td>Systematic review with meta-analysis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Smith et al, 1999 (41)</td>
<td>RCT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Kang et al, 2009 (42)</td>
<td>RCT</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Vitamin C

Vitamin E

Vitamin E with other antioxidants
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Vitamin Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaffe et al, 2004(43)</td>
<td>RCT</td>
<td>X        X           X</td>
<td>Participants of the AREDS (n=2,166, 61-87 years,) showed no evidence of effect of dietary supplements and zinc and cupric oxide taken daily for a median duration of 6.9 years on cognition, measured at study completion, compared to a placebo group.</td>
</tr>
<tr>
<td>Devore et al, 2013(44)</td>
<td>Longitudinal study</td>
<td>X        X           X</td>
<td>Dietary intake study of 16,010 female participants, mean age 74.4 years, with 2 year follow up over 6 years found that vitamins E &amp; C intakes were not consistently related to cognition but carotenoid consumption may have cognitive benefit in older adults.</td>
</tr>
</tbody>
</table>

Abbreviations: AD; Alzheimer’s disease, AREDS; Age-Related Eye Disease Study, CVD; Cardiovascular disease, MCI; Mild cognitive impairment, RCT, randomised controlled trial.
3.3 Vitamin D

There have been several systematic reviews of a number of largely cross-sectional and observational studies published as shown in Table 4.

A series of recent systematic reviews and meta-analyses have pooled and evaluated the data from primary studies (45-48). Etgen et al assessed the association between cognitive impairment and vitamin D deficiency using a meta-analysis of studies of 100 or more participants (46). The meta-analysis of 5 cross-sectional and 2 longitudinal studies showed an increased risk of cognitive impairment in those with low vitamin D compared to normal vitamin D status (Odds Ratio (OR) 2.39, 95% Confidence Interval (CI) 1.91-3.00; p<0.0001). The authors noted a large variability in assessment of cognitive function between studies, where specific aspects of cognition such as learning and memory tasks showed no association with vitamin D, while studies assessing global cognitive performance (e.g. via MMSE) showed significant association with vitamin D insufficiency.

Another systematic review (45) of 37, mainly cross-sectional studies examined the association between cognitive function and dementia with vitamin D level in adults. A meta-analysis of eight studies that compared mean MMSE scores between individuals with vitamin D <50nM (deficient) and ≥50nM (adequate) showed MMSE scores were lower in individuals with lower 25OHD, with a weighted mean difference (WMD) of 1.2 (0.5 to 1.9) and statistically significant heterogeneity (I² =0.65; p= 0.002). The study concluded that lower vitamin D levels were associated with poorer cognitive function.

Another very recent systematic review on the association between vitamin D and cognition collated the findings of 28 more recent cross-sectional and prospective studies (48) and reached similar conclusions that low vitamin D levels were associated with poorer outcomes on one or more cognitive function tests or a higher frequency of dementia.

There has been a lack of consistency of cognitive tests used to assess cognitive domains making comparison between studies difficult. Hence, rather than focussing on global cognitive impairment, which is generally assessed using composite cognitive tests such as MMSE or Clinical Dementia Rating scale (CDR), Annweiler and colleagues (47) have very recently published a meta-analysis of
the association of 25OHD serum levels with the domain specific cognitive functions of episodic memory and executive functions. Through pooling the results of 17 studies, it was found that lower serum 25OHD concentrations were predictive of the executive dysfunction of processing speed, information updating and mental shifting, but the association with episodic memory remains uncertain (47). A recent cross-sectional study of 127 frail or pre-frail elderly Dutch subjects, aged 65 years and older reported similar results, with 25OHD levels being positively associated with executive function, but there was no association with information processing speed, attention and working memory or episodic memory (49).

Although subjects with confirmed AD were outside the scope of this review, it is of interest to note that meta-analyses of three studies (45, 50, 51), showed that serum 25OHD levels were lower in AD patients compared to healthy controls, however causative links were not established.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annweiler et al 2013(47)</td>
<td>Systematic review with meta-analysis</td>
<td>Critical appraisal of 14 cohort and 3 interventional studies of 44-5,692 participants, age 18–100 years. Meta-analysis of studies, found that lower serum 25OHD levels could predict executive dysfunctions in some domains of cognitive performance</td>
</tr>
<tr>
<td>Balion et al 2012(45)</td>
<td>Systematic review with meta-analysis</td>
<td>Critical appraisal of 37 studies of 27–17,099 participants, mainly ≥ 65 years. Meta-analysis of 8 studies of 80-1,080 participants showed MMSE scores were lower in individuals with lower 25OHD levels.</td>
</tr>
<tr>
<td>Etgen et al 2012(46)</td>
<td>Systematic review with meta-analysis</td>
<td>Meta-analysis of 5 cross-sectional and 2 longitudinal studies of 7,688 participants, mainly ≥ 60 years showed an increased risk of cognitive impairment for low vitamin D compared with normal vitamin D status</td>
</tr>
<tr>
<td>van der Schaft et al 2013(48)</td>
<td>Systematic review</td>
<td>Critical appraisal of 25 cross-sectional studies of 25–14,735 participants, mean age 20–80 years, and 6 prospective studies of 40-6,257 participants, ≥ 65 years, with a mean follow up range of 4-7 years, found that low vitamin D levels are associated with poorer outcomes in one or more cognitive function tests.</td>
</tr>
<tr>
<td>Annweiler et al 2009(9)</td>
<td>Systematic review</td>
<td>Critical appraisal of 5 observational studies of 32–9,556 participants, age 20–90 years found insufficient evidence of effect on cognition</td>
</tr>
<tr>
<td>Pogge 2010(10)</td>
<td>Clinical review</td>
<td>Review of 9 cohort studies of 60-1,604 participants, mean age 66-80 years, found insufficient evidence of effect on cognition</td>
</tr>
<tr>
<td>Brouwer-Broslma et al 2013(49)</td>
<td>Cross-sectional study</td>
<td>25OHD levels associated with executive functioning and near significant association with information processing speed, but not with attention and working memory or episodic memory in an elderly cohort of 127 frail or pre-frail men, mean age 79 years.</td>
</tr>
</tbody>
</table>

Abbreviations: 25OHD; 25-hydroxyvitamin D, AD; Alzheimer’s disease MCI; Mild cognitive impairment,
3.4 Vitamin E

A summary of vitamin E studies related to cognitive decline are shown in Table 3. A recent Cochrane Review (39) updating the previous Cochrane review of Isaac et al. (52) considered evidence published up to 2012 and concluded that there is no convincing evidence that vitamin E is of benefit in the treatment of MCI. This concurs with the previous Cochrane Review (52) that considered evidence published up to 2006, which concluded that there was no evidence of efficacy of vitamin E in the prevention or treatment of people with MCI.

The most widely used supplemental form of vitamin E is α-tocopherol and it has recently been reported that its use can diminish the bioavailability of other forms of tocopherols and tocotrienols (8, 53). Two cross-sectional studies (8, 54) have investigated the association between plasma levels of the eight forms of vitamin E and the incidence of MCI and / or AD in two separate populations, the Kungsholmen project in Sweden and the AddNeuroMed-Project, a multi-centre European study. Both studies reached similar conclusions, that participants with AD or MCI had lower plasma levels of total tocopherols, total tocotrienols and total vitamin E compared to cognitively normal participants. Overall there were no significant differences between the different vitamin E forms and risk of AD.

3.5 Vitamin E and other antioxidant vitamins

Vitamin E has also been commonly used in conjunction with other antioxidant vitamins, particularly vitamin C and sometimes vitamin A in studies on the prevention of AD.

3.5.1 RANDOMISED CONTROLLED STUDIES

Several RCTs have studied the effects of combinations of vitamin supplements on cognition (41-43) reaching similar conclusions with a range of vitamin E (400 – 600 IU) and β-carotene (12 – 50 mg) but consistent vitamin C (500mg) levels across studies. A double-blind placebo controlled trial assessing the effects of the daily supplementation of 600 IU α-tocopherol, 500mg ascorbic acid and 12mg β-carotene on mental performance in the elderly at 4, 8 and 12 months showed little effect of supplementation on mental performance (41). Similar results were observed among a cohort of 2,824 women studied over a 5.4 year period with pre-existing cardiovascular disease or cardiovascular disease risk factors in ‘The Women’s Antioxidant Cardiovascular Study’ (42).
Antioxidant supplementation with vitamin E (600 IU every other day), β-carotene (50 mg every other day), and vitamin C (500 mg daily) did not slow cognitive change. As the test group had been taking the supplements for a mean of 3.5 years prior to initial cognitive assessment, cognitive change could not be compared over the study duration within the treat group and only compared to the placebo group. A further randomised controlled trial of 2,166 elderly people from the Age-Related Eye Disease Study reported that supplementation with vitamin E (400 IU), vitamin C (500mg), beta-carotene (15mg) with or without zinc (80mg) and copper (cupric oxide 2mg) had no significant effect on cognitive performance compared to a placebo, following a battery of 6 cognitive tests administered at the end of the study, after a median of 6.9 years of treatment (43).

3.5.2 DIETARY INTAKE STUDIES

The role of vitamins for the prevention of AD has been widely studied using dietary intake and / or vitamins from supplements with conflicting results. A recent meta-analysis of seven studies (40) evaluated the association between the dietary intake of vitamin E, vitamin C, and β-carotene and risk of AD. For vitamin E, three of the seven studies evaluated accounted for 80% of the weighting, giving a Relative Risk (RR) (95%CI) of 0.76 (0.67-0.84). For vitamin C, two of the six studies accounted for 71% of the weighting giving a RR (95%CI) of 0.83 (0.72-0.94) and for β-carotene two of the five studies accounted for 83% of the weighting giving a RR (95%CI) of 0.88 (0.73-1.03). The results suggested that vitamin E, vitamin C and β-carotene intake from dietary sources may help lower the risk of AD, with vitamin E showing the most protective effect. A more recent study (44) of a cohort of 16,010 participants aged ≥70 years from the Nurses’ Health Study found that long term vitamin E and C intakes were not consistently related to cognition and that greater consumption of carotenoids, particularly lycopene may have cognitive benefits in older adults.

Although out of the scope of this review, recently completed clinical studies have begun to focus on antioxidant levels in CSF to determine whether antioxidant supplement interventions are reaching and impacting on AD pathways (55, 56), however trials to date have not resulted in positive clinical findings.
4 Discussion

The role of vitamin intake on cognitive decline has been extensively studied through an array of case control, observational, cross-sectional and clinical trial studies. This has enabled the pooling of study results and critical appraisal of the various levels of evidence in a series of systematic reviews and meta-analyses. However, this has not translated to definitive conclusions, with many studies discussing limitations such as heterogeneity in cognitive testing, differences in thresholds low vitamin status, the short duration of many studies, the focus of studies on elderly cohorts, very large variations in supplement doses administered in studies and a lack of quality studies.

For the B vitamins, either as monotherapies or in combination, twelve systematic reviews reached similar conclusions, that there is currently insufficient evidence of any effect of these vitamins on cognition. This concurs with Williams et al (25) who concluded that there is a moderate level of evidence for no association of vitamin B6, B9 (folate) and B12 supplements in the prevention of cognitive decline. The validity of B vitamin status especially from dietary intake or food frequency questionnaire data needs careful consideration, particularly in elderly populations, due to malabsorption often caused by medications or gastrointestinal absorption in conditions such as diabetes and gastrointestinal diseases. Furthermore, the introduction of folate fortification of food in different countries at different times makes comparisons between studies from different countries difficult.

The developments in brain imaging techniques has enabled a further diagnostic tool for researchers to make comparisons between the clinically diagnosed healthy, MCI and AD groups, with studies showing that there is evidence for MCI participants with high homocysteine levels, that B vitamins decrease brain atrophy in areas of the brain associated with cognitive decline. The mechanism for the homocysteine lowering effect is still under investigation as Smith et al, (33) reported that the effect was likely to be from folate and vitamin B12 rather than vitamin B6, while a study from Faux et al (57) found no clear relationship between folate and vitamin B12 in modulating homocysteine levels.
For vitamin D, five systematic reviews and a clinical review have largely assessed evidence derived from observational, cross-sectional and small randomised clinical trials. While meta-analyses from the systematic reviews have shown an association between low vitamin D levels and diminished cognitive function, causality was not proven, and all studies highlighted the need for well designed randomised controlled trials to confirm any relationship between vitamin D and cognition. The majority of participants in these studies were older adults where there is evidence of a prevalence of vitamin D deficiency. This has led to investigators raising the question of reverse causality as individuals with cognitive decline are more likely to have poor nutrition and spend less time outdoors. Furthermore, many older studies have not consistently controlled for confounding factors including chronic kidney disease, depression, sun exposure which varies throughout the year, use of supplements, fortified foods, natural food sources, age and genetic factors which are considered factors that can impact significantly on vitamin D status. Some studies also highlighted the need for consistency in assay methods of vitamin D (25OHD) measurement and cognitive testing.

The variation in the definition of vitamin D deficiency between studies has also made comparisons difficult with some studies using ≥ 50nmol/L as adequate while other studies were using ≥75nmol/L for comparison with vitamin D deficiency in statistical analyses. Current adequacy levels (≥ 50nmol/L) for vitamin D recommended by the recent Institute of Medicine report (IOM) (58) relate only to bone health and may differ for other health outcomes, including cognition.

While the plasma levels of vitamin E have been shown to be lower in MCI and AD patients when compared to the cognitively normal from cross-sectional studies, the balance of the various forms of tocopherols and tocotrienols is relatively consistent, across cognitive states. However the effects of supplementation may alter the balance of various tocopherols and tocotrienols plasma levels (53), so studies utilising a variety of forms of tocopherols and tocotrienols, rather than only α-tocopherol could be considered.

Although not focussed on cognition, meta-analyses and large multicentre, prospective clinical trials have raised serious concerns regarding increased morbidity and mortality risks with high dose vitamin E treatments over 400 IU daily for more than one year (59). Hence, in light of the recent systematic reviews concluding that there is no clear evidence for benefits of vitamin E intake on the delay of cognitive decline, and in the absence of prospective, randomized, controlled clinical trials
documenting benefits in the prevention or treatment of AD that outweigh documented morbidity and mortality risks, vitamin E supplements should not be recommended for prevention of AD. Further, the Cochrane review of Bjelakovic et al, (60) highlighted concerns of the long term use of antioxidant supplements, β-carotene, vitamin A and vitamin E due to an increased risk of all-cause mortality.

Specifically related to cognition, three recent reviews reported that there is insufficient evidence for an effect of vitamin C on cognition (36-38) while RCTs of combinations of vitamin C, β-carotene, vitamin A and vitamin E found no evidence for the effect of dietary supplements on cognition. Williams et al (25) concluded that there was a high level of evidence for no association of vitamin C, vitamin E and β-carotene in prevention of cognitive decline. In contrast, a meta-analysis of seven dietary intake studies (40) found a lower risk of AD. However, as dietary intake studies are mostly based on food frequency questionnaires and affected by measurement errors such as recall bias, vitamin levels transposed from food frequency surveys may not reflect blood plasma levels, as previously identified by Harrison et al (36) for vitamin C and should be considered to represent a lower level of evidence than RCTs and systematic reviews.

The potential of nutritional interventions to prevent or delay cognitive impairment and the development of Alzheimer’s disease continues to gain momentum, with an array of studies enabling the systematic review and meta-analysis of some studies. However, the broad range of cognitive function tests applied across studies has made comparison between studies challenging (61). Hence consensus by cognition researchers on a subset of cognitive function tests that should be common to all nutritional studies to enable comparison across investigations is essential. Furthermore, studies are questioning the benefits of vitamin supplementation on well-nourished individuals and suggesting that supplements may only be of benefit when there is deficiency or an inability to absorb or metabolise essential micronutrients (62). There continues to be a need for nutritional/ clinical trials over sufficient lengths of time (12 months minimum, 18 months or longer preferable), focussed on younger age groups (viz.40-50years), which control for confounding dietary and lifestyle factors, and incorporate a combination of screening tools such as brain imaging techniques, biomarker and cognitive test batteries relevant to nutritional outcomes.
5 Concluding Remarks

While low plasma vitamin levels have often been associated with cognitive decline, particularly in elderly populations, currently there is no clear evidence that supplementation with vitamin B6, B12 and/or folic acid, improves dementia or slows cognitive decline, even though it may normalise homocysteine levels. There is no convincing evidence for an association of vitamin C, and vitamin E either as a monotherapy or in combination with other antioxidant vitamins such as vitamin C, A and β-carotene and the prevention of cognitive decline. For vitamin D, there is a high level of evidence of association between low vitamin D levels and diminished cognitive function, particularly in the elderly, however causality cannot be confirmed from the available evidence. Evaluation of the totality of the currently available evidence indicates that vitamin intake, either as a monotherapy, or in combination with other vitamins, has no clinically-relevant effect on delaying cognitive decline or the onset of AD.
6 Acknowledgements

The authors would like to acknowledge Professor Michael Fenech, Dr Malcolm Riley and Dr Lance Macaulay for their ongoing fruitful discussions.
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Ms Krause has a Bachelor of Science degree from Deakin University, Melbourne with over 30 years experience in food research organisations. Ms Krause is currently part of the Joanna Briggs Institute (JBI) Centre of Nutrition and Health in CSIRO Animal, Food and Health Sciences, undertaking scientific literature searches and reviews for a range of projects and project proposals. Ms Krause is accredited as a Systematic Scientific Reviewer by the JBI, an international collaboration of JBI Centres in 40 countries focussed on evidence-based healthcare and practice.

Ms Krause has also had 10 years dairy and meat research and extension experience, 3 years business development experience, 10 years experience in confectionery research and applications, including 5 years concurrent experience in milkfat research and extension activities. Ms Krause has held Secretariat roles for Dairy Australia’s Ingredients by Design program and for CSIRO’s Innovative Foods Centre (IFC) ‘Advanced processing and innovative foods program’, where she has organised and participated in industry days and conferences, prepared fact sheets, industry awareness articles, annual and final reports, liaised with stakeholders from government, universities, research directors, researchers and companies to deliver outcomes of the $9.8M IFC program.

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Dr Roupas obtained his PhD from the Department of Medicine at Monash University, Melbourne, Australia in 1988 and completed his postdoctoral research at the University of Michigan Medical School, USA. During his 3 years at the University of Michigan, he was awarded fellowships from the American Diabetes Association (Michigan) and the Juvenile Diabetes Foundation International (New York). On his return to Australia, to the Department of Clinical Biochemistry at the Royal Children’s Hospital, Melbourne, he was awarded the 1991 Eli Lilly Diabetes Fellowship and a 4-year fellowship from the National Health and Medical Research Council (NHMRC) of Australia. For the past 18 years, Dr Roupas has been a Research Team Leader at CSIRO and a Project Leader of projects for the CSIRO Food Futures Flagship, the Preventative Health Flagship, and the National Centre of Excellence in Functional Foods relating to the scientific substantiation of health messages for dietary guidelines and health claims for food standards / regulatory applications. He is currently the Team Leader of the Joanna Briggs Institute (JBI) Centre of Nutrition and Health within CSIRO
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References


Effect of vitamin intake on cognitive decline: Evaluation of the evidence