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Malouf R, Grimley Evans J

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[Intervention Review]

Vitamin B6 for cognition

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ABSTRACT

Background

Micronutrient status can affect cognitive function at all ages. Vitamin deficiencies could influence memory function and might contribute to age-associated cognitive impairment and dementia. Vitamin B6, comprising three chemically distinct compounds, pyridoxal, pyridoxamine, and pyridoxine, is involved in the regulation of mental function and mood. Vitamin B6 is also an essential homocysteine re-methylation cofactor, and deficiency is associated with an increase in blood homocysteine levels. Homocysteine is a risk factor for cerebrovascular disease and may also have directly toxic effects on neurons of the central nervous system. Neuropsychiatric disorders including seizures, migraine, chronic pain and depression have been linked to vitamin B6 deficiency. Epidemiological studies indicate that poor vitamin B6 status is common among older people. Hyperhomocysteinaemia has been suggested as a cause or mechanism in the development Alzheimer's disease and other forms of dementia. Supplementation with B vitamins including vitamin B6 has been shown to reduce blood homocysteine levels.

Objectives

To assess the efficacy of vitamin B6 supplementation in reducing the risk of developing cognitive impairment by older healthy people, or improving cognitive functioning of people with cognitive decline and dementia, whether or not vitamin B6 deficiency has been diagnosed.

Search methods

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 16 March 2008 using the terms: B6, "B 6", B-6, pyridoxine, pyridoxamine, pyridoxal. The CDCIG Specialized Register contains records from all major health care databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many trials databases and grey literature sources.

Selection criteria

All unconfounded, double-blind randomized controlled trials in which the intervention with vitamin B6 was compared with placebo for healthy older people or people with cognitive decline or dementia. The primary outcome of interest was the efficacy of vitamin B6 supplementation on cognitive function.

Data collection and analysis

The two reviewers independently evaluated all studies identified as possibly meeting the criteria for inclusion. One reviewer independently extracted the data. Studies were rated for their overall quality. The weighted mean differences between treatment and placebo groups, with 95% confidence intervals, were calculated for each outcome. Review Manager version 4.2 was used to analyse the variance.

Main results

No trials of vitamin B6 involving people with cognitive impairment or dementia were found.

The two trials included in the review (Bryan 2002; Deijen 1992) used a double-blind, randomized, placebo-controlled design and involved 109 healthy older people. One trial restricted enrolment to women and the other to men.

Vitamin B6 supplementation and healthy older women:

Bryan 2002, enrolled 211 healthy women from various age groups into a five-week study. The trial was of multifactorial design with folic acid, vitamin B12, vitamin B6 and placebo in its four arms. Twelve healthy women aged 65 to 92 years received 75 mg vitamin B6 orally per day and were compared with 21 healthy women who were allocated to placebo. No statistically significant benefits from vitamin B6 on mood or cognition were observed.

Vitamin B6 supplementation and healthy older men:

Deijen 1992, recruited 76 healthy men aged 70 to 79 years. They were divided into 38 matched pairs, one member of each pair randomly allocated to 20 mg of vitamin B6 (pyridoxine hydrochloride) per day for 12 weeks the other to placebo. No statistically significant differences between treatment and placebo were found in their effects on cognition or mood.

Effect of vitamin B6 supplementation on vitamin B6 status:

Deijen 1992, reported that 20 mg of pyridoxine hydrochloride per day for 12 weeks increased blood vitamin B6 activity as assessed as by plasma pyridoxal-5'-phosphate (WMD 238, 95%CI 211.58 to 264.42, P<0.00001) and erythrocyte enzyme asparate aminotransferase (WMD 0.43, 95%CI 0.30 to 0.56, P<0.00001)

Effect of vitamin B6 supplementation on blood homocysteine concentration:

Neither of the included trials measured homocysteine levels.

Drop-outs:

All participants allocated to vitamin B6 or placebo completed the trial protocol.

Adverse events:

No adverse effects were reported.

Effect of vitamin B6 on carer burden, care costs and institutionalization rate:

We found no trials in which these outcomes were assessed.

Authors' conclusions

This review found no evidence for short-term benefit from vitamin B6 in improving mood (depression, fatigue and tension symptoms) or cognitive functions. For the older people included in one of the two trials included in the review, oral vitamin B6 supplements improved biochemical indices of vitamin B6 status, but potential effects on blood homocysteine levels were not assessed in either study.

This review found evidence that there is scope for increasing some biochemical indices of vitamin B6 status among older people. More randomized controlled trials are needed to explore possible benefits from vitamin B6 supplementation for healthy older people and for those with cognitive impairment or dementia.

PLAIN LANGUAGE SUMMARY

No evidence of benefit from vitamin B6 supplementation on mood or cognition of older people with normal vitamin B6 status or with vitamin B6 deficiency

Micronutrient status can affect cognitive function at all ages. Vitamin deficiencies could influence memory function and might contribute to age-associated cognitive impairment and dementia. Vitamin B6 is involved in the regulation of mental function and mood and in the metabolism of homocysteine, a risk factor for vascular disease. Two trials of vitamin B6 supplements for healthy elderly people qualified for this review, with no beneficial effects on mood or mental function detectable. Homocysteine levels were not assessed. No ill effects of vitamin B6 were observed. No trials studying effects of vitamin B6 treatment for people with dementia or cognitive impairment were identified.

BACKGROUND

Description of the condition

Dementia is characterized by progressive intellectual deterioration that is sufficiently severe to interfere with social or occupational functions (Rowland 2000). Dementia is a worldwide and serious public health problem (Miller 1999). Age is a recognized risk factor (Carr 1997) in that the prevalence and incidence of the disease increases with advancing age (Callahan 1995). There are many causes of dementia, the two pathologically distinct types that comprise the majority of cases are Alzheimer's disease and vascular dementia. Alzheimer's disease, the most common form of dementia, is a neurodegenerative disorder with memory loss and progressive decline in cognitive functions (Knopman 1998). Half of the population aged over 85 suffers from the disease (White 1996). The economic cost of Alzheimer's disease is higher than that of heart disease and cancer together (Schneider 1990). Vascular dementia is the second most frequent type of dementia accounting for 20 to 30% of cases (Fabbender 1999), and stroke is a major cause (Miller 1999).

Genetic and non-genetic factors, such as head trauma, education, stress, and nutrition, interact with the biology of the ageing brain in the development of dementia. Recently greater attention has been paid to non-genetic factors, in the hope of establishing a basis for preventing dementia or altering its course particularly in the early stages. Nutrition is a modifiable lifestyle factor, and may be relevant to the pathogenesis of dementia. About 30% of healthy older people have subclinical malnutrition of one or more dietary components, such as vitamins (Blumberg 1944). Correction of such deficiencies might have a role in preventing or retarding cognitive decline in later life.

Description of the intervention

Vitamin B6 is water-soluble, and occurs in three closely related compounds with similar physiological actions, pyridoxine, pyridoxal and pyridoxamine. The first is found in large quantities in plant sources and the other two in animal tissues (Evans 2002). Liver, whole grain cereals, peanuts, and bananas are rich in vitamin B6. A significant increase in vitamin B6 status has been noted after the consumption of moderate amounts of alcohol (Walmusley 1999). In humans, vitamin B6 is synthesized by microorganisms of the large gut, but the amount utilized by the human host is uncertain. Adult requirements are about 2 mg/day (Evans 2002). Pharmacological doses of vitamin B6 have been used in treatment for autism syndromes and in the hope of improving speech and language functions of some children with learning difficulties. It is also used as an over-the-counter medication for premenstrual syndromes and for vomiting in pregnancy.

Features of vitamin B6 deficiency include convulsions, peripheral neuropathy and skin diseases (dermatitis, cheilosis, glossitis and angular stomatitis) (Evans 2002). Some drugs such as isoniazid, hydralazine and penicillamine which act as chemical antagonists to B6 may induce deficiency. Heavy overdoses (200 mg/day or more) of vitamin B6 for several weeks may cause a peripheral sensory neuropathy.

How the intervention might work

The vitamin participates in an important coenzyme system in protein synthesis and is involved in fat and carbohydrate metabolism. Vitamin B6 deficiency has a serious effect on brain function (McCormick 2001), as the vitamin plays a pivotal role in the synthesis of several neurotransmitters including, serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid. Lack of these neurotransmitters may be linked to the development of some neuropsychological disorders such as parkinsonism, tardive dyskinesia and depression. Vitamin B6 affects immune function (Talbott 1987), and deficiency results in impaired cell-mediated immunity and reduced antibody responses.

The biologically active form of the vitamin, pyridoxal phosphate, is available for use by tissues; 4-pyridoxic acid is an inactive form and represents a major vitamin B6 catabolite, excreted in the urine. Vitamin B6 is required as an essential cofactor in homocysteine metabolism through a trans-sulphuration pathway. Particularly the active form of vitamin B6 plays a key role as a coenzyme of

cystathionine synthase and cystathioninelyase. Both enzymes are required for the metabolism of homocysteine to cysteine.

Elevated total homocysteine levels have been recognized as an independent risk factor for atherosclerosis, cardiovascular diseases (Bots 1997; Bostom 1999), carotid atherosclerosis (Selhub 1995), and stroke. Therefore, several studies have postulated the role of hyperhomocysteinaemia in the aetiology of Alzheimer's disease (Clarke 1998; McCddon 1998). Evidence from observational studies has demonstrated that plasma homocysteine levels are influenced by several B-vitamins, including vitamin B6 (Joosten 1993, Riggs 1996).

An inverse relationship between plasma pyridoxal concentration and age has been documented in several studies (Rose 1976; Joosten 1993; Pannemans 1994; Bates 1999). Poor vitamin B6 status and low dietary vitamin B6 intakes and other necessary nutrients have been observed in older people (Rose 1976, Kant 1988, Lowik 1989, Riggs 1996), with approximately 20% of aged people having inadequate vitamin B6 status (Selhub 1993). The prevalence of deficiency is higher in people who are institutionalized than in those living in their own homes (Chen 1981; Lowik 1992). The prevailing hypothesis for the possible downward trend of vitamin B6 status in later life involves low intake, less efficient retention, and increased catabolism of the vitamin (Kant 1988; Lowik 1989, Bates 1999). A correlation between blood levels of B vitamins and cognitive function has been documented in several studies (Goodwin 1983; La Rue 1997). In the Boston Normative Aging Study, high vitamin B6 concentration has been correlated with better performance in memorization tests (Riggs 1996). In another experimental study, a 2 mg daily supplement of vitamin B6 for one year was associated with a significant effect on responses to the visual reproduction battery test (Tolonen 1988). It has been reported that patients with Alzheimer's disease are more likely than controls to have low plasma pyridoxal-5-phosphate concentrations (Miller 2002).

Why it is important to do this review

Despite these observations, the number of controlled trials that have explored the possibility that enhancing vitamin B6 status may improve cognition of healthy or cognitively impaired older people is very low. Here we systematically review the published evidence.

OBJECTIVES

To assess effects of vitamin B6 supplementation on cognitive function of healthy, demented, or cognitively impaired people, in terms of preventing the onset or slowing the progression of cognitive impairment.

METHODS

Criteria for considering studies for this review

Types of studies

The review sought all unconfounded, randomized, double-blind trials comparing the effects of vitamin B6 and placebo on the cognitive functions of healthy older people and of those with cognitive impairment or dementia. Trials in which the allocation to treatment or placebo was not randomized were excluded. This is because prior knowledge of treatment allocation may lead to biased allocation (Schulz 1995). Trials of combinations of different vitamins were also excluded.

Types of participants

Eligible studies were those involving healthy elderly people, people with cognitive impairment or any type of dementia of any severity, with or without evidence of vitamin B6 deficiency. The diagnosis of dementia may be based on accepted standardized criteria such as ICD (International Classification of Diseases), DSM (American Psychiatric Association) (APA 1987) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association) (McKhann 1984). The diagnosis of cognitive impairment was based on validated rating scales.

Types of interventions

Vitamin B6 by any route of administration, at any dosage, for any duration, in comparison with placebo.

Types of outcome measures

The outcomes of interest were:

Primary outcomes

- Cognitive function
- Functional performance
- Behavioural disorders

Secondary outcomes

- Blood homocysteine levels
- Vitamin B6 status
- Safety and adverse effects

Search methods for identification of studies

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 16 March 2008 for all years up to December 2005. This register contains records from the following major healthcare databases *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, and many ongoing trial databases and other grey literature sources. The following search terms were used: B6, "B 6", B-6, pyridoxine, pyridoxamine, pyridoxal.

The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL were searched separately on 16 March 2008 for records added to these databases after December 2005 to March 2008. The search terms used to identify relevant controlled trials on dementia, Alzheimer's disease and mild cognitive impairment for the Group's Specialized Register can be found in the Group's module on *The Cochrane Library*. These search terms were combined with the following search terms and adapted for each database, where appropriate: B6, "B 6", B-6, pyridoxine, pyridoxamine, pyridoxal. On 16 March 2008, the Specialized Register consisted of records from the following databases:

Healthcare databases:

- *The Cochrane Library*: (2006, Issue 1);
- MEDLINE (1966 to 2006/07, week 5);
- EMBASE (1980 to 2006/07);
- PsycINFO (1887 to 2006/08, week 1);
- CINAHL (1982 to 2006/06);
- SIGLE (Grey Literature in Europe) (1980 to 2005/03);
- LILACS: Latin American and Caribbean Health Science Literature (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F) (last searched 29 August 2006).

Conference proceedings:

- ISTP (http://portal.isiknowledge.com/portal.cgi) (Index to Scientific and Technical Proceedings) (to 29 August 2006);
- INSIDE (BL database of Conference Proceedings and Journals) (to June 2000);.

Theses:

- Index to Theses (formerly ASLIB) (http://www.theses.com/) (UK and Ireland theses) (1716 to 11 August 2006);
- Australian Digital Theses Program (http://adt.caul.edu.au/): (last update 24 March 2006);
- Canadian Theses and Dissertations (http://www.collectionscanada.ca/thesescanada/index-e.html): 1989 to 28 August 2006);
- DATAD - Database of African Theses and Dissertations (http://www.aau.org/datad/backgrd.htm);
- Dissertation Abstract Online (USA) (http://wwwlib.umi.com/dissertations/gateway) (1861 to 28 August 2006).

Ongoing trials:

UK

- National Research Register (http://www.update-software.com/projects/nrr/) (last searched issue 3/2006);
- ReFeR (http://www.refer.nhs.uk/ViewWebPage.asp?Page=Home) (last searched 30 August 2006);
- Current Controlled trials: Meta Register of Controlled trials (mRCT) (http://www.controlled-trials.com/) (last searched 30 August 2006) :
- ISRCTN Register - trials registered with a unique identifier
- Action medical research
- Kings College London
- Laxdale Ltd
- Medical Research Council (UK)
- NHS Trusts Clinical Trials Register
- National Health Service Research and Development Health Technology Assessment Programme (HTA)
- National Health Service Research and Development Programme 'Time-Limited' National Programmes
- National Health Service Research and Development Regional Programmes
- The Wellcome Trust
- Stroke Trials Registry (http://www.strokecenter.org/trials/index.aspx) (last searched 31 August 2006);

Netherlands

- Nederlands Trial Register (http://www.trialregister.nl/trialreg/index.asp) (last searched 31 August 2006);

USA/International

ClinicalTrials.gov (http://www.ClinicalTrials.gov) (last searched 31 August 2006) (contains all records from http://clinicalstudies.info.nih.gov/);

IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html. The Ongoing Trials database within this Register searches http://www.controlled-trials.com/isrctn, http://www.ClinicalTrials.gov and http://www.centerwatch.com/. The ISRCTN register and Clinicaltrials.gov are searched separately. Centerwatch is very difficult to search for our purposes and no update searches have been done since 2003.

The IFPMA Trial Results databases searches a wide variety of sources among which are:

- http://www.astrazenecaclinicaltrials.com (seroquel, statins)
- http://www.centerwatch.com
- http://www.clinicalstudyresults.org
- http://clinicaltrials.gov
- http://www.controlled-trials.com
- http://ctr.gsk.co.uk
- http://www.lillytrials.com (zyprexa)
- http://www.roche-trials.com (anti-abeta antibody)
- http://www.organon.com
- http://www.novartisclinicaltrials.com (rivastigmine)
- http://www.bayerhealthcare.com
- http://trials.boehringer-ingelheim.com

- http://www.cmrinteract.com
- http://www.esteve.es
- http://www.clinicaltrials.jp

This part of the IPFMA database is searched and was last updated on 4 September 2006;

- Lundbeck Clinical Trial Registry (http://www.lundbecktrials.com) (last searched 15 August 2006);
- Forest Clinical trial Registry (http://www.forestclinicaltrials.com/) (last searched 15 August 2006).

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on *The Cochrane Library.*

The following search strategies were used to detect randomized controlled trials of Vitamin B6 on healthy elderly people:

MEDLINE 1966-2008/March:

#1 explode "Vitamin-B-6"/ all subheadings
#2 B6 or "b 6" or B-6 or pyridoxine or pyridoxamine or pyridoxal
#3 #1 or #2
#4 random* or placebo* or double-blind* or "double blind*"
#5 #3 and #4
#6 #5 and (cognit* or memor* or MMSE or ADAS-cog)

EMBASE 1980-2008/11:

#1 "pyridoxine"/ all subheadings
#2 B6 or "b 6" or B-6 or pyridoxine or pyridoxamine or pyridoxal
#3 #1 or #2
#4 random* or placebo* or double-blind* or "double blind*"
#5 #3 and #4
#6 #5 and (cognit* or memor* or MMSE or ADAS-cog)

Reference lists of retrieved articles were examined for additional trials.

Books concerning vitamin B6 and cognition were handsearched for additional trials.

Dr Eva Calvaresi (Bryan 2002) was contacted on 18 June 2003 for data on the total number of elderly participants in the vitamin B6 and placebo group, and the number of drop-outs. She replied the same day with the requested data.

Data collection and analysis

Selection of studies

Abstracts of the references retrieved by the search were read by one reviewer who discarded any that were clearly not eligible for inclusion. If the article could possibly be relevant, it was retrieved for further assessment. Both reviewers independently selected the trials for inclusion in the review from the citation list. Disagreements were to be resolved by discussion.

Quality assessment

The reviewers assessed the methodological quality of each trial, using the Cochrane Collaboration guidelines (Mulrow 1997):

Grade A: Adequate concealment is where the report describe the allocation of treatment by: (i) some centralised randomized scheme, when the trial provides details of an enrolment of the participants by phone; or (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers in which capsules form identical-looking numbered bottles are administrated in order participants; (iv) coded computer system in which confirms that the allocations were in locked unreadable file; or (v) if the envelopes were used for assignment the report should declare that they were sequentially numbered, sealed, opaque envelopes.

Grade B: Uncertain concealment, is where the allocation of treatment was described by: (i) use a "list" of "table" to allocate assignments; (ii) use of "envelopes" or sealed envelopes; (iii) stating the study as "randomized" without any further dentails of the method of randomization.

Grade C: Inadequate concealment, where the report describes allocation of treatment by: (i) alternation; (ii) using date of birth, gender, day of week, or any other approach; (iii) the allocation strategy is entirely transparent before assignment.

Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but less pronounced than inadequately concealed trials (Schulz 1995; Chalmers 1983). Trials were included if they conformed to categories A or B, and those falling into category C were excluded.

Data collection

Data were extracted from the published reports. The summary statistics required for each trial and each outcome for continuous data were the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation and the number of people for each treatment group at each time point were extracted if available.

For binary data the numbers in each treatment group and the numbers experiencing the outcome of interest were sought.

The baseline assessment was defined as the latest available assessment prior to randomization, but no longer than two months before.

For each outcome measure, data were sought on every person assessed. To allow an intention-to-treat analysis, the data would be sought irrespective of compliance, whether or not the person was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data are not available in the publications, "on-treatment" or the data of those who completed the trial were to be sought and indicated as such.

Data from 'open-label' follow-on phases after the randomized study were not used to assess safety or efficacy because patients were usually not randomized, nor were treatments concealed.

Data analysis

The outcomes measured in trials of dementia and cognitive impairment often arise from ordinal rating scales. Where the rating scales used in the trials have a reasonably large number of categories (more than 10) the data can be treated as continuous outcomes arising from a normal distribution.

Summary statistics (n, mean, and standard deviation) were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. When change from baseline results were not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measurements at baseline and assessment time was assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable in a meta-analysis.

The meta-analysis requires the combination of data from trials that may not use the same rating scale to assess an outcome. The measure of the treatment difference for any outcome is the weighted mean difference when the pooled trials used the same rating scale or test, and the standardized mean difference (the absolute mean difference divided by the pooled standard deviation) when they used different rating scales or tests.

For binary outcomes, such as improvement or no improvement, the odds ratio is used to measure treatment effect. A weighted estimate of the typical treatment effect across trials is calculated.

Overall estimates of the treatment difference are presented. In all cases the overall estimate from a fixed-effects model is presented and a test for heterogeneity using a standard chi-square statistic performed. If there is evidence of heterogeneity of the treatment effect between trials then either only homogeneous results are pooled, or a random-effects model used (in which case the confidence intervals would be broader than those of a fixed-effects model).

Subgroup analysis

Where relevant, and where data were available, subgroup analysis includes age, sex, whether B6 deficiency was present, duration of treatment and whether cognitive impairment was present at baseline.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

2006 search

Results from the new search revealed one RCT trial (Stott 2006), which was excluded.

2008 search

The latest search yielded 11 articles. All citations identified through the new search were screened according to the eligibility criteria in this review. None of the studies retrieved in the search were included in this update. Most of the trials were randomized controlled studies that compared the efficacy of vitamin B combinations versus placebo.

Included studies

No randomized controlled trials of the impact of B6 on cognitive impairment of people with dementia were found. The two studies that fulfilled the randomization criteria for inclusion (Deijen 1992; Bryan 2002) were concerned with the effect of vitamin B6 intervention on healthy older people.

Bryan 2002, studied the action of vitamin supplements on mood and cognitive performance of healthy women across the life span. Two hundred and eleven healthy Australian women were enrolled; recruitment criteria were: good health, non-smokers, not taking hormone replacement therapy or any medication that might affect mental status. Participants were also required to have English as mother language or to be proficient in English as many assessments were language-dependent. Participants were assigned into three age groups: younger, middle and older. The trial used a multifactorial design with participants randomly assigned to one of four treatment arms providing daily doses of 750 μg of folic acid, or 15 μg of vitamin B12, or 75 mg of vitamin B6, or placebo. Twelve women aged 65 to 92 received 75 mg of vitamin B6 orally per day for five weeks and 21 were on placebo. Standardized measures of cognition and were applied at baseline and at the end of the trial. Mood questionnaires were administered at the end of the intervention period. Background dietary intakes were estimated from a self-completed questionnaire.

Deijen 1992 restricted enrolment to healthy men aged 70 to 79 years and with scores above 80 on a condensed version of the Groninger Intelligence Test. The required entry criteria were: good health, limited alcohol consumption, not using medication interacting with vitamin B6 or using supplementation within the period of three months before the trial. Seventy six men were divided into 38 pairs matched for age, vitamin B6 status and Intelligent quotient. By random allocation one member of each pair received 20 mg of pyridoxine hydrochloride orally a day for 12 weeks and the other received placebo. Seveneteen percent of the participants were marginally B6 deficient as defined by levels of plasma pyridoxal-5-phosphate and erythrocyte enzyme asparate aminotransferase. Nine of these were in the placebo and four in the supplement group.

- Adverse effect:
- No adverse effects of vitamin B6 were reported.

Withdrawn:
All participants receiving vitamin B6 in both trials reached end-point.

Outcome measures

The following standardized neuropsychological batteries were used to evaluate cognitive and mood performance on healthy women (Bryan 2002):

1-Speed of processing:

- The Boxes Test (Earles 1995): a paper-and pencil test that measures sensory-motor speed. It consists of 100 open boxes and participants are asked to draw lines to complete each box. The score is the total number of boxes completed in 30 seconds.
- Digit Symbol Coding (Wechsler 1997), a measure of perceptual speed, requires participants to substitute symbols for 133 digits on a printed sheet. The score is the number of correct substitutions completed in 120 seconds.
- Symbol Search Task (Wechsler 1997): is a subtest of the Wechsler Adult Intelligence Scale III and measures perceptual speed. Two columns of symbols are presented and participants required to scan the columns and indicate if a symbol in one column appears also in the other. Final score is the number of symbols identified correctly in 60 seconds.

2-Working Memory:

Digit Span Backwards Test (Wechsler 1997): The is the digit span test used in the intelligence and memory scales of the Wechsler batteries as a measure immediate verbal recall. It involves a range of different mental activities including auditory attention and short-term retention. The test consists of two trials for each span length, each string consists of two to eight random number sequences that the examiner read aloud at the rate of one number per second. The participants are required to repeat the number strings in reverse sequence. One point is awarded for each string was recalled correctly; if neither list is repeated successfully, a score of zero is given and the test ended. Average scores on this task decrease about one point during the seventh decade (Lezak 1995).

- Letter Number Sequencing Test (Wechsler 1997): Chains of numbers and letters (from two to eight with three trials in each chain) are read to participants who are required to repeat first the numbers in given order then the letters in alphabetical order. One point was given for each chain recalled correctly.

3-Memory:

- The Rey Auditory Verbal Learning Test (RAVLT) (Rey 1964) is an easily administered test lasting 10 to 15 minutes, that allows comparison between retrieval efficacy and learning. It measures immediate memory span and both short term and longer term retention of a five times presented 15-word list following interpolated activity. that allows a comparison between retrieval efficacy and learning. Scores were range from 1 to 5.
- Symbol Recall requires recall of symbol-digit pairs from the Digit Symbol Coding test after completing the task.
- Activity Recall tests ability to remember information that was not explicitly presented as part of a memory task. A recall memory task required the participants to rename the 13 tasks that they had been exposed to and one point was given for each name recalled correctly according to order.

4-Executive Function:

Executive function is a higher order cognitive ability controlling other cognitive abilities including planning strategies for performance and using feedback to adjust future planning (Lezak 1995).

- Stroop Test (Dodrill 1978): this test based on the finding that it takes longer to call out a colour name than to read a word and even longer to read printed colour names printed in a colour different from that named by the word (Dyer 1973; Jensen 1966). Dodrill's format of the Stroop test consists of one sheet containing 176 colour names ("red", "orange", "green" and "blue") printed in a random order and in assorted colours. In phase one of the task the participants are required to read the printed word. The requirement in phase two is to report the colour of each word. The scorer was evaluated as the total time for phase one and the difference in time between phase one and two.
- Self-Ordered Pointing Task (Bryan 2001). This assesses planning and organizing ability as it relies on self-initiated responses (Petrides 1982). The task presents arrays of stimulus items, usually abstract designs, in different random-ordered arrays on as many pages as there are items. Participants are required to point at one item per page without repeating an item already pointes at. The participants need to remember each item they have selected and to develop a policy for cumulatively pointing to all the items in the trial.
- The Common Objects Uses Task (Getzels 1962) requires participants to suggest uses for objects that normally have a single stereotyped function associated with them. Scores are based on the number and originality of the uses proposed.
- The Trail Making Test (Reitan 1985) is a test of visual concept and visuomotor tracking in two parts. In part A participants are given a printed sheet with 1 to 25 randomly printed numbers and the requirement is to draw lines to connect the numbers consecutively. Scores are the times in seconds taken to complete the task. In part B, participants are presented with a sheet with numbers 1-13 and letters A-L printed randomly. The requirement is to connect the numbers and letters in alphabetical and numerical order. Scores are based on the time spent in completing the task.
- The Verbal Fluency Task has two parts, initial letter fluency and excluded letter fluency.

i)The Initial letter Fluency Task (Benton 1989) comprises two 60-second trials. The requirement is to generate as many words as possible that start with a specified letter. The score is calculated by the number of words generated correctly.
ii)The Excluded Letter Fluency Task (Bryan 1997) also comprises two 60-second trials. The requirement is to produce as many words

as possible that do not contain a specific letter. The score is the sum of the numbers of words produced correctly in the two trials.
5-Verbal Ability:

- The WAIS-III Vocabulary (Wechsler 1997) is a task that evaluates an individual's abilities to define the meanings of 15 words. The score ranges 0, 1 or 2 and is based on the accuracy, precision, and aptness of the definitions offered. Average vocabulary scores peak at middle age and decline slowly in the sixth to seventh decades (Wechsler 1955, Wechsler 1981). Education affects vocabulary scores more than age (Malec 1992).
- Spot the Word Test (Baddeley 1988) evaluates ability of identify real from non-real words. Scores are the number of words identified correctly minus the errors (to correct for guessing)..

6-Mood assessment:

- The Center for Epidemiological Studies-Depression Scale (CESD) (Radloff 1977) is a short self-report test designed to assess depressive symptomatology in the general population. The components of the scale include depressive mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. Each of 20 times is scored 1 to 4 point with higher scores indicating more symptoms of depressed mood.
- The Profile of Mood States questionnaire (POMS) (McNair 1971) is an assessment of six aspects of mood: tension and anxiety, depression and dejection, anger and hostility, vigour and activity, fatigue and inertia, and confusion. The scale ranges from 1 point (no symptoms) to 5 (extreme).

The following tests were administered to measure mood and cognition functions in men (Deijen 1992):
A computerized testing system was used to apply most of the tasks.
1-Mood:

- The list of adjectives test (Janke 1978) presents 161 items to assess six aspects of mood. The requirement is to agree or disagree with the adjective presented as a description of each mood aspect.

2-Memory:

- Sperling whole report task (Sperling 1960). Whole reports are usually called immediate-memory reports.The span of immediate memory is a span of apprehension for particular stimulus material under stated observation conditions as assessed by the maximum number of items an individual can report. Thirty slides of 12 letters are presented for a very short time of 250, 150 and 50 ms within the same overall presentation time. The requirement is to report as many letters as possible in 6 s.
- As a measure of short-term verbal memory the Associated Learning Task (Emmen 1988) was applied. Participants undergo three trials in which nine pairs of names and occupations appear on a computer screen at rate of one pair every three seconds. After this presentation, participants are presented with nine slides each showing one name with the nine alternative occupations. Participants press a keyboard digit to identify the appropriate matching occupation. The score is the number of associations correctly identified.
- Long term verbal memory: The Associated Recognition Task is used to evaluate long term verbal memory. The Associated Learning Task was applied after a delay for one hour. The requirement is to remember as much as possible of the associated learning task. The number of correct response is a measure of long term memory.
- Long term memory storage: The "forget score" for each participant was calculated as his Associated Learning Test score minus his Associated Recognition Task score. Higher sores indicated poorer long-term memory storage.
- Long term visual memory. Participants were presented for 15 seconds with a slide of nine pictures. They were then presented with 15 pictures required to decide which had been on the original slide. There was no time limit to performing this task. The score was the number of correct identifications.
- Attention and performance: The cognition computer program (Klemenjak 1983) was used to assess attention, perception and concentration. The participants were presented with five display fields, four at the top of the computer screen and one at the bottom. The requirement is to decide whether the figure at the bottom is matched by one of those at the top. Scores reflect the number of correct responses and the time needed to complete the task.
- Perceptual motor skill: The Vienna Determination Unit was used to assess perceptual-motor skills. This requires different motor responses to a range of stimuli, visual and auditory, presented simultaneously.

3-Measurement of pupil size:
The pupillary dilatation reflex is a sensitive and reliable indicator of sympathetic nervous system activity aroused by mental information processing (Beatty 1977). Kahneman 1967 documented that the magnitude of the pupillary dilation is directly related to the difficulty of the task being undertaken. Pupil dilatation in response to a short-term memory task and to a speed of processing task was measured.
4-Vitamin B6 status:

- Plasma pyridoxine-5'-phosphate was measured in blood samples collected in the morning after a light breakfast.
- Erythrocyte asparate aminotransferase was measured in vitro as a response to excess pyridoxine-5'-phosphate. A low response indicates an already high saturation indicative of adequate vitamin B6 status.

Vitamin B6 status was assessed at baseline and immediately after the study period was completed.

Excluded studies

Stott 2006 did not fulfil the inclusion criteria for this review as it had been performed on 185 elderly patients (age >65 years) with

various ischaemic vascular diseases: angina pectoris, acute myocardial infarction, signs of major ischaemia or previous acute myocardial infarction on the electro cardio gram (ECG), ischemic stroke, Transient ischaemic attack (TIA), intermittent claudication, surgery for peripheral arterial disease. Patients with a diagnosis of dementia or major cognitive impairment were excluded, and having contacted the trialists it is clear that they did not record any patients with mild cognitive impairment Mini-Mental State Examination score (MMSE >19).

Most of the excluded studies were randomized-controlled trials recruiting heathy elderly population to evaluate the efficacy of the combinations of B6, B12 and folic acid on the cognition function, well-being and the homocysteine level. Sun 2007 recruited a population of patients with mild to moderate Alzheimer's disease (AD) and studied the efficacy of multivitamin supplement containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase inhibitor for 26 weeks. The effect of a walking programme and vitamin B supplementation on the rate of cognitive decline in patients with mild cognitive impairment (MCI) was assessed in Van Uffelen 2007.

Risk of bias in included studies

The included trials were double-blind and allocation to treatment was randomized. In Bryan 2002 randomization was secured through a sealed list provided by an independent agency. The method of randomization was not detailed in Deijen 1992. The dose of vitamin B6 was set at 75% of the tolerable daily upper limit (100 mg for adults) in Bryan 2002, and about 10 times of the recommended daily allowance in Deijen 1992. No adverse effects or drop-outs were reported.

Effects of interventions

Continuous variables were used in analysing the outcome data. Time and age effects on the outcomes were adjusted for baseline values. Analysis of variance was used for comparing outcomes in treatment and placebo groups. Statistical significance was defined as P<0.05. No beneficial effects from short term vitamin B6 supplementation were found for any measure of mood and cognition in either men or women.

Data analysis revealed the following results:

Effect of vitamin B6 on mood and cognition of healthy older women:

- 75 mg vitamin B6 per day for 5 weeks compared with placebo showed no statistically significant benefit on Memory Speed as measured by the Boxes Tests (WMD 1.57, 95% CI -14.08 to 17.22, P=0.84), Digit- Symbol Coding (WMD 3.89, 95% CI -10.69 to 18.47, P=0.60) and Symbol Search Test (WMD 0.06, 95%CI -3.61 to 3.73, P=0.97)

- For Working Memory Tasks there was no significant statistical difference between vitamin B6 and placebo groups on Digit Span-Backwards (WMD -0.48, 95% CI -2.73 to 1.77, P= 0.68) and on the Letter-Number Sequencing Task (WMD -0.55, 95% CI -3.45 to 2.35, P= 0.71).

- Vitmin B6 conferred no benefit on free recall as assessed by Immediate Recall A (RAVLT A) (WMD -2.21,95% CI -11.40 to 6.98, P=0.64), Immediate Recall B (RAVLT B) (WMD 1.07, 95% CI -0.63 to 2.77, P=0,22), Delayed Recall (RAVLT6) (WMD-0.32, 95% CI -3.49 to 2.85, P= 0.84), Delayed Recall (RAVLT 7) (WMD 0.67, 95% CI -212.77 to 214.11, P=1.00), Recognition Task (RAVL list A) (WMD 0.28, 95% CI -2.61 to 3.17, P=0.85), Recogntion (RAVAL list B) (WMD 1.23, 95% CI -2.15 to 4.61, P=0.48).

- No statistically significant differences between placebo and vitamin B6 groups emerged in any of the Executive Function measures: Stroop Test (WMD -0.06, 95% CI -0.50 to 0.38, P= 0.79); Uses of Objects Task (WMD 1.16, 95% CI -3.92 to 6.24, P=0.65); Trail Making Test part A (WMD -12.73, 95% CI -29.05 to 3.59, P=0.13); Trail Making Test part B (WMD -6.05, 95%CI -46.55 to 34.45, P=0.77); Verbal Fluency Letter - Initial Letter (WMD -2.08, 95% CI -10.00 to 5.84, P=0.61); Verbal Fluency - Excluded Letter (WMD 6.57, 95% CI -2.97 to 16.11, P=0.18).

- No statistically significant evidence in favour of vitamin B6 emerged in the Vocabulary Test (WMD 0.74, 95%CI -6.02 to 7.50, P=0.83) or Spot the Word Test (WMD -1.65, 95% CI -14.14 to 10.84, P=0.80).

- The effect of the intervention on Incidental Recall tasks was not analysed as baseline data were not provided in the trial report.

- There was no statistically significant evidence for any benefit of vitamin B6 supplementation on Profile of Mood States: total score (WMD 2.77, 95% CI -12.28 to 17.82, P= 0.72); tension (WMD 0.20, 95% CI -4.27 to 4.67, P=0.93); fatigue (WMD 1.38, 95% CI -2.16 to 4.92, P=0.450); depression (WMD -0.64, 95% CI -4.78 to 3.50, P=0.76); anger (WMD -1.28, 95% CI -5.22 to 2.66, P=0.52); vigour (WMD -2.35, 95% CI -8.42 to 3.72, P=0.45); confusion (WMD 0.40, 95% CI -1.90 to 2.70, P= 0.73)

- There was no significant impact of 75 mg of vitamin B6 supplementation on depression symptoms as assessed by The Center for Epidemiological Studies-Depression Scale (WMD 0.61, 95% CI -4.78 to 6.00, P=0.82).

Effects of vitamin B6 on cognition function in healthy older men:

- On the Associated Recognition Task there was no benefit of vitamin B6 supplementation compared with placebo (WMD -1.02, 95% CI -2.40 to 0.36, P=0.15).

- Vitamin B6 supplementation had no statistical significant benefit in reducing the forget score in comparison with placebo (WMD 0.79, 95% CI -0.34 to 1.92, P=0.17).

- For pupil size measures data were available only for 31 participants in the placebo group and 28 in the supplement. The system failed to register pupils size that less than 2 mm, and data from subjects who blinked too frequently were not analysed. The available data were insufficient for interpretation.

Effects of vitamin B6 supplementation on vitamin B6 status of older men:

- Plasma pyridoxal-5'-phosphate levels increased significantly in the vitamin B6 group compared with placebo group (WMD 238, 95% CI 211.58 to 264.42, P<0.00001)
- Erythrocyte enzyme asparate aminotransferase saturation decreased significantly in the vitamin B group compared with placebo (WMD 0.43, 95% CI 0.30 to0.56, P<0.00001).

Homocysteine levels were not measured.

DISCUSSION

Conclusions from this review are necessarily limited. There were no data on the effects of vitamin B6 on older people with dementia, and there have been no long-term studies. The trials reviewed involved small numbers of healthy participants over a short period of intervention of 5 to 12 weeks. The two studies enrolled participants of different sexes, used varied doses of vitamin B6, different trial period and different rating scales to assess the outcomes. Some cognitive differences between the sexes have been documented. For example, women tend to outperform men in psychomotor speed and accuracy (Majeres 1988; Majeres 1990), while men score better in visuospatial tests (Karnovsky 1974).

Bryan 2002 assessed cognition and mood performance on a set of scales that correlate significantly with the educational background of the participants and task repetition had affected the time of completion of the performance on cognition batteries of both placebo and supplement groups.The treatment interaction effects of supplementation was significant in the vitamin B6 and placebo groups.

This review provides some evidence that 20 mg of vitamin B6 daily has an impact on vitamin B6 levels as measured biochemically in healthy older healthy men. Although no overall effects on cognition or mood were observed in the study groups as a whole and in the short term, this cannot exclude the possibility of longer term benefit for a subgroup of older people with vitamin B6 deficiency. A further possible complication is that high doses of vitamin B6 may actually impair memorization (Molimard 1980).

At present there is no evidence to support the use of vitamin B6 supplements for improving cognitive function or mood of older people.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that vitamin B6 supplementation has any effect an mood or cognitive functions of older people. Vitamin B6 supplementation improves biochemical indices of vitamin B6 status in older men, suggesting that some may be deficient in the vitamin.

Implications for research

Further randomized controlled studies are needed to evaluate the effects of vitamin B6 in reducing the risk of developing cognitive decline in the general population and in improving the cognitive and mood functions in people with dementia. Studies need to be long term and to be designed to permit subgroup analysis restricted to individuals with biochemical evidence of vitamin B6 deficiency.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bryan 2002

Methods	A 35 days randomized, double-blind, placebo-controlled study, a mixed factorial design was used
Participants	Country: Australia 211 participants were divided into three groups; *56 in younger aged group (20 and 30 y) *80 in middle aged group (45 and 55y) *75 in older aged group (65-92 y): 1) 21 received placebo 2)12 received vitamin B6 Selection criteria: *Non-smokers *Not on HRT *Not using any medication that affects mental performance or mood *Not used vitamin supplementation within 2 weeks before start of the study *English as first language or proficiency in English
Interventions	1. placebo 2. folate 750 mcg 3. vitamin B12 15 mcg 4. vitamin B6 75 mg
Outcomes	A) Cognitive measures: 1-Speed of processing using the following batteries of tests: *Boxes test *Digit-Symbol Coding *Symbol Search 2-Working memory *Digit Span-Backward *Letter-Number Sequencing 3-Memory Measures: *Free recall: i-Immediate Recall ii-Delayed Recall iii-Recognition 4-Incidental Recall: *Digit Symbol *Symbol position *Activities 5-Executive function: *Stroop *Self-Ordered Pointing Task *Trial Making Test *Verbal Fluency: i-Initial Letter

Bryan 2002 (*Continued*)

	ii-Excluded Letter 6-Verbal Ability: *Vocabulary *Spot the word B) Mood Measures 1-CESD 2-Tension/anxiety 3-Depression/dejection 4-Anger/hostility 5-Vigour/activity 6-Fatigue/inertia 7-Confusion/bewilderment
Notes	One participant dropped out from the folic acid group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Deijen 1992

Methods	A 12 week randomized, double-blind, placebo-controlled trial
Participants	Country: The Netherlands 76 men were divided into two pair-matched groups, placebo and vitamin B6 groups Entry criteria: 1) Healthy men 2) Aged between 70 and 79 3) Restricted alcohol use, a maximum of four glasses a day 4) Intelligence score above 80 Exclusion criteria: 1) On any medication affecting vitamin B6 metabolism 2) Use of vitamin B6 supplements within 3 months before the trial 3) Suffering from auto-immune disease
Interventions	1) Placebo 2) Vitamin B6 20 mg/day for 12 weeks
Outcomes	A) Vitamin B6 status: 1-PLP 2-Alpha-EAST B) Mood using the list of adjective C) Memory: 1-Immediate memory 2-Short-Term Verbal Memory 3-Long-Term Verbal Memory using the associated recognition task

Deijen 1992 (*Continued*)

	4-Long-term memory storage 5-Long-term visual memory 6-Attention and performance 7-Perceptual-motor skill D) Pupil size: A) Short term memory task B) Speed of processing task
Notes	The pairs were matching in age, vitamin B6 status and IQ

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

HRT: Hormone Replacement Therapy
CESD: The Center for Epidemiological Studies Depression Scale
POMS: The Profile of Mood States Questionnaire
PLP: Plasma Pyridoxal-5'-Phosphate
Alpha-EAST: Erythrocyte Aspartate Aminotransferase
IQ: Intelligence Quotient

Characteristics of excluded studies *[ordered by year of study]*

Study	Reason for exclusion
Cockle 2000	RCT of multi-vitamins
Stott 2006	RCT, using folic acid plus vitamin B12, vitamin B6, vitamin B2 and placebo in patients with vascular disease. Patients with MCI and dementia were excluded
Schroecksandel 2006	Not RCT, B vitamin supplementation in Alzheimer's disease, vascular dementia, mild cognitive impairment patients
Chandra 2001	Interventional study of multi-vitamins and elements
Carney 1976	The intervention included the combination of the following vitamins: B1, B6, B12 and C
Wouters 2002	RCT of micronutrient-enriched liquid
McMahon 2006	RCT, Comparing B vitamins (B6, B12, folic acid) with placebo in elderly healthy people

(*Continued)*

Van Uffelen 2007	RCT, Comparing B vitamin (B6, B12, folic acid) plus a walking programme with placebo in mild cognitive impairment patients
Flicker 2007	RCT, comparing B vitamins (B6, B12, folic acid) with placebo in older men
Balk 2007	A review of the effect of B vitamins (B6, B12 , folic acid) on cognitive function
Clarke 2007	RCT, comparing B vitamins (B6,B12, folic acid) to placebo
Sun 2007	RCT comparing B6, B12 and folic acid with placebo in demented persons

MCI: Mild Cognitive Impairment

DATA AND ANALYSES

Comparison 1. 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Speed of processing	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Boxes Test	1	33	Mean Difference (IV, Fixed, 95% CI)	1.57 [-14.08, 17.22]
1.2 Digit-Symbol Coding	1	33	Mean Difference (IV, Fixed, 95% CI)	3.89 [-10.69, 18.47]
1.3 Symbol Search	1	33	Mean Difference (IV, Fixed, 95% CI)	0.06 [-3.61, 3.73]
2 Working Memory	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Digit Span-Backwards	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-2.73, 1.77]
2.2 Letter-Number Sequencing	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-3.45, 2.35]
3 Free Recall	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Immediate Recall: RAVLT 1-5	1	33	Mean Difference (IV, Fixed, 95% CI)	-2.21 [-11.40, 6.98]
3.2 Immediate Recall: RAVLT B	1	33	Mean Difference (IV, Fixed, 95% CI)	1.07 [-0.63, 2.77]
3.3 Delayed Recall: RAVLT 6	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-3.49, 2.85]
3.4 Delayed Recall: RAVLT 7	1	33	Mean Difference (IV, Fixed, 95% CI)	0.67 [-212.77, 214.11]
3.5 Recognition: RAVLT A	1	33	Mean Difference (IV, Fixed, 95% CI)	0.28 [-2.61, 3.17]
3.6 Recogntion -RAVLT B	1	33	Mean Difference (IV, Fixed, 95% CI)	1.23 [-2.15, 4.61]
4 Executive Function	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Stroop Test	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.50, 0.38]
4.2 Uses of Objects	1	33	Mean Difference (IV, Fixed, 95% CI)	1.16 [-3.92, 6.24]
4.3 Trail Making Test A	1	33	Mean Difference (IV, Fixed, 95% CI)	-12.73 [-29.05, 3.59]
4.4 Trail Making Test B	1	33	Mean Difference (IV, Fixed, 95% CI)	-6.05 [-46.55, 34.45]
4.5 Verbal Fluency -Initial Letter	1	33	Mean Difference (IV, Fixed, 95% CI)	-2.08 [-8.00, 5.84]
4.6 Verbal Fluency Excluded Letter	1	33	Mean Difference (IV, Fixed, 95% CI)	6.57 [-2.97, 16.11]
5 Verbal Ability	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Vocabulary	1	33	Mean Difference (IV, Fixed, 95% CI)	0.74 [-6.02, 7.50]
5.2 Spot the Word	1	33	Mean Difference (IV, Fixed, 95% CI)	-1.65 [-14.14, 10.84]
6 Mood Measures	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 CESD	1	33	Mean Difference (IV, Fixed, 95% CI)	0.61 [-4.78, 6.00]
6.2 POMS total	1	33	Mean Difference (IV, Fixed, 95% CI)	2.77 [-12.28, 17.82]
6.3 Tension/Anxiety	1	33	Mean Difference (IV, Fixed, 95% CI)	0.20 [-4.27, 4.67]
6.4 Depression/dejection	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-4.78, 3.50]
6.5 Anger/hostility	1	33	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-5.22, 2.66]
6.6 Vigour/Activity	1	33	Mean Difference (IV, Fixed, 95% CI)	-2.35 [-8.42, 3.72]
6.7 Fatigue/inertia	1	33	Mean Difference (IV, Fixed, 95% CI)	1.38 [-2.16, 4.92]
6.8 Confusion/bewilderment	1	33	Mean Difference (IV, Fixed, 95% CI)	0.4 [-1.90, 2.70]

Comparison 2. 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PLP	1	76	Mean Difference (IV, Fixed, 95% CI)	238.00 [211.58, 264.42]
2 Alpha-EAST	1	76	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.30, 0.56]
3 Associated Recognition Task	1	76	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-2.40, 0.36]
4 Forget Scores	1	76	Mean Difference (IV, Fixed, 95% CI)	0.79 [-0.34, 1.92]

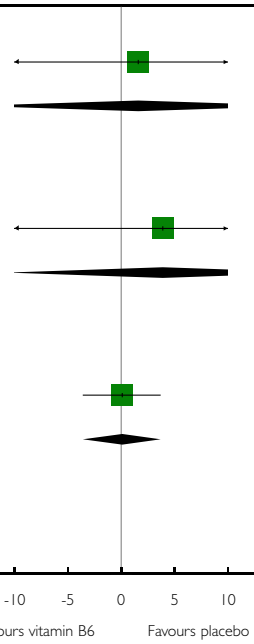
Analysis 1.1. Comparison 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women, Outcome 1 Speed of processing.

Review: Vitamin B6 for cognition

Comparison: 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome: 1 Speed of processing

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Boxes Test							
Bryan 2002	12	6.34 (22.14)	21	4.77 (21.93)		100.0 %	1.57 [-14.08, 17.22]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**1.57 [-14.08, 17.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.20 (P = 0.84)							
2 Digit-Symbol Coding							
Bryan 2002	12	7.41 (23.5)	21	3.52 (14)		100.0 %	3.89 [-10.69, 18.47]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**3.89 [-10.69, 18.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.52 (P = 0.60)							
3 Symbol Search							
Bryan 2002	12	-0.08 (4.95)	21	-0.14 (5.56)		100.0 %	0.06 [-3.61, 3.73]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**0.06 [-3.61, 3.73]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.03 (P = 0.97)							
Test for subgroup differences: Chi^2 = 0.27, df = 2 (P = 0.87), I^2 =0.0%							



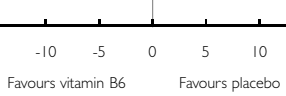
Analysis 1.2. Comparison 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women, Outcome 2 Working Memory.

Review: Vitamin B6 for cognition

Comparison: 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome: 2 Working Memory

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Digit Span-Backwards							
Bryan 2002	12	0 (2.51)	21	0.48 (4.08)		100.0 %	-0.48 [-2.73, 1.77]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**-0.48 [-2.73, 1.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.68)							
2 Letter-Number Sequencing							
Bryan 2002	12	0.17 (3.9)	21	0.72 (4.39)		100.0 %	-0.55 [-3.45, 2.35]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**-0.55 [-3.45, 2.35]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%							

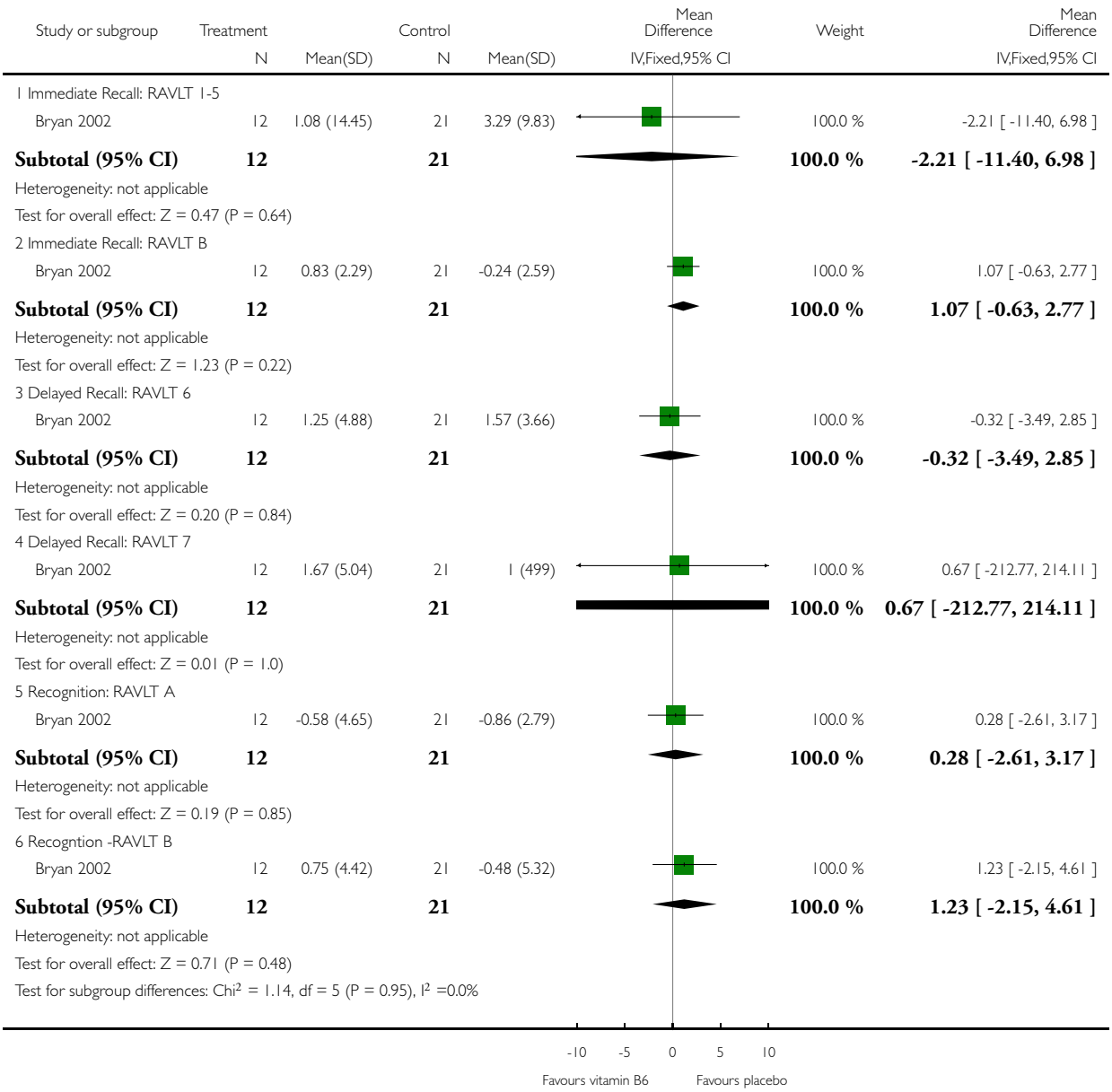


Analysis 1.3. Comparison 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women, Outcome 3 Free Recall.

Review: Vitamin B6 for cognition

Comparison: 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome: 3 Free Recall

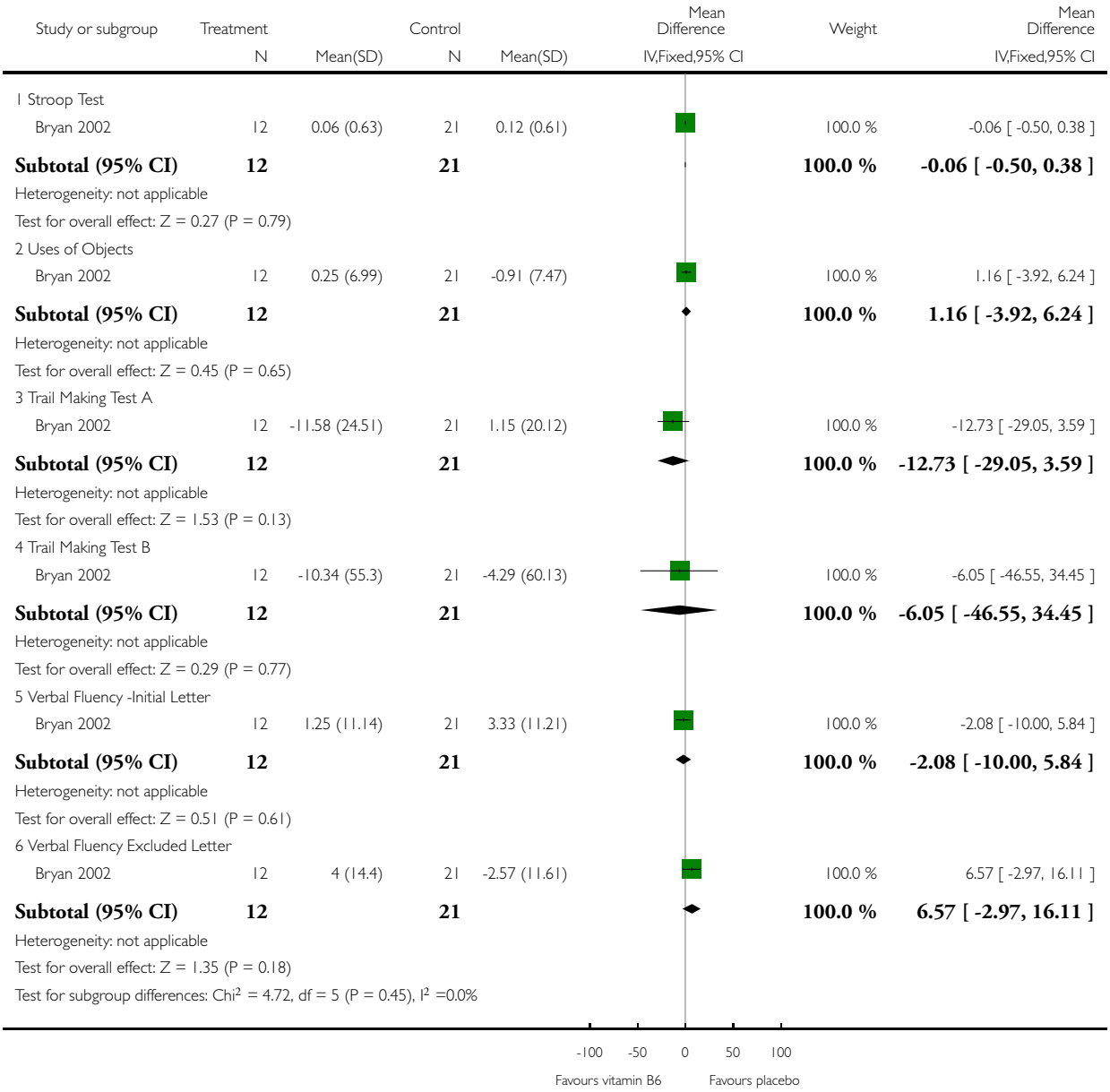


Analysis 1.4. Comparison 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women, Outcome 4 Executive Function.

Review: Vitamin B6 for cognition

Comparison: 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome: 4 Executive Function



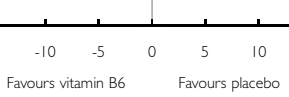
Analysis 1.5. Comparison 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women, Outcome 5 Verbal Ability.

Review: Vitamin B6 for cognition

Comparison: 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome: 5 Verbal Ability

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Vocabulary							
Bryan 2002	12	0.59 (10.53)	21	-0.15 (7.48)		100.0 %	0.74 [-6.02, 7.50]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**0.74 [-6.02, 7.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.21 (P = 0.83)							
2 Spot the Word							
Bryan 2002	12	-1.08 (19.87)	21	0.57 (12.7)		100.0 %	-1.65 [-14.14, 10.84]
Subtotal (95% CI)	**12**		**21**			**100.0 %**	**-1.65 [-14.14, 10.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.80)							
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 =0.0%							



Analysis 1.6. Comparison 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women, Outcome 6 Mood Measures.

Review: Vitamin B6 for cognition

Comparison: 1 75 mg Vitamin B6/day for five weeks vs placebo in healthy older women

Outcome: 6 Mood Measures

Study or subgroup	control N	Mean(SD)	treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 CESD							
Bryan 2002	21	-1.06 (9.28)	12	-1.67 (6.45)		100.0 %	0.61 [-4.78, 6.00]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**0.61 [-4.78, 6.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.22 (P = 0.82)							
2 POMS total							
Bryan 2002	21	-3.15 (28.78)	12	-5.92 (15.3)		100.0 %	2.77 [-12.28, 17.82]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**2.77 [-12.28, 17.82]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.36 (P = 0.72)							
3 Tension/Anxiety							
Bryan 2002	21	-1.3 (8.29)	12	-1.5 (4.82)		100.0 %	0.20 [-4.27, 4.67]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**0.20 [-4.27, 4.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.09 (P = 0.93)							
4 Depression/dejection							
Bryan 2002	21	-1.3 (8.29)	12	-0.66 (3.79)		100.0 %	-0.64 [-4.78, 3.50]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**-0.64 [-4.78, 3.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.30 (P = 0.76)							
5 Anger/hostility							
Bryan 2002	21	-1.2 (8.18)	12	0.08 (3.21)		100.0 %	-1.28 [-5.22, 2.66]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**-1.28 [-5.22, 2.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
6 Vigour/Activity							
Bryan 2002	21	-0.6 (7.32)	12	1.75 (9.19)		100.0 %	-2.35 [-8.42, 3.72]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**-2.35 [-8.42, 3.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
7 Fatigue/inertia							
Bryan 2002	21	0.3 (5.63)	12	-1.08 (4.59)		100.0 %	1.38 [-2.16, 4.92]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	control N	Mean(SD)	treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**1.38 [-2.16, 4.92]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
8 Confusion/bewilderment							
Bryan 2002	21	-0.6 (4.37)	12	-1 (2.36)		100.0 %	0.40 [-1.90, 2.70]
Subtotal (95% CI)	**21**		**12**			**100.0 %**	**0.40 [-1.90, 2.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
Test for subgroup differences: Chi^2 = 1.94, df = 7 (P = 0.96), I^2 =0.0%							

-100 -50 0 50 100

Favours placebo Favours vitamin B6

Analysis 2.1. Comparison 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men, Outcome 1 PLP.

Review: Vitamin B6 for cognition

Comparison: 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men

Outcome: 1 PLP

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Deijen 1992	38	238 (81.61)	38	0 (15.62)		100.0 %	238.00 [211.58, 264.42]
Total (95% CI)	**38**		**38**			**100.0 %**	**238.00 [211.58, 264.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 17.66 (P < 0.00001)							
Test for subgroup differences: Not applicable							

-1000 -500 0 500 1000

vitamin B6 placebo

Analysis 2.2. Comparison 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men, Outcome 2 Alpha-EAST.

Review: Vitamin B6 for cognition

Comparison: 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men

Outcome: 2 Alpha-EAST

Study or subgroup	Control N	Mean(SD)	Treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Deijen 1992	38	0.03 (0.38)	38	-0.4 (0.18)		100.0 %	0.43 [0.30, 0.56]
Total (95% CI)	**38**		**38**			**100.0 %**	**0.43 [0.30, 0.56]**

Heterogeneity: not applicable

Test for overall effect: Z = 6.30 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men, Outcome 3 Associated Recognition Task.

Review: Vitamin B6 for cognition

Comparison: 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men

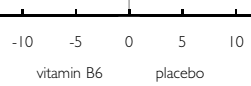
Outcome: 3 Associated Recognition Task

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Deijen 1992	38	0.03 (3.25)	38	1.05 (2.9)		100.0 %	-1.02 [-2.40, 0.36]
Total (95% CI)	**38**		**38**			**100.0 %**	**-1.02 [-2.40, 0.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men, Outcome 4 Forget Scores.

Review: Vitamin B6 for cognition

Comparison: 2 20 mg vitamin B6/day for 12 weeks vs placebo in healthy older men

Outcome: 4 Forget Scores

Study or subgroup	control N	Mean(SD)	treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Deijen 1992	38	0.47 (2.96)	38	-0.32 (1.97)		100.0 %	0.79 [-0.34, 1.92]
Total (95% CI)	**38**		**38**			**100.0 %**	**0.79 [-0.34, 1.92]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.37 (P = 0.17)

Test for subgroup differences: Not applicable

WHAT'S NEW

Last assessed as up-to-date: 2 April 2008.

Date	Event	Description
3 April 2008	New search has been performed	Search of 16 March 2008 retrieved 11 studies for consideration by the author, none of the studies fulfilled the inclusion criteria for this review

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2003

Date	Event	Description
21 January 2006	New search has been performed	January 2006: No additional studies have been included. Results from the update search showed one RCT (Stott 2006), which had been performed on elderly patients with vascular disease excluding demented and cognitively impaired patients

(*Continued*)

25 August 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

RM: all correspondence; selection of trials; inclusion and exclusion of trials; data extraction; input into RevMan; data-analyses; drafting of review versions

JGE: selection of trials; in and exclusion of trials; drafting review versions

Original search and update searches: Dymphna Hermans and Vittoria Lutje.

Consumer editor: Corinne Cavender.

This review has been peer reviewed anonymously.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Division of Clinical Geratology, Nuffield Department of Clinical Medicine, University of Oxford, UK.
- NHS R&D, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cognition Disorders [therapy]; Dementia [*therapy]; Vitamin B 6 [*therapeutic use]; Vitamin B 6 Deficiency [*complications; therapy]

MeSH check words

Aged; Humans