Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people (Review)

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[Intervention Review]

Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2009.
Review content assessed as up-to-date: 21 July 2008.

Citation: Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD004514. DOI: 10.1002/14651858.CD004514.pub2.

ABSTRACT

Background

Folate deficiency can result in congenital neural tube defects and megaloblastic anaemia. Low folate levels may be due to insufficient dietary intake or inefficient absorption, but impaired metabolic utilization also occurs.

Because B12 deficiency can produce a similar anaemia to folate deficiency, there is a risk that folate supplementation can delay the diagnosis of B12 deficiency, which can cause irreversible neurological damage. Folic acid supplements may sometimes therefore include vitamin B12 supplements with simultaneous administration of vitamin B12.

Lesser degrees of folate inadequacy are associated with high blood levels of the amino acid homocysteine which has been linked with the risk of arterial disease, dementia and Alzheimer's disease. There is therefore interest in whether dietary supplementation can improve cognitive function in the elderly.

However, any apparent benefit from folic acid which was given in combination with B12 needs to be "corrected" for any effect of vitamin B12 alone. A separate Cochrane review of vitamin B12 and cognitive function has therefore been published.

Objectives

To examine the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy or demented people, in preventing cognitive impairment or retarding its progress.

Search methods

Trials were identified from a search of the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 10 October 2007 using the terms: folic acid, folate, vitamin B9, leucovorin, methyltetrahydrofolate, vitamin B12, cobalamin and cyanocobalamin. This Register contains references from all major health care databases and many ongoing trials databases. In addition MEDLINE, EMBASE, CINAHL, PsychINFO and LILACS were searched (years 2003-2007) for additional trials of folate with or without vitamin B12 on healthy elderly people.

Selection criteria

All double-blind, placebo-controlled, randomized trials, in which supplements of folic acid with or without vitamin B12 were compared with placebo for elderly healthy people or people with any type of dementia or cognitive impairment.

Data collection and analysis

The reviewers independently applied the selection criteria and assessed study quality. One reviewer extracted and analysed the data. In comparing intervention with placebo, weighted mean differences and standardized mean difference or odds ratios were estimated.

Main results

Eight randomized controlled trials fulfilled the inclusion criteria for this review. Four trials enrolled healthy older people, and four recruited participants with mild to moderate cognitive impairment or dementia with or without diagnosed folate deficiency. Pooling the data was not possible owing to heterogeneity in sample selections, outcomes, trial duration, and dosage. Two studies involved a combination of folic acid and vitamin B12.

There is no adequate evidence of benefit from folic acid supplemententation with or without vitamin B12 on cognitive function and mood of unselected healthy elderly people. However, in one trial enrolling a selected group of healthy elderly people with high homocysteine levels, 800 mcg/day folic acid supplementation over three years was associated with significant benefit in terms of global functioning (WMD 0.05, 95% CI 0.004 to 0.096, P = 0.033); memory storage (WMD 0.14, 95% CI 0.04 to 0.24, P = 0.006) and information-processing speed (WMD 0.09, 95% CI 0.02 to 0.16, P = 0.016).

Four trials involved people with cognitive impairment. In one pilot trial enrolling people with Alzheimer's disease, the overall response to cholinesterase inhibitors significantly improved with folic acid at a dose of 1mg/day (odds ratio: 4.06, 95% CI 1.22 to 13.53; P = 0.02) and there was a significant improvement in scores on the Instrumental Activities of Daily Living and the Social Behaviour subscale of the Nurse's Observation Scale for Geriatric Patients (WMD 4.01, 95% CI 0.50 to 7.52, P = 0.02). Other trials involving people with cognitive impairment did not show any benefit in measures of cognitive function from folic acid, with or without vitamin B12.

Folic acid plus vitamin B12 was effective in reducing serum homocysteine concentrations (WMD -5.90, 95% CI -8.43 to -3.37, P < 0.00001). Folic acid was well tolerated and no adverse effects were reported.

Authors' conclusions

The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer's disease to cholinesterase inhibitors. In another, long-term use appeared to improve the cognitive function of healthy older people with high homocysteine levels. More studies are needed on this important issue.

PLAIN LANGUAGE SUMMARY

No evidence that folic acid with or without vitamin B12 improves cognitive function of unselected elderly people with or without dementia. Long-term supplementation may benefit cognitive function of healthy older people with high homocysteine levels

In the economically developed world, folate deficiency is one of the commonest vitamin deficiencies. Several reports suggest a higher prevalence of various psychiatric disorders in elderly people with folate deficiency. There is interest in whether dietary supplements of folic acid (an artificial chemical analogue of naturally occurring folates) can improve cognitive function of people at risk of cognitive decline associated with ageing or dementia, whether by affecting homocysteine metabolism or through other mechanisms. Eight trials met the criteria for inclusion. It was not possible to pool the data because the trials studied different populations, tested folic acid in different doses, and used different outcome measures. There were two trials of folic acid in conjunction with B12. The analysis showed significant benefit of folic acid over placebo in some measures of cognition in a long-term trial recruiting elderly people with high homocysteine levels from a general population. In one pilot trial, 1 mg/day of folic acid was associated with significant improvement in behavioural response to cholinesterase inhibitors in people with Alzheimer's disease.

BACKGROUND

Description of the condition

Dementia is a syndrome characterized by an acquired global impairment of memory and other cognitive functions sufficient to interfere with normal life (Gottfries 1998). There are many causes of the syndrome including Alzheimer's disease and cerebrovascular disorders, and most are progressive. Worldwide, 24·3 million people have dementia, with 4·6 million new cases of dementia every year (one new case every seven seconds) (Ferri 2005). In Western populations, Alzheimer's disease accounts for more than 70% of cases of dementia. Approximately 6 to 8% of all older people over the age of 65 years have the disease (Small 1997), and the prevalence increases steeply with age (Jorm 1987). There are promising developments in treatment of the established disease, but it is more important to find means of preventing its onset. This requires observational studies to identify risk factors and so generate hypotheses on pathogenesis to be tested in intervention trials. The possible involvement of nutritional factors in the aetiology (causes) or pathogenesis (mechanisms of brain damage) of dementia has been widely considered. In particular, dietary deficiency of folates has been postulated as contributing to the aetiology of both Alzheimer's disease and vascular dementia.

Folates are essential components of the human diet, and are synthesized by microorganisms and plants. They occur widely as polyglutamates in dihydrofolate or tetrahydrofolate forms. Leafy vegetables, fruits, mushrooms, yeast and animal protein are all rich sources of folates (Antony 1995). Prolonged cooking (more than 15 minutes) destroys 60 to 90% of a food's content of folates. The minimum daily requirement is 50 micrograms and the recommended daily intake is 100 micrograms for adults but in pregnancy this rises to 500 micrograms. The body's storage of the vitamin is adequate for about four months of dietary deficiency (Herbert 1985; Chanarin 1979).

Description of the intervention

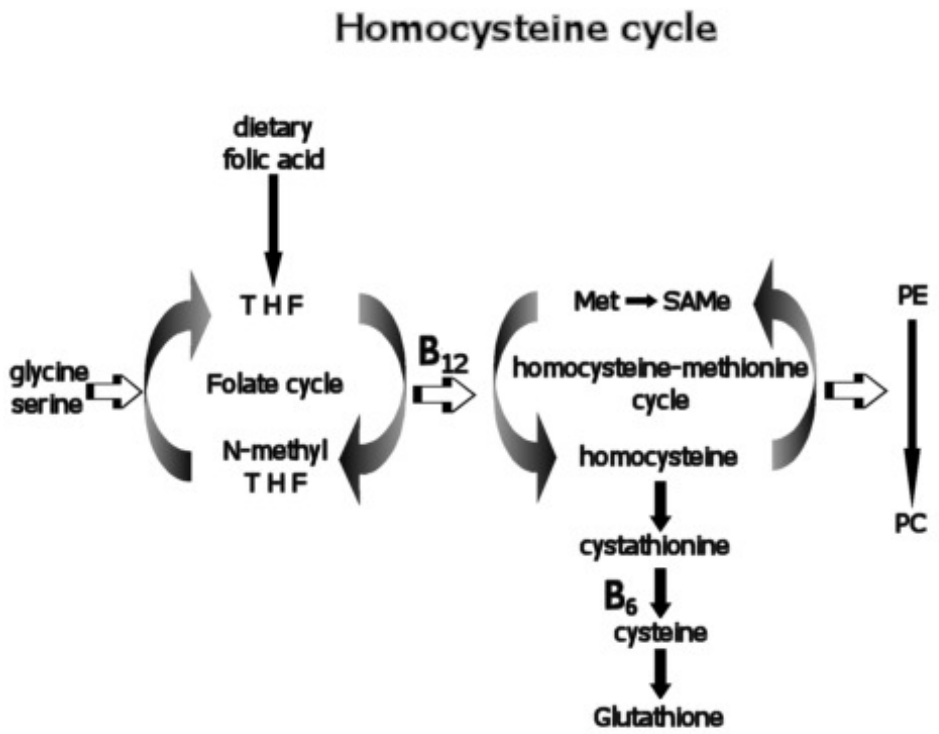
Folate is absorbed in the upper jejunum in monoglutamate form and converted to methyltetrahydrofolate which is the main form in serum. The primary mechanism of folate absorption across the small intestine is passive diffusion (Rosenberg 1985), but absorption is influenced by genotypic variation in the enzyme methylenetetrahydrofolate reductase (MTHFR). One identified genotype is the 677 C->T mutation. People with the 677 TT (thymine/thymine) genotype absorb folate less efficiently than people with the CT (cytosine/thymine) or CC (cytosine/cytosine) variants. The C677T mutation is associated with decreased MTHFR activity, low plasma and red cell folate concentrations, and high plasma homocysteine levels. It occurs at above general population frequency in mothers of spina bifida offspring (Whitehead 1995). Two thirds of the folate in the plasma is free and one third nonspecifically bound to albumin and possibly other proteins. Folate concentration in the cerebrospinal fluid (CSF) is three times that in the serum (Botez 1979), and concentrations decline with age (Bottiglieri 2000).

Folic acid and folinic acid are artificial compounds that can substitute for the naturally occurring folates. Folic acid is well tolerated, and adverse effects are rare and limited to hypersensitivity reactions (Smith 2002). Folinic acid is more stable than folic acid and has a longer half-life in the body. Folinic acid also crosses the blood-brain barrier and is cleared more slowly than folic acid which is poorly transported into the brain and rapidly cleared from the central nervous system. Smith 2008 has published an important review on this subject.

How the intervention might work

Folate is particularly important during the early development of the brain, and in later life is involved in methylation processes that are essential for the maintenance of normal brain function. Folate acts as a donor of methyl groups in a reaction catalysed by the enzyme methionine synthase to produce methylcobalamin needed for methylation of homocysteine to methionine (Figure 1). Folate deficiency therefore leads to an increase in blood and intracellular levels of homocysteine. Homocysteine is a specific chemical compound, but is readily and partly reversibly transformed into other compounds. It has become conventional for the term "total homocysteine" (tHcy) to be used for the sum of these inter-related forms as measured chemically. High intraneuronal levels of homocysteine are one mechanism whereby inadequate methylation could disturb brain metabolism, and cause cognitive impairment (La Rue 1997), but high blood homocysteine levels are also a risk factor for atherosclerosis and cerebrovascular disease. In addition to lack of folate activity, other causes of elevated total homocysteine levels are deficiency of vitamins B12 or B6, and renal impairment.

Figure 1. THF: Tetra Hydro Folate Met: Methionine SAMe: S-Adenosylmethionine PC: Phosphatidyl Choline PE: Phosphatidyl Ethanolamine



In addition to its effect in lowering homocysteine levels, folate improves nitric oxide availability in the brain. It also plays a number of other crucial roles in the brain, as coenzyme in the synthesis of serotonin and catecholamine neurotransmitters and also of S-adenosylmethionine, which has antidepressant properties (Levitt 1989; Shane 1985). Folate deficiency impairs DNA repair in neurons, and sensitizes neurons to oxidative damage and the toxicity of amyloid beta-peptide (Abeta) (Kruman 2002).

Low folate levels can be the result of inadequate dietary intake, diminished absorption from the gastrointestinal tract or increased utilization. Folate deficiency is common in economically less developed countries (Cooper 1986), as a consequence of malnutrition, poverty, ethnic diets, cooking techniques and chronic illness. In more developed countries, dietary deficiency associated with alcoholism is the most common cause, but slimming diets have also been incriminated. Some medications interact with folate metabolism and can cause deficiency; examples include anticonvulsant medications (such as dilantin, phenytoin and primidone), metformin (sometimes prescribed to control blood sugar in type 2 diabetes), sulfasalazine (used to control inflammation associated with Crohn's disease and ulcerative colitis), triamterene (a diuretic), methotrexate (used for cancer and other diseases such as rheumatoid arthritis), pyrimethamine, trimethoprim and barbiturates (used as sedatives).

Why it is important to do this review

Folate deficiency can cause megaloblastic anaemia, congestive heart failure, pigmentation, premature greying of hair, infertility, cervical dysplasia, uterine dysplasia, neuropathy, psychiatric disorders, cognitive dysfunction and dementia. Behavioural abnormalities have been noted in folate-deficient mice (Gospe 1995). Other studies have found an association between folate deficiency and psychiatric diseases including schizophrenia and organic psychosis (Reynolds 1976; Ortega 1996). Prospective studies on folate intake in the United States (Corrada 2005), and on serum folate concentrations in Italy (Ravaglia 2005) have produced evidence of low folate intake or status as a risk factor for dementia.

Folate status is assessed by measuring plasma and blood red cell folate concentrations and plasma or serum total homocysteine levels. Red cell folate is more stable than serum folate levels and better correlated with the tissue stores (Chanarin 1989; Shane

1985). Serum total homocysteine concentration is a sensitive but non-specific indicator of folate deficiency (Ueland 1993).

In observational studies, hyperhomocysteinaemia is a risk factor for coronary heart disease (Mayer 1996; Nygard 1997), extracranial carotid artery stenosis (Aronow 1997) and stroke (Perry 1995). High homocysteine levels are associated with a decrease in cognitive function and dementia (Breteler 1994; Hofman 1997). Individuals with Alzheimer's disease have been found to have higher plasma homocysteine levels than age-matched controls (McCaddon 1998), and it has been reported that elevation of plasma homocysteine levels precedes clinical manifestations of Alzheimer's disease (Seshadri 2002). The underlying mechanisms of homocysteine as a risk factor for both vascular and Alzheimer's dementia are still uncertain, but there are many ways in which homocysteine could damage neurons, including impairment of blood supply through endothelial dysfunction in arteries, cerebral microangiopathy. Increased oxidative stress may also be relevant. In rats, homocysteine induces apoptosis in hippocampal neurons, and in vivo it increases excitotoxicity and oxidative damage (Kruman 2002). Folate supplementation causes a significant decline in blood total homocysteine levels (Stabler 1986; Stabler 1988), and many studies are in progress to assess the effects of reducing homocysteine levels by dietary supplements of folic acid alone or in combination with vitamins B12 and B6.

Serum total homocysteine levels vary between population groups. High blood levels are more common in the Netherlands than in the United States, probably because of greater use of folic acid supplementation and food fortification in the USA (Stehouwer 1998). The US government has legislated for all flour to be fortified with folic acid at a level of 140 mcg per 100 g in order to reduce the incidence of congenital neural tube defects. Such mandatory fortification has not yet been adopted in Europe, although some manufacturers are adding folic acid to breakfast cereals, and may introduce it into spreadable fats. Fortification of milk with folic acid has been shown to be acceptable and sufficient for preventing folate deficiency among older people (Keane 1998). The prevalence of low folate and high homocysteine concentrations in the USA declined from 22.0 to18.7% respectively before the fortification programme was introduced to 1.7% and 9.8% respectively afterwards (Jacques 1999).

Giving folic acid to someone who has unrecognized deficiency of vitamin B12 will prevent the anaemia of that condition but not the irreversible neurological damage that may occur as the deficiency continues. Thus by "masking" the early signs and symptoms of vitamin B12 deficiency, folic acid may increase the incidence of neuropathy. There is also concern, based on observations in the 1940s when pernicious anaemia was treated with high doses of folic acid, that giving folic acid to someone who is deficient in vitamin B12 may make the neurological consequences of that deficiency more rapid and more severe. For these reasons doctors do not prescribe high doses of folic acid for patients whose vitamin B12 status is unknown. The prevalence of vitamin B12 deficiency in the general population is uncertain but is known to be significantly common in later life (Clarke 2007). This is one concern raised by the possibility of a folic acid fortification programme in the United Kingdom. A prospective study was performed after six months of the Chilean government fortification programme of 220 microgram of folic acid per 100 gram of wheat flour. One hundred and eight elderly people who consumed fortified flour showed a moderate decline in their homocysteine levels, but one third of the participants had subclinical vitamin B12 deficiency (Hirsch 2002).

Folate deficiency is one of the commonest forms of vitamin deficiency, occurring in about 10% of the USA population (Senti 1985). Folate deficiency is common in geriatric patients: approximately 30 to 35% have metabolic evidence of deficiency (elevated homocysteine) (Selhub 1993). In one study, low serum and red cell folate concentrations were found in 42% of healthy older people (Bottiglieri 1994). Several reports suggest a higher prevalence of psychiatric disorders in elderly patients with folate deficiency (Bottiglieri 1994).

Older people with low folate status are more likely to be demented, institutionalized or depressed (Ebly 1998). In observational studies, low serum folate levels have been associated with Alzheimer's disease and with all types of dementia (Meindok 1970; Sneath 1973; Renvall 1989; Clarke 1998; Ebly 1998). It has been noted that low serum folate levels were associated with atrophy of the cerebral cortex (Snowdon 2000). The Mini Mental State Examination (MMSE) scores of people with high serum and erythrocyte folic acid concentrations were significantly greater than those of people with lower concentrations (Ortega 1996). A correlation has been reported between low serum levels of folate and specific cognitive functions such as recall and recognition (Hassing 1999; Wahlin 1996). Red cell folate and CSF folate levels are lower in patients with Alzheimer's disease than in controls (Abalan 1996). Insomnia, fatigue and forgetfulness after a four-month folate-deficient diet were reported by Herbet 1961. Older people with low levels of folate are twice as likely to develop Alzheimer's disease as are those with normal levels (Wang 2001). In an open clinical study three patients with dementia and folate deficiency recovered completely after taking 50 mg folic acid daily for 21 days (Brocker 1986).

It is not yet clear to what extent these associations between folate deficiency and cognitive impairment represent cause or effect. Low intakes of folate could be a consequence of mental dysfunction. In particular demented patients may be anorexic and can suffer from agnosia (impairment of interpretation of sense data) and apraxia (inability to carry out feeding behaviour) that can impair dietary intake (Marcus 1998). Conversely, as reviewed above, folate deficiency may be a cause of cognitive deficits. It is therefore important to review the evidence from randomized clinical trials on whether supplements of folic acid can prevent or retard cognitive impairment in older people with or without diagnosed dementia. Because of the possibility of folic acid supplements harming people

with unrecognized deficiency of vitamin B12, trials may involve simultaneous administration of vitamin B12 with folic acid. Apparent benefit from folic acid given in combination would therefore need to be "corrected" for any effect of vitamin B12 alone. A separate Cochrane review of vitamin B12 and cognitive function has been published (Malouf 2003 a).

Apart from its possible risk for people with deficiency of vitamin B12 activity discussed above, folic acid produces few documented adverse effects. However, there has recently been concern that introducing folic acid into the food chain in North America may have caused an increase in colorectal cancer (Cole 2007; Mason 2007). This might reflect an increase in the growth rate of pre-existing cancers. However, for various reasons, levels of folic acid intake in North American populations is higher than was envisaged in fortification programmes. High levels of folic acid in the diet can saturate the biochemical processes that convert it into naturally occurring folate derivatives, and little is known of possible effects of unmetabolized folic acid circulating in the body.

In contrast to the earlier reports that folate might improve cognitive function, a prospective study in the United States, conducted after fortification, has reported that a high intake of folic acid was associated with an increased risk of cognitive decline in older people, especially in those who took vitamin supplements containing > 400 µg folic acid/day (Morris 2005). A later study found that this relationship was restricted to older people with impaired vitamin B12 status (Morris 2007). Furthermore, in those without low B12, high folate levels were associated with better cognitive function. This raises the possibility that a subclinical form of the neurological damage which can the affect spinal cord might also affect the brain in those with low B2 and high folate.

OBJECTIVES

The aim of the review is to examine the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy or demented people in preventing cognitive impairment or retarding its progress.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized double-blind, placebo-controlled trials in which folic acid with or without vitamin B12 was compared with placebo.

Types of participants

Healthy older people or people with cognitive impairment or any type of dementia, Alzheimer's disease, vascular, mixed dementia and others. Patients should be diagnosed with dementia using accepted criteria such as those of the International Classification of Diseases (ICD-10 1992), DSM American Psychiatric Association (APA 1987) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) (McKhann 1984). The diagnosis of cognitive impairment is made according to the results of reliable and valid rating scales.

Types of interventions

Folic acid with or without vitamin B12 at any dose and by any route of administration.

Types of outcome measures

Primary outcomes

- Cognitive measurements

Secondary outcomes

- Blood folate levels
- Serum or plasma levels of total homocysteine
- Mood changes

Search methods for identification of studies

See Cochrane Dementia and Cognitive Improvement Group methods used in reviews.

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 10 October 2007 for all years up to December 2005. This register contains records from the 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: folic, folinic, folate, "vitamin B9", VITAMIN-B9, leucovorin, methyltetrahydrofolate.

The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched separately on 10 October 2007 to identify randomized controlled trials with healthy elderly people for the years 2003 to 2007. The search terms used to identify relevant controlled trials on cognition and dementia 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: folic, folinic, folate, "vitamin B9", VITAMIN-B9, leucovorin, methyltetrahydrofolate.

On 10 October 2007, the Register consisted of records from the following databases:

Healthcare databases

- CENTRAL: (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 CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on *The Cochrane Library*.

The authors of trial reports were approached where necessary (Bryan 2002; Sommer 1998; Clarke 2003) and asked for additional data. We obtained no reply from Dr Sommer (Sommer 1998), but both Dr Eva Calvaresi (Bryan 2002) and Dr Robert Clarke (Clarke 2003) replied and provided the data requested.

Data collection and analysis

Selection of studies

The abstracts of trial reports discovered in the search were read and selected for retrieval by the reviewers (RM and JGE) acting independently. Trial reports thought to be eligible were retrieved and any disagreements over eligibility for inclusion were resolved by discussion.

Quality assessment

The reviewers assessed the methodological quality of randomization in each trial using one of the approaches described in the Cochrane Reviewers' Handbook (Higgins 2008):

- In category A (adequate), the report describes allocation of treatment by: (i) some form of centralized randomized scheme, such as having to provide details of an enrolled participant to an office by telephone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administrated sequentially to enrolled participants; (iv) an on-site or coded computer system, provided that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participants; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, and opaque; (vi) other combinations of described elements of the process that provide assurance of adequate concealment.
- Category B (intermediate) is where the report describes allocation of treatment by: (i) use of a "list" of "table" to allocate assignments; (ii) use of "envelopes" or "sealed envelopes"; (iii) stating the study as "randomized" without further detail.
- Category C (inadequate) is where the report describes allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any such approach; (iii) any allocation procedure that is transparent before assignment, such as an open list of random numbers or assignments. Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown liable to yield more pronounced estimates of treatment effects than trials that have adequate measure to conceal allocation schedules, but the effect is less pronounced than inadequately concealed trials (Chalmers 1983; Schulz 1995). Trials were considered if they conformed to categories A or B, but those falling in category C were excluded. Other aspects of trial quality were not assessed by a scoring system but details of blinding, appropriateness of methods and the number of patients lost to follow-up were noted.

Only trials in which outcome assessments were made without knowledge of treatment allocation were eligible for inclusion.

Data extraction

One reviewer (RM) extracted data 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 deviation, 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 patients 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 is 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 patient assessed. To allow an intention-to-treat analysis, the data were sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data were not available in the publications, "on-treatment" data of participants who completed the trial were sought and indicated as such.
In studies where a cross-over design was used, only data from the first treatment phase after randomization were eligible for inclusion. Data from titration phases prior to the randomized phase were not used to assess safety or efficacy because patients were usually not randomized, nor were treatments concealed.

Data analysis

The outcomes measured in clinical 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 were 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. For cross-over trials only the data from the first treatment period were used.

When change from baseline results were not reported, the required summary statistics would be calculated from the baseline and assessment time treatment group means and standard deviations. In this case, 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 for meta-analysis.

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

The duration of the trials may vary considerably. If the range was considered too great to combine all trials into one meta-analysis it was divided into smaller time periods and a separate meta-analysis conducted for each period. Some trials might contribute data to more than one time period if multiple assessments were made.

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

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

RESULTS

Description of studies

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

Four randomized double-blind controlled trials were identified that met the criteria for inclusion in this review. The trial reports were published between 1997 to 2003. Bryan 2002 enrolled healthy women and Fioravanti 1997; Sommer 1998; Clarke 2003 enrolled cognitively impaired and demented participants.

Bryan 2002, enrolled 211 healthy women of various age groups in a multifactorial trial of randomized placebo-controlled design. Vitamin B6, vitamin B12 and folic acid were compared with placebo. The entry criteria were that participants should be non-smokers, not pregnant, not lactating, and not taking oral contraceptives or hormone replacement therapy or any medication likely to affect mood or mental function. In addition participants needed to have English as mother language or to be proficient in English as many assessments were language-dependent. Seventy-five participants aged 65 to 92 years comprised the older group eligible for this review; 19 received 750 μg folic acid orally per day for five weeks and 21 were randomized to placebo.

Fioravanti 1997 restricted enrolment to community-living people with a history of cognitive impairment over the previous two years, whose cognitive decline was diagnosed as very mild to moderately severe by the Global Deterioration Scale (GDS) and on the Mini-Mental State Examination (MMSE) between 16 to 24. Patients with clear diagnosis of dementia were excluded, as were people with serum folate levels above 3 ng/ml.

Sommer 1998, did not provide enough data for interpretation. Enrolment involved an unspecified small number of patients with dementia who received 10 mg of folic acid for an unspecified period, and measures of cognition and mood were not reported.

Participants eligible for the Clarke 2003 trial had either a clinical diagnosis of dementia (by DSM-IV) and MMSE scores between 12 and 26 inclusive, or mild cognitive impairment defined by symptoms of memory problems and a Modified Telephone Interview for Cognitive Status(TICS-M) score below 27 (Prince 1999). Eighty-four patients had Alzheimer's disease, 11 mixed dementia, 47 cognitive impairment, and 4 had unclassified memory deficits. Use of multivitamins containing less than 200μg daily of folic acid and less than 100 mg daily of vitamin E was permitted. Drugs that affect cognitive function (donepezil, metrifonate, rivastigmine) were also permitted in this trial. Baseline serum homocysteine and folate levels were measured. Participants were living in the community.

The sample sizes of the included studies on cognitive impairment and demented patients were small and the number of participants ranged from 30 in Fioravanti 1997 to 147 in Clarke 2003. No concomitant illnesses were reported in the trials.

2008 update

The combined searches identified 98 articles. A total of four randomized trials published between 2003 and 2008 were retained for inclusion. Three trials, Eussen 2006, Pathansali 2006 and Durga 2007 enrolled healthy elderly people and one Connelly 2008 recruited people with Alzheimer's disease. One preliminary trial on people with dementia (Sommer 1998) had originally been included on the basis of a conference proceeding but has since been published more fully (Sommer 2003). The trials were similar in their inclusion criteria with regard to previous history of vascular disease, hypertension, diabetes or smoking, normal kidney function, and not taking any supplements or any medications that might interfere with the metabolism of folic acid. Eussen 2006 enrolled healthy elderly people with mild vitamin B12 deficiency and compared combined folic acid and B12 with placebo. Pathansali

2006 and Durga 2007 enrolled healthy elderly people with normal folate levels and compared folic acid alone with placebo. Connelly 2008 recruited people with probable Alzheimer's disease and assessed the relationship between changes in homocysteine levels and the response to treatment with cholinesterase inhibitors.

Eussen 2006 recruited 195 home-living and care-facility living elderly people. The objective of this trial was to assess the effect of vitamin B12 with or without folic acid supplements on cognitive function of healthy elderly people with mild vitamin B12 deficiency. Mild vitamin B12 deficiency was defined as serum vitamin B12 concentration 100 to 200 pmol/L or serum vitamin B12 concentration 200 to 300 pmol/L and MMA plasma >32 mcmol/L. People scoring less than 19 on the MMSE were excluded. In a six-month, double-blind trial, folic acid (400 mcg/day) in combination with vitamin B12 (1000 mcg/day) was compared with vitamin B12 (1000 mcg/day) alone and with placebo.

Pathansali 2006 enrolled 24 healthy elderly people aged 73 (SD 5.6 years) (mean±SD) with normal folic acid levels (6.3 ± 2.4 mcg/l) and normal cognitive function defined as MMSE > 27. A dose of 5 mg/day folic acid was compared with placebo in a four-week trial.

Durga 2007 recruited 818 people aged 50 to 70 years with normal serum vitamin B12 to a three-year double-blind trial of 800 mcg folic acid per day versus placebo. This study was part of the Folic Acid and Carotid Intimamedia Thickness Trial (FACIT) investigating the effect of folic acid supplementation on progression of atherosclerosis. The participants were selected to benefit from folic acid's homocysteine-lowering effect, and participants with plasma total homocysteine of less than 13 micmol/L were excluded. Adequate compliance in a six-week placebo run-in period was required before acceptance into the study. Participants were required to score 24 or more on the MMSE. Cognitive function was assessed as memory, sensorimotor speed, complex speed, information processing and word fluency.

Sommer 2003: Eleven people who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria for dementia and with normal or low serum folate levels (2 to 5 mcg/L) and normal vitamin B12 levels (>200 ng/L) were randomized to 10 mg/day folic acid or placebo for 10 weeks. Baseline MMSE range (14 to 27). Seven participants completed the trial (three with probable AD, one with vascular dementia, one with Lewy body dementia, two with unspecified dementia).

Connelly 2008 enrolled 57 people with probable Alzheimer's disease according to the NINCDS-ADRDA criteria and who scored 11 to 30 on MMSE, 0 or 1 on the Modified Hachinski Ischaemia Scale, and < 2 on the Rosen scale (Rosen 1984). In a six-month, double-blind trial participants received a cholinesterase inhibitor and were randomized to a daily dose of 1 mg of folic acid or to placebo. Outcomes were categorized according to criteria of the National Insitute of Clinical Excellence (NICE 2006a). The primary outcome was the number of participants showing a good response (improvement or no deterioration in MMSE with global improvement on behavioural and/or functional assessment).

Baseline characteristics of the included studies were presented in Table 1.

Intervention

The doses of folic acid compared with placebo varied from 750 microgram to 15 milligram orally per day. The durations of the trials ranged from five weeks to three years. Clarke 2003 compared a combination of folic acid and vitamin B12 with placebo as part of a 2 x 2 x 2 factorial design that also included vitamin C plus vitamin E against placebo and aspirin against placebo. In Bryan 2002 the four arms in a parallel group study were vitamin B12, vitamin B6, folic acid and placebo. Connelly 2008 compared 1 mg/day of folic acid against placebo for people with Alzheimer's disease who also took a cholinesterase inhibitor. Eussen 2006, compared the combination of folic acid and Vitamin B12 with Vitamin B12 alone or placebo. A dose of 5 mg/day of folic acid was used in Pathansali 2006. Durga 2007 compared 800 mcg/day folic acid against placebo.

Dietary assessment

Daily dietary intake was assessed only in three trials (Bryan 2002, Eussen 2006; Durga 2007) using a self-reported food frequency questionnaire.

Outcome measures

The following cognitive and mood measures were involved in assessing the outcome on healthy people:

Speed of processing

- Boxes test (Earles 1995) is a paper-and-pencil test to assess sensory-motor speed; it comprises 100 three-sided boxes with a requirement to draw lines to complete each box. The score represents the number of boxes completed correctly in 30 seconds.
- Digit Symbol Coding Task (Wechsler 1997) is a symbol substitution task measuring the ability of participants to complete 133 substitutions 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 measuring perceptual speed. Two columns of symbols are presented and the participants required to scan the columns and indicate if a symbol of one column appears also in the other. Final score represents the number of symbols identified correctly in 60 seconds.
- Continuous Attention Test (CAT) (Kalra 1993; Bryant 1998). This test assesses attention, visuo-spatial memory, and response speed. A series of 240 geometric shapes with 40 repetitions build up from a random pattern of four light and five

dark squares arranged in a 3 x 3 grid. The duration of each stimulation was 0.1 second, and the interval between successive stimuli was 2 to 4 seconds. The task was to touch the response box with a touching pen whenever two patterns were the same. The number of repetitions identified correctly (cat-c) and incorrect responses was scored (cat-i). The error index was measured by expressing the total number of false negative and false positive responses as a proportion of the total response speed.

- Four-Choice Reaction Time (FCRT) (Kalra 1993; Bryant 1998). This test assessed attention, reaction time, and visuomotor coordination. Four circles could be arranged in the shape of a square. The task was to place the touch pen on an equivalent series of circles arranged in a square below on the same screen. At random intervals one of the circles was illuminated and the correct response was to touch the equivalent circle on the lower part of the screen as fast as possible. Three measures of accuracy and reaction time needed to be obtained: response to random stimuli, to fixed stimuli and the transition between the two. The results were the correct (fc-c) and incorrect response (fc-i) and the mean reaction time of the correct (fc-rtc) and the incorrect reaction responses (fc-rti).
- Digit-Symbol substitution (DSS). This test assessed attention, associative memory, and reaction time. A series of 10 digits appeared on top of the screen with corresponding symbols. A digit and a symbol were then projected on to the screen and the task was to touch a yes or no button depending on whether the combination was correct or not. The task was to idenitfy as many combinations as possible in 90 seconds. The score was the total number of correct (dsyn-c) and incorrect responses (dsyn-i). The mean correct reaction time (dsyn-rtc) and incorrect reaction time (dsyn-irtc) were scored.

Working memory

- Digit Span-Backwards (Wechsler 1997). This is the digit span test used in the intelligence and memory scales of the Wechsler batteries as a measure of 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 reads 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 recalled correctly; if neither list is repeated successfully, a score of zero is given and the test ended.
- Letter Number Sequencing (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 is given for each chain recalled correctly.

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 and longer term retention of a 15-word list following interpolated activity. Scores 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 have been exposed to and one point was given for each name recalled correctly according to order.
- Word learning test (Van der Elst 2006 a): involves memorizing 15 commonly used monosyllabic words that are printed on cards and presented in a fixed sequence at 2 s intervals. The task is to recall the words immediately and 20 minutes after presentation of the cards. The score is the maximum and the total number of correctly repeated words in the immediate recall test and in the delayed recall test.
- Scanning Memory Sets (SMS) (Kalra 1993; Bryant 1998): three numbers appeared on a screen for one minute and then disappeared. Then a single digit appeared on the screen. The task was to touch a yes or no button to indicate whether or not the number had been in the set. The subsequent set contained four numbers and the final set contained five. The total number of correct (sms-c) and incorrect (sms-ic) and the mean reaction time to the correct (sms-rti) and incorrect (sms-rti) responses was the total score.

Executive function

Executive function is a higher order cognitive activity controlling other cognitive activities including planning strategies for performance and using feedback to adjust future planning (Lezak 1995). The following measures were used for its assessment:

- Stroop Test (Dodrill 1978). Dodrill's format of the Stroop test consists of one sheet containing 176 colour word names ("red", "orange", "green" and "blue") printed in a random order and in randomly assorted colours. In phase one of the task the participants are required to read the printed word name. The requirement in phase two is to report the colours in which the words are printed. The score is evaluated as the total time for phase one and the difference in time between phases one and two.
- Self-Ordered Pointing Task (Spreen 1998). This task assesses planning and organizing abilities as it relies on self-initiated responses (Petrides 1982). It assesses capacity to initiate and execute a sequence of responses with constant monitoring of performance. The participant is required is to point to one item on each page of a sequence without repeating an item already

indicated. The participants therefore need to memorize items previously selected and to develop a strategy for pointing to all items available.

- Uses of Common Objects (Getzels 1962) test requires participants to give as many uses as they can for objects that customarily have a single function associated with them. The scores are based on the number and originality of the uses suggested.
- The Trail Making Test (Reitan 1985) has two parts. In part A participants are presented with a sheet randomly printed with numbers 1 to 25. The requirement is to join the numbers in sequence by tracing. Scores are derived as the time in seconds taken to complete the task. Part B presents numbers from 1 to 13 and letters from A to L in random placement. The requirement is to join the number and letters in numerical and alphabetical order. Scores are calculated by the time taken in seconds to complete the task.
- Verbal Fluency Task (Benton 1989; Benton 1994) comprises two parts, initial letter fluency and excluded letter fluency. In the first part, participants are asked to generate as many words as possible beginning with an allocated letter. The score is calculated as the number of words generated correctly in two trials of 60 seconds each. The excluded letter fluency task is to generate as many words as possible that do not contain the specified letter. The score is the number of correct words produced in two trials of 60 seconds each.
- Verbal fluency test (Van der Elst 2006 b). This test involves naming as many animals as possible in one minute. It measures word fluency or the ability to draw on one's encyclopaedic memory in a strategic manner.
- Concept shifting test (Van der Elst 2006 b). A timed test with four subtests testing flexibility in switching between two psychological concepts. Each subtest contained 16 circles (15 mm diameter) arranged in a large circle (16 cm diameter). For the first subtest, crossing off the circles in numerical and alphabetical order was required.
- Letter digit substitution test (Van der Elst 2006 b). A test to assess the speed of visual information processing. Nine different letters were assigned a unique number (1 to 9) in a key at the top of the form. A random series of letters in cells were presented and participants were instructed to add the corresponding digit to the letters. The score is the number of correctly corresponding digits in 90 seconds.

Verbal abilities

Two batteries were used to assess verbal ability, Vocabulary (WAIS-III) (Earles 1995) and spot the word (Baddeley 1988).

- Vocabulary (WAIS-III) (Earles 1995) evaluates an individual's ability to define the meanings of 15 words. The score is 0, 1, or 2 based on the accuracy, precision, and aptness of definition. Vocabulary scores peak at middle age and show a slow average decline in the sixth to seventh decades.
- Spot- the-Word Task (Baddeley 1988). Two printed sheets each containing 60 real word paired with non-words, the participant's task being to identify the real word in each pair. Scores are calculated as the number of words identified correctly minus the number of errors (to correct for guessing).

Mood

- 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. There is a 1 to 4 point scale for each of 20 items with higher scores indicating more symptoms of depressive mood.
- The Profile of Mood State Questionnaire (POMS) (McNair 1971) assesses six aspects of mood: tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment. The score is on a five-point ranging from 1 (no symptoms) to 5 (extreme symptoms).

The following range of outcome measures were used in trials with cognitively impaired participants:

Primary global measures

- Global Deterioration Scale (Reisberg 1982). This scale consists of a description of seven stages of dementia from 1 being normal to 7 where all verbal ability is lost. This scale has been shown to have a significant relation with anatomical brain changes as visualized on computerized tomographic scans (CT):

Stage 1: No cognitive decline. There is no complaint or evidence of memory deficits. In the Psychometric Concomitants questionnaire, the individual scores on at least 3 of the 5 subtests of the Guide Memory Test are average or above the standard for the subject's age and WAIS vocabulary score.
Stage 2: Very Mild Cognitive Decline. There are complaints of memory deficits, but no objective evidence of memory deficits in clinical interview. In the Psychometric Concomitants questionnaire, performance is below average for the patient's age and WAIS vocabulary score on 3 of the 5 Guide Memory subtests.
Stage 3: Mild Cognitive decline. There is objective evidence of memory and concentration deficits accompanied by mild to moderate anxiety. In the Psychometric Concomitants questionnaire performance is one standard deviation or more below average for the subject's age and WAIS vocabulary score on at least 3 of the 5 Guide Memory subtests.
Stage 4: There are deficits in many areas of cognition, in concentration, remembering recent events and there may be deficits in respondents' memories of their personal history. Orientation to

time and person is preserved. In the Psychometric Concomitants evaluation, respondents make 3 or more errors on the Mental Status Questionnaire.
Stage 5: Moderately Severe Cognitive Decline. This represents the early phase of dementia. Some assistance is required with activities of daily living but subjects can manage toileting and eating. Disorientation in time or place occur frequently. Deficits are evident in the Mental Status Questionnaire.
Stage 6: Severe Cognitive Decline. In this middle phase of dementia, full assistance is required with activities daily living. Subjects make 5 to 10 errors on the Mental Status Questionnaire.
Stage 7: Very severe Cognitive Decline. All verbal abilities are lost and assistance is required in toileting and eating. Signs and symptoms of cortical and focal neurological damage may be present. Assessment of the patients on the Mental Status Questionnaire shows 10 errors.

- Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA 1994). This schedule provides clinical criteria for the listed categories of dementia - Alzheimer's disease, vascular dementia and dementia due to multiple aetiologies. The criteria include memory impairment and at least one of: aphasia, apraxia, agnosia, and disturbance in executive functioning. The cognitive deficits are required to cause significant impairment in social and occupational functioning, and the deficits do not occur exclusively during delirium and are not accounted for by depression.

- Rosen scale (Rosen 1984). This scale distinguishes between Alzheimer's dementia and vascular dementia in patients with known histological diagnosis. Scores ranging from 0 to 2 for Alzheimer's disease and 4 to 10 for vascular dementia. Features of primary importance are: abrupt onset, stepwise deterioration, history of stroke, focal neurological signs, and focal neurological symptoms. A feature of secondary importance is a history of hypertension.

Cognitive function and memory measures

- The Mini Mental State Examination (Folstein 1975) is the most widely used test of cognitive function. It is a short performance test (5 to 15 minutes) and has been validated for screening for dementia with a sensitivity of 69% and a specificity of 90% (Feher 1992). The test evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall and language. Scores range from 0 (severe impairment) to 30 (normal). Scores below 24 (25 for well-educated subjects) are suggestive of dementia (Galasko 1990).
- Randt Memory Test (RMT) (Randt 1983) is a memory test for longitudinal assessment of mild and/or moderate memory storage and retrieval functions. It takes approximately 20 minutes and comprises five different parallel forms of acquisition, recall, and memory subtests. Scores are adjusted for age.
- The Modified Telephone Interview for Cognitive Status (TICS-M) (Prince 1999) was developed to provide follow-up documentation on patients already examined in the clinic or research project. Validated as a sensitive and specific screening instrument for dementia, the test lasts less than 30 minutes and assesses orientation, concentration, immediate and delayed memory, naming, calculation, comprehension and reasoning. TICTS-m has several different versions, the version used in Clarke 2003 comprised 13 items with a maximum score of 39 points. It includes an effortful list-learning task with delayed recall.
- Cognitive section of the Alzheimer's disease Scale (ADAS-Cog) (Rosen 1984) comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (O-5), word-finding (0-5), following instructions (0-5), naming objects (0-5), construction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-2). The scores range from 0 to 70, a higher score indicating impairment.
- Digit Symbol Substitution Test (DSST) (Wecshler 1981).
- Prorated Verbal IQ. This is a measure of intellectual function. Items from the Information, Vocabulary, and Similarities subtests of the Wechsler Adult Intelligence Scale-revised was used Welchsler 1982.
- Boston Naming Test Kaplan 1983. Object-naming test detected difficulties in confrontation naming.
- Controlled Oral Word Association Test (Benton 1955). A measure of verbal fluency.
- Logical Memory and Associated Learning subtests from the Wechsler Memory Scale. A measure of short-term verbal memory (Wechsler 1955).
- Benton Visual Retention Test (Benton 1955). A measure of the visuospatial memory.
- Trial Making Test A and B (Reitan 1992). A measure of visual scanning, conceptual flexibility, and motor speed.
- Finger tapping Test (Reitan 1974). A measure of motor speed for both dominant and nondominant hands.

Activities of daily living and behaviour

- Bristol Activities of Daily Living Scale (Bucks 1996). This 20-item scale uses a five-point severity grading for basic activities of daily living such as feeding, eating, dressing, toileting and instrumental activities of daily living (more complex tasks such as shopping, travelling and handling finances). It is an easy test that can be used by carers.
- Social Behaviour (SB) subscale of the Nurses' Observation Scale for Geriatric patients (NOSGER) (Spiegel 1991). The NOSGER contains 30 items of behaviour, each rated a five-point scale according to frequency of occurrence. Item scores are summarized into six dimension scores (memory, instrumental activities of daily life, self-care, social behaviour, and disturbing

behaviour).

Homocysteine level was assessed in Connelly 2008 and Pathansali 2006 at baseline and at end point.

Risk of bias in included studies

The included trials were of randomized, double-blind, and placebo-controlled design, but the methods of randomization to treatment and placebo were not reported in all. The numbers of drop-outs were small. Seven participants did not reach the end-point of the treatment period in the Clarke 2003 trial but their treatment group was not specified. One woman withdrew from the folic acid group in Bryan 2002. One participant dropped out from the placebo group in Fioravanti 1997. In Connelly 2008, 40 patients completed the study with no drop-outs due to side-effects reported during the study. Durga 2007 reported that five participants allocated folic acid reported adverse events, compared with seven in the placebo group; five participants were lost to follow-up.

Two trials were multifactorial evaluating more than one intervention and allowing detection of their interactions. Disadvantages of this design with a large number of factors is that interactions become difficult to interpret and the number of participants apportionable to each treatment smaller.

Effects of interventions

Eight trials met the criteria for inclusion and seven (Bryan 2002; Fioravanti 1997; Clarke 2003; Connelly 2008; Durga 2007; Pathansali 2006; Eussen 2006) provided sufficient data for analysis. Bryan 2002, Eussen 2006, Durga 2007 , Pathansali 2006 enrolled healthy elderly participants and in Durga 2007 the high plasma homocysteine level (> 13 micmol/L) was an inclusion criteria for enrolment in the study. It was not possible to pool the data because the trials studied different populations, different doses of folic acid, assessed different outcomes, and in the case of two trials vitamin B12 was also given.

Effect of folic acid on healthy older people

0.75 mg/day folic acid at five weeks - homocysteine level was not measured at baseline:

- No statistically significant results in favour of folic acid on cognitive processing functions as measured by speed of processing tests were found. The Boxes Task showed WMD 2.12 (95% CI -11.28 to 15.52, P = 0.76), Digit-Symbol Coding WMD 2.19 (95% CI -7.40 to 11.78, P = 0.65), and Symbol Search Test WMD 1.59 (95% CI -1.55 to 4.73, P = 0.32).
- There were no statistically significant differences between folic acid and placebo in any of the free recall tasks. Results were: Immediate Recall A WMD -0.06 (95% CI -6.87 to 6.75, P = 0.99); Immediate Recall B WMD -0.54 (95% CI -2.05 to 0.97, P = 0.48); Delayed Recall WMD -0.07 (95% CI -2.85 to 217, P = 0.79); Recognition A WMD 1.42 (95% CI -0.24 to 3.08, P = 0.09); Recognition B WMD 1.59 (95% CI -1.35 to 4.53, P = 0.29). No statistically significant differences between folic acid and placebo emerged in measures of working memory as assessed by Digit Span-Backwards (WMD -0.31, 95% CI -2.66 to 2.04, P = 0.80) or the Letter-Number Sequencing (WMD -050, 95% CI -2.78 to 1.78, P = 0.67).
- There were no statistically significant differences between folic acid and placebo groups in Executive Function as assessed by the Stroop Test (WMD -0.09, 95% CI -0.44 to 0.26, P = 0.61), Trail Making Test A (WMD 2.29, 95% CI -11.40 to 15.89, P = 0.74), Trail Making Test B (WMD -5.21 95% CI -37.01 to 26.59, P = 0.75), Verbal Fluency Initial (WMD -3.44, 95% CI -11.20 to 4.32, P = 0.39) or Excluded Letter test (WMD 0.57, 95% CI -6.76 to 7.90, P = 0.88).
- Verbal Ability Tests: the meta-analysis revealed no superiority of folic acid supplementation over placebo as assessed by the Vocabulary Task (WMD -0.13, 95% CI -4.87 to 4.61, P = 0.96) and Spot the Word Test (WMD 0.87, 95% CI -7.92 to 9.66, P = 0.85).
- Measures of mood revealed no statistically significant advantage of folic acid over placebo: total Profile of Mood States Questionnaire (POMS) WMD -3.14 (95% CI -23.56 to 17.28, P = 0.73); tension symptoms WMD 0.30 (95% CI -3.93 to 4.53, P = 0.89); depression WMD 0.59 (95% CI -5.45 to 6.63, P = 0.85); anger WMD 0.97 (95% CI -3.29 to 5.23, P = 0.66); activity WMD 3.13 (95% CI -2.26 to 8.52, P = 0.26); fatigue WMD -1.83 (95% CI -5.85 to 2.19, P =0.37); confusion WMD -0.05 (95% CI -3.05 to 2.95, P = 0.97).

There was no statistically significant difference between folic acid and placebo in depressive symptoms as assessed by the Center for Epidemiological Studies-Depression Scale (WMD -1.11, 95% CI -7.31 to 5.09, P = 0.73).

Effect of folic acid on healthy older people with normal folate levels

5 mg/day folic acid for four weeks

- There was no significant difference in psychomotor performance between the placebo and folic acid group in all the domains, except on the outcome Digit-Symbol Substitution reaction time DSS WMD 0.21(95% CI 0.01 to 0.41, P = 0.04) where the data was in favour of folic acid. The following results were nonsignificant: Four-Choice Reaction Time fixed FRCT (f-c) WMD -6.00 (95% CI -16.29 to 4.29, P = 0.25), Four-Choice Reaction Time fixed FRCT correct WMD 6.75 (-3.70 to 17.20); Four-Choice Reaction Time random correct FC RT (fc-i) random incorrect WMD -0.75 (95% CI -1.82 to 0.32, P = 0.17); FC RT random reaction time WMD -0.02 (95% CI -

0.11 to 0.07, P = 0.63); Continuous Attention Test correct CAT WMD 1.94 (95% CI -1.00 to 4.88; P = 0.20); Continuous Attention Test incorrect CAT WMD -0.19 (95% CI -1.55 to 1.17, P = 0.78); Continuous Attention Test error index CAT WMD -0.04 (95% CI -0.11 to 0.03; P = 0.27); Digit-Symbol Substitution correct DSS WMD 0.66 (95% CI -0.49 to 1.8; P = 0.27); Digit-Symbol Substitution incorrect DSS WMD -0.66 (95% CI -1.81 to 0.49, P = 0.26); Scanning Memory Test SMS three digits correct WMD -0.58 (95% CI -1.60 to 0.44, P = 0.26); Scanning Memory Test SMS three digits reaction time WMD 0.04 (95% CI -0.05 to 0.13, P = 0.4); Scanning Memory Test SMS four digits correct WMD -0.01 (95% CI -1.69 to 1.67, P = 0.99); Scanning Memory Test SMS Reaction WMD -0.01 (95% -0.14 to 0.12, P = 0.88); Scanning Memory Test SMS five digits correct WMD 0.15 (95% CI -1.97 to 2.27, P = 0.89); Scanning Memory Test SMS five digits reaction time WMD 0.00 (95% CI -0.12 to 0.12, P = 1.00).

- There was no significant benefit in favour of 5 mg/day of folic acid over placebo at week 4 in reducing the plasma homocysteine level WMD -1.60 (95% CI -4.28 to 1.08, P = 0.24)

Effect of folic acid on healthy older people with high plasma homocysteine level

800 mcg/day folic acid for three years:

- A statistically significant difference in favour of folic acid over placebo, illustrated in the global cognitive function domains at the end point of three years WMD 0.05 (95% CI 0.004 to 0.096 , P = 0.033).

- Folic acid administration significantly improved memory storage over placebo; the results showed WMD 0.14 (95% CI 0.04 to 0.24, P = 0.006)

- The three-year change in cognitive function was significantly better with folic acid than with placebo in the domains of information-processing speed; WMD 0.09 (95% CI 0.02 to 0.16, P = 0.016).

- There were no statistically significant differences in sensorimotor speed, complex speed and word fluency assessment between folic acid and placebo: WMD 0.06 (95% CI 0.00 to 0.120, P = 0.07); WMD 0.04; (95% -0.05 to 0.13, P = 0.36) and WMD -0.06 (95% CI -0.18 to 0.06, P = 0.32) respectively.

Effect of folic acid with vitamin B12 on healthy older people

400 mcg/day folic acid combined with 1000 mcg/day vitamin B12 for 24 weeks:

- The combination of folic acid with vitamin B12 produced no improvement in cognitive function. There was no significant difference between folic acid with B12 and placebo with the complex figure of Rey WMD -0.5 (95% CI -5.33 to -4.33, P = 0.84).

- There was no benefit in favour of folic acid with B12 for improving attention as assessed by using the digit span forward WMD -0.30 (95% CI -1.17 to -0.57, P = 0.50).

- There was no statistically significant difference between placebo and folic acid with vitamin B12 on sensorimotor speed as measured by motor planning WMD 84 (95% CI -8.38 to -248.38, P = 32) or finger tapping WMD 3 (95% CI -11.50 to -125.50, P = 0.96), trial making test part A, WMD -9 (95% CI -34.41 to -16.41, P = 0.49).

- Measures of memory: there was no significant difference between placebo and folic acid with B12 in 15-word learning (immediate recall) WMD 0.50 (95% CI -5.25 to -6.25, P = 0.86), (delayed recall) WMD 060 (95% CI -1.42 to -2.62, P = 0.56), word recognition WMD 0.08 (95% CI -1.62 to -0.02, P = 0.06).

- There was no statistically significant difference between placebo and folic acid with vitamin B12 in executive function as assessed by: motor planning 3 WMD 35 (95% CI -247.33 to -317.33; P = 0.81); trail making test WMD 0.50 (95% CI -0.2 to -1.20, P = 0.16); no changes in the Stroop test from baseline for folic acid with Vitamin B12 arm; similarities WAIS WMD; Raven WMD 0.50 (95% CI -1.55 to 2.55, P = 0.63); word fluency, animals and number of nouns WMD -0.60 (95% CI -3.55 to 2.35; P = 0.39); word fluency, letter, number of nouns WMD -1.80 (95% CI -8.43 to 3.37, P = 0.39).

- Effect on total homocysteine level: folic acid with B12 significantly reduced serum total homocysteine levels in comparison with placebo at both 12 and 24 weeks WMD -4.50 (95% CI -7.05 to 1.95, P = 0.0006) and WMD -5.90 (95% CI -8.43 to 3.37; P < 0.0001) respectively.

Effect of folic acid on patients with Alzheimer's dementia, vascular dementia and unclassified cognitive decline

- On the Mini Mental State Examination (MMSE), there was no statistically significant difference between 2 mg per day folic acid plus vitamin B12 1 mg per day for 12 weeks and placebo groups (WMD 0.39, 95% CI -0.43 to 1.21, P = 0.35).

- There was no statistically significant benefit from 2 mg folic acid per day plus 1 mg vitamin B12 for 12 weeks compared with placebo on ADAS-Cog scales (WMD 0.41, 95% CI -1.25 to 2.07, P = 0.63).

- No statistically significant difference was seen between 2 mg folic acid plus 1 mg vitamin B12 per day for 12 weeks and placebo for the Bristol Activity of Daily Living (BADL) (WMD -0.57, 95% CI -1.95 to 0.81, P = 0.42).

- No statistically significant differences were found between 15 mg folic acid per day and placebo on any part of the Randt Memory Test (RMT) tests: acquisition and recall assessment

WMD 5.47 (95% CI -10.05 to 20.99, P = 0.49); delayed recall WMD 7.38 (95% CI -8.58 to 23.34, P = 0.36); encoding subtest WMD 0.67 (95% CI -1.89 to 3.23, P = 0.61); Memory Index WMD 7.34 (95% CI -9.67 to 24.35, P = 0.40); Cognitive Efficiency Test WMD 0.57 (95% CI -1.97 to 3.11, P = 0.66); Attention Efficiency WMD 1.05 (95%, -0.17 to 2.27, P = 0.09). In comparison with placebo, 10 mg/day folic acid had no effect on memory at 10 weeks: WMS Logical Memory Subtest WMD -1.70 (95% CI -12.26 to 8.86, P = 0.72) and Associated Learning Subtest WMD -7.40 (95% CI -15.54 to 0.74, P = 0.07).

- There was no effect of folic acid on language as assessed by WAIS-R: Pro-rated Verbal IQ: WMD -15.00 (95% CI -51.92 to 21.92, P = 0.43), Boston naming Test WMD -0.20 (-37.30 to 36.90, P = 0.99) and Controlled Oral Word Association Test WMD 8.30 (95% CI -36.94 to 53.54, P = 0.72).
- Speed and Concentration measures: there were no differences between placebo and 10 mg/day folic acid at week 10 over placebo in measures of speed or concentration:Trial A WMD 31.50 (95% CI -574.18 to 637.18, P = 0.92), Trial B WMD175.00 (95% CI -354.94 to 704.94, P = 0.52) and Finger Tapping Test WMD 7.90 (95% CI -15.83 to 31.63, P = 0.51).

Effect of folic acid on patients with Alzheimer's disease treated with cholinesterase inhibitors

1 mg/day folic acid for 24 weeks:

- The results revealed no statistically significant benefit of folic acid compared with placebo on the Mini-Mental State Examination (MMSE) WMD -0.13 (95% CI -1.96 to 1.70, P = 0.89) or Digit Symbol Substitution Test (DSST) WMD 0.26 (95% CI -4.12 to 4.46.1; P = 0.91).
- On the Instrumental Activities of Daily Living (IADL) scale, 1 mg/day folic acid was significantly better than placebo: WMD 2.67 (95% CI 0.25 to 5.09; P = 0.03). On the Social Behaviour Subscale (SB) there was no difference between the treatment and control: WMD 1.38 (95% CI-1.13 to 3.89; P = 0.28). There was a significant benefit in favour of folic acid over placebo on the combined IADL/SB: WMD 4.01 (95% CI 0.50 to 7.52, P = 0.02).
- Response to treatment with cholinesterase inhibitors was significantly better in the folic acid group than in the placebo group: 20/28 were classified as responders in the folic acid group compared with 8/21 in the placebo group: odds ratio: 4.06 (95% CI 1.22 to 13.53; P = 0.02).

Effect of folic acid with or without vitamin B12 on healthy and cognitively impaired older people

- One meta-analysis of the effect folic acid on healthy people was performed regardless of the dose, duration and combination with vitamin B12. The results showed no benefit of folic acid on memory and word fluency: for memory immediate recall WMD 0.27 (95% CI -4.14 to 4.67, P = 0.91); delayed recall WMD 0.23 (95% CI -1.34 to 1.80, P = 0.77); word recognition WMD 0.46 (95% CI -0.81 to 1.73, P=0.48); verbal ability WMD -0.06 (95% CI -0.18 to 0.06, P = 0.31).
- There was no statistically significant difference between folic acid with or without vitamin B12 on cognitive function as assessed by changes in MMSE in cognitively impairment and demented patients: WMD 0.30 (95% CI -0.45 to 1.05, P = 0.43).

Effect of folic acid on serum homocysteine levels

- Clarke 2003 was the only trial to present data on the efficacy of the vitamin supplements in lowering serum homocysteine levels. The dose of 2 mg folic acid plus 1 mg vitamin B12 significantly reduced serum homocysteine concentration (P < 0.001).
- In Durga 2007, the baseline plasma total homocysteine level in the folic acid group was 13 (11.6 to 14.7) mcmol/L compared with 10.1 (9.0 to 11.3) mcmol/L at three years. In the placebo group the values were 12.9 (11.4 to 14.8) mcmol/L at baseline compared with 13.4 (11.5 to 15.2) mcmol/L at the three-year end point. Data were given as only as median and interquartile ranges and therefore could not be used in meta-analysis.
- In Connelly 2008, there was no significant difference between placebo and folic acid 5 mg/day folic acid for 24 weeks in reducing blood total homocysteine levels: WMD -1.60 (95% CI -5.13 to 1.93; P = 0.37).

Adverse effects

In one trial only, Durga 2007 with an intervention period of three years, were adverse events reported and no seriuos side effects were noted: five participants allocated to folic acid supplement reported adverse events of forgetfulness, sun allergies, weight gain, tinnitus, and dark urine. In the placebo group, seven participants reported having adverse effects in the form of muscle aches, headaches, weight gain, queasiness, bitter taste and skin irritations.

Withdrawal

The numbers of drop-outs were small: 17 participants in total across all the trials. Seven participants did not reach the endpoint of the treatment period in Clarke 2003 but their treatment group was not specified. One woman withdrew from the folic acid group in Bryan 2002. One participant dropped out from the placebo group in Fioravanti 1997. In Connelly 2008, eight patients did not reach the end point, three owing to non-compliance, four were hospitalized with unrelated problems, and one participant proved intolerant to cholinesterase inhibitors.

There were no data on effects on caregiver burden or costs of treatment.

DISCUSSION

Eight trials of folic acid with or without vitamin B12 qualified for inclusion in this review. Four were performed on healthy elderly populations and four enrolled cognitively impaired and demented participants.

The review provides some evidence of benefit from dietary supplementation with folic acid, with or without vitamin B12, on cognitive function of healthy, cognitively impaired or demented older people. There are some limitations on the interpretation of these findings. The range of folic acid dosage in the reviewed studies was limited and may have been too low at 750 mcg or too high at 15 mg daily. The included trials were mostly of short duration. In one large study, Durga 2007, that lasted for three years, no attempt was made to measure the prevalence of dementia at baseline or during the trial.

The trials on healthy elderly people drew on different populations and used more than 50 different cognitive measures. In some cognitive tests greater improvement was seen in the placebo than in the treatment groups. It is possible that results may have been affected by learning from repetition, although attempts to reduce learning effects were made in Pathansali 2006. In a selected group of older people with elevated levels of blood homocysteine, prolonged folic acid supplementation was associated with better memory performance tests, but no benefit was seen in measures of sensorimotor speed and verbal fluency. Restriction to older people with mild B12 deficiency limited the applicability of the trial by Pathansali 2006. The main aim of this trial was to assess the efficacy of vitamin B12 supplementation on cognitive function. This issue will be discussed in Malouf 2003 a.

Participants with cognitive impairment or dementia were heterogeneous and some aetiological subgroups could be more susceptible than others to benefit from folic acid. Different degrees of metabolic deficiency of folic acid among participants may also affect results. If high blood homocysteine concentrations are relevant and precede clinical manifestations of dementia (Seshadri 2002), benefit may only emerge in very large studies of normal populations over long periods. In Connelly 2008, there were some indications that folic acid supplementation improved general response to cholinesterase inhibitors by patients with Alzheimer's disease as determined by improved functional, though not cognitive measures.The number needed to treat (NNT) is four with a 95% confidence interval of 1.7 to 23.8 . This means that about one in every four AD patients will benefit from combined treatment of cholinesterase inhibitors and folic acid for six months. This suggests that folic acid might act synergistically with cholinesterase inhibitors in addition to the role of reducing homocysteine levels. However, no firm recommendations can be drawn from a pilot study of only 49 people with Alzheimer's disease treated only for six months.

Only two studies met the criteria for evaluation of folic acid supplementation (Connelly 2008; Durga 2007). In both trials folic acid supplementation was associated with improvement in some domains of cognitive status. The two studies involved people with high blood homocysteine levels.

Given the plausible rationale for there being beneficial effects from folic acid at least among people with evidence of metabolic insufficiency, more trials seem necessary. The increasing dietary intakes of folic acid as a consequence of official and commercial fortification will make trials harder to design and implement. It also needs to be emphasised that without adequate trials the possibility of harm from high intakes of folic acid, an artificial substance, cannot be excluded.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of a single large study suggest a possible benefit from folic acid supplementation over long periods in preserving some aspects of cognitive function of healthy people with high homocysteine levels. The risks of malignancy with long term folate supplementation are unknown and folate supplementation may worsen cognitive function in the presence of low B12. Until further safety data accrue, and the effect is replicated, the risk-benefit ratio remains unknown and practice should not change.

Implications for research

Because the risk-benefit ratio for cognitive function of folate supplementation may be unfavourable (as well as favourable), further large scale RCTs should be undertaken before recommending either population treatment with fortification of flour or folate supplementation. Such RCTs should incorporate multiple dosing regimes, stratification by homocysteine and B12 levels and include careful follow-up of malignancy risk beyond the end of the treatment period. Future trialists should agree on the range of outcome measures assessed to ensure consistency across trials.

ACKNOWLEDGEMENTS

We thank Almudena Areosa Sastre for her work on the protocol and the first version of the review (selection of studies for inclusion and checking drafts). We thank Dr. Robert Clarke for providing original data from the VITAL trial and Dr Bryan for providing the data requested. We are also grateful to Corinne Cavender as consumer editor of the first version of the review. We wish to thank the following consumer editors for their comment on the latest update of this review: Ann E. Finfa, Morio Aihara and U. Hla Htay.

REFERENCES

References to studies included in this review

Bryan 2002 *{published data only}*

Bryan J, Calvaresi E, Hughes D. Short term folate vitamin B12 or vitamin B6 supplementation slightly affects memory performance but not mood in women of various ages. *Journal of Nutrition* 2002;**132**(6):1345–56.

Clarke 2003 *{published data only}*

Clarke R, Harrison G, Richards S, VITAL Trial Collaborative Group. Effect of vitamins and aspirin on markers of platelet activations oxidative stress and homocysteine in people at high risk of dementia. *Journal of Internal Medicine* 2003;**254**(1):67–75.

Connelly 2008 *{published data only}*

Connelly PJ, Prentice NP, Cousland G, Bonham J. A randomised double-blind placeblo controlled trial of folic acid supplementation of cholinesterase inhibitors in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 2008;**23**(2):155–60.

Durga 2007 *{published data only}*

* Durga J, Van Boxtel MPV, Schouten EG, Kok FJ, Katan MB, Verhoef P. Effect of 3-year folic acid supplementation on cognition function in older adults in the FACIT trial a randomized double blind controlled trial. *The Lancet* 2007; **369**:208–16.

Eussen 2006 *{published data only}*

Eussen SJ, Groot LC, Joosten LW, Bloo RJ, Clarke R, et al.Effect of oral vitamin B12 with or without folic acid on cognitive function in older people with mild vitamin deficiency a randomized placebo controlled trial. *American Journal of Clinical Nutrition* 2006;**84**:361–70.

Fioravanti 1997 *{published data only}*

Fioravanti M, Ferrario E, Massaia M, Cappa G, Rivolta G, Grossi E, Buckley AE. Low folate levels in the cognitive decline of elderly patients and efficacy of folate as a treatment for improving memory deficits. *Archives of Gerontology and Geriatrics* 1997;**26**(1):1–13.

Pathansali 2006 *{published data only}*

Pathansali R, Mangoni A, Creagh-Brown B, Lan Z, Ngow G, et al.Effects of folic acid supplementation on psychomotor performance and hemorheology in healthy elderly subjects. *Archives of Gerontology and Geriatrics* 2006; **43**:127–37.

Sommer 2003 *{published data only}*

* Sommer BR, Hoff AL, Costa M. Folic acid supplementation in dementia: a preliminary report. *Journal of Geriatric Psychiatry and Neurology* 2003;**16**:156–9.

Sommer BR, Hoff AL, Costa M. Folic acid supplementation in dementia a preliminary report. Proceedings of the 11th Annual Meeting of the American Association for Geriatric Psychiatry, 1998 8-11 March, San Diego. 1998.

References to studies excluded from this review

Brouwer 2000 *{published data only}*

* Brouwer IA, Van Dusseldorp M, Thomas CMG, Duran M, Hautvast JGAJ, Eskes TK, et al.Low dose folic acid supplementation decreases plasma homocysteine concentrations a randomised trial. *Indian Heart Journal* 2000;**7**(S52):S53–8.

Cockle 2000 *{published data only}*

Cockle SM, Haller J, Kimber S, Dawe RA, Hindmarch I. The influence of multivitamins on cognitive function and mood in the elderly. *Aging and Mental Health* 2000;**4**(4): 339–53.

Jong 2001 *{published data only}*

Jong ND, Paw MC, Groot L, Rutten R, Swinkels DW, Kok FJ, Staveren WAV. Nutrient dense foods and exercise in frail elderly effects on B vitamins homocysteine methylmalonic acid and neuropsychological functioning. *American Journal of Clinical Nutrition* 2001;**73**:338–46.

Lewerin 2005 *{published data only}*

Lewerin C, Matousek M, Steen G, Johansson B, Steen B, Nilson-Ehle H. Significant correlations of plasma homocysteine and serum methylmalonic acid with movement and cognitive performance in elderly subjects but no improvement from short-term vitamin therapy: a placebo-controlled randomized study. *American Journal of Clinical Nutrition* 2005;**81**:1155–62.

McMahon 2006 *{published data only}*

McMahon JA, Green TJ, Skeaff M, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. *New England Journal of Medicine* 2006;**354**:2764–72.

Passeri 1993 *{published data only}*

Passeri M, Cucinotta D, Abate G, Senin U, Ventura A, Badiale MS, Diana R, Greca PL, Grazie L. Oral 5 methyltetrahydrofolic acid in senile organic mental disorders with depression results of a double blind multicenter study. *Aging Clinical and Experimental Research* 1993;**5**(1):63–71.

Ralph 1974 *{published data only}*

Magnus RV, Cooper AJ. A controlled study of reactivan in geriatrics. *Modern Geriatrics* 1974;**June**:270–76.

Stott 2005 *{published data only}*

Stott DJ, MacIntosh G, DO Lowe J, Rumley A, MacMahon AD, Langhorne P, et al.Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. *The American Journal of Clinical Nutrition* 2005;**82**:1320–6.

Tucker 2004 *{published data only}*

* Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B6, and vitamin B12 increases vitamin concentrations and reduces homocysteine concentrations a randomized trial. *American Journal of Clinical Nutrition* 2004;**79**:805–11.

Walker J, Christensen H. Beyond ageing: A study for the prevention of depression cognitive impairment and

the improvement of knowledge about mental health. www.clinicaltrials.gov 2007.

Additional references

Abalan 1996
Abalan F, Zittoun J, Boutami C. Plasma red cell and cerebrospinal fluid folate in Alzheimer's disease. *Encephale* 1996;**6**:430–4.

Antony 1995
Antony AC. *Heamatology basic principles and practice*. 2nd Edition. New York: Chirchill Livingstone, 1995:552–86.

APA 1987
Americam Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd Edition. Washington: APA, 1987.

APA 1994
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington DC: APA, 1994.

Aronow 1997
Aronow WS, Ahn C, Schoenfed MR. Association between plasma homocysteine and extracranial carotid disease in older persons. *American Journal of Cardiology* 1997;**79**: 1432.

Baddeley 1988
Baddeley A, Emslie H, Nimmo-Smith I. Estimating premorbid intelligence. *Journal of Clinical Neuropsychology* 1988;**10**:326.

Benton 1955
Benton AL. *Revised Visual Retention Test*. 5th Edition. New York: The Psychological Corporation, Harcourt, Brace and Jovanovich, 1955.

Benton 1989
Benton AL, Hamsher D. *Multilingual Aphasia Examination*. Iowa City, IA: Universty of Iowa, 1989.

Benton 1994
Benton AL, Hamsher K, Sivan AB. *Multilingual aphasia examination*. 3rd Edition. Iowa: AJA Associated, 1994.

Botez 1979
Botez MT, Reynolds EH. *Folic acid in neurology psychiatry and internal medicine*. Botez MT, Reynolds EH. New York: Raven press, 1979.

Bottiglieri 1994
Bottiglieri T, Crellin R, Reynolds EH. *Folate and Neuropsychiatry*. In Bailey. New York: Marcel Dekker, 1994:435–63.

Bottiglieri 2000
Bottiglieri T, Reynolds EH. Folate in CSF and age. *Journal of Neurology, Neurosurgry and Psychiatry* 2000;**69**:562.

Breteler 1994
Breteler MMB, Claus JJ, Grobbee DE. Cardiovascular disease and distribution of cognitive function in elderly people the Rotterdam study. *British Medical Journal* 1994; **308**:1604–8.

Brocker 1986
Brocker P, Lebel C, Maurine H, Lods JC. Carences en folates chez les sujets ages interet de leir correction dans le traitment des troubles du comportement [Carences en folates chez les sujets ages interet de leir correction dans le traitment des troubles du comportement]. *Semaine Hopital. Paris* 1986;**27**:2135–39.

Bryant 1998
Bryant CA, Farmer A, Tiplady J, Sherwood R, Swift CG, Jackson SH. Psychomotor performance: investigating the dose-response relationship for caffeine and theophylline in elderly volunteers. *European Journal of Clinical Pharmacology* 1998;**54**:309–13.

Bucks 1996
Bucks RS, Ashworth D, Wilcock GK, Siegfried K. Assessment of activities of daily living in dementia development of the Bristol activities of daily living scale. *Age and Ageing* 1996;**25**:113–20.

Chalmers 1983
Chalmers TC, Celano P, Sacks HS, Smith H. Bais in treatment assignment in controlled clinical trials. *New England Journal of Medicine* 1983;**309**:1358–61.

Chanarin 1979
Chanarin I. *The Megaloblastic Anemias*. Oxford: Blackwell Scientific Publications, 1979.

Chanarin 1989
Chanarin I, Deacon R, Lumb M, Perry J. Cobalamin folate interrelations. *Blood Review* 1989;**3**:211–15.

Clarke 1998
Clarke R, Smith AD, Jobst KA. Folate vitamin B12 and serum total homocysteine levels in confirmed Alzehimer's disease. *Archives of Neurology* 1998;**55**:1449–55.

Clarke 2007
Clarke R, Sherliker P, Hin H, Nexo E, Hvas AM, Schneede J. Detection of vitamin B12 deficiency in older people by measuring vitamin B12 or the active fraction of vitamin B12, holotranscobalamin. *Clinical Chemistry* 2007;**53**: 963–70.

Cole 2007
Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, et al.Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *Journal of the American Medical Association* 2007;**297**:2351–9.

Cooper 1986
Cooper BA. *Nutritional Pharmacological and Physiological Aspects /Folate nutrition in man and animals*. Blakley R. New York: Blakley RL, Whitehead VM, 1986.

Corrada 2005
Corrada M, Kawas CH, Hallfrisch J, Muller D, Brookmeyer R. Reduced risk of Alzheimer's disease with high folate intake: the Baltimore Longitudinal Study of Aging. *Alzheimer Disease and Associated Disorders* 2005;**1**:11–18.

Dodrill 1978
Dodrill CB. A neuropsychological battery for epilepsy. *Epilepsia* 1978;**19**:611–23.

Earles 1995
Earles JL, Salthouse TA. Interrelations of age health and speed. *Journals of Gerontology B. Psychology and Social Sciences* 1995;**50B**:33–41.

Ebly 1998
Ebly EM, Schaefer JP, Campbell NRC. Folate status vascular disease and cognition in elderly Canadians. *Age and Ageing* 1998;**27**:485–91.

Feher 1992
Feher EP, Mahurin RK, Doody RS, Cooke N, Sims J, Prizzolo FJ. Establishing the limits of the mini mental state examination of subtests. *Archives of Neurology* 1992;**49**(1): 87–92.

Ferri 2005
Ferri PC, Prince M, Brayne C, Brodaty H, Fratiglioni H, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, et al.Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;**366**:2112–7.

Folstein 1975
Folstein MF, Folstein SE, McHugh PR. Mini mental state, a practical method for grading cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;**313**: 1419–20.

Galasko 1990
Galasko D, Klauber MR, Hofstetter CR. The Mini Mental State examination in the early diagnosis of Alzheimer's disease. *Archives of Neurology* 1990;**47**:49–52.

Getzels 1962
Getzels JW, Jackson PW. *Creativity and Intelligence*. New York: Wiley, 1962.

Gospe 1995
Gospe SM, Gietzen DW, Summers PJ, Lunetta JM, Miller JW, Selhub J. Behavioral and neurochemical changes in folate deficient mice. *Journal of Physiology and Behavior* 1995;**58**:935–41.

Gottfries 1998
Gottfries CG, Lehman W, Regland B. Early diagnosis of cognitive impairment in the elderly with the focus on Alzheimer's disease. *Journal of Neural Transmission* 1998; **105**:773–86.

Hassing 1999
Hassing L, Wahlin A, Winblad B. Further evidence for the effects of vitamin B12 and folate status on episodic memory functioning a population based study of very old adults. *Biological Psychiatry* 1999;**45**(11):1472–80.

Herbert 1985
Herbert V. Megaloblastic anemias. *Laboratory Investigation* 1985;**52**:3.

Herbet 1961
Herbet V. Experimental nutritional folate deficiency in men. *Transactions of the Association of American Physicians* 1961;**75**:307–20.

Higgins 2008
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Hirsch 2002
Hirsch S, Maza P, Barrera G, Gattas V, Petermann M, Bunout D. The Chilean folic acid fortification program reduces serum homocysteine levels and masks vitamin B12 deficiency in elderly people. *Journal of Nutrition* 2002;**132**: 289–91.

Hofman 1997
Hofman A, Ott A, Breteler MMB. Atherosclerosis apolipoprotein E and the prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *The Lancet* 1997;**349**:151–4.

ICD-10 1992
World Health Organizition. *The ICD-10 classification of mental and behavioural disorders clinical description and diagnostic guidelines*. Geneva: World Health Organisation, Division of Mental Health, 1992.

Jacques 1999
Jacques PF, Selhub J, Bostom A, Peter WF, Wilson P, et al.The effect of folic acid fortification on plasma and total homocysteine concentrations. *The New England Journal of Medicine* 1999;**340**:1449–54.

Jorm 1987
Jorm AF, Korten AE, Henderson AS. The prevalence of dementia a quantitative integration of the literature. *Acta Psychiatrica Scandanavica* 1987;**76**:465–79.

Kalra 1993
Kalra L, Jakson SH, Swift CG. Assessment of changes in psychomotor performance in elderly subjects. *British Journal of Pharmacology* 1993;**36**:383–89.

Kaplan 1983
Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Philadelphia: Lea and Febiger, 1983.

Keane 1998
Keane EM, O'Broin S, Kelleher B, Coakley D, Walsh JB. Use of folic acid fortified milk in the elderly population. *Gerontology* 1998;**44**:336–9.

Kruman 2002
Kruman Inna I, Kumaravel TS, Lohani A. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of alzheimer's disease. *Journal of Neuroscience* 2002;**22**:1752–62.

La Rue 1997
La Rue A, Koehler Km, Wayne SJ, Chiulli SJ, Haaland KY, Garry PJ. Nutritional status and cognitive functioning in a normally aging sample a 6 year reassessment. *American Journal of Clinical Nutrition* 1997;**65**:20–9.

Levitt 1989
Levitt AJ, Joffe RT. Folate vitamin B12 and life course of depressive illness. *Biological Psychiatry* 1989;**25**:867–72.

Lezak 1995
Lezak MD. *Neuropsychological Assessment*. Third Edition. Oxford University Press, 1995.

Malouf 2003 a
Malouf R, Areosa Sastre A. Vitamin B12 for cognition. *Cochrane Database of Systematic Reviews* 2003, Issue 4.[Art. No.: CD004394. DOI: 10.1002/14651858.CD004394]

Marcus 1998
Marcus EL, Berry EM. Refused to eat in the elderly. *Nutrition Reviews* 1998;**56**:163–171.

Mason 2007
Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G, et al.A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. *Cancer Epidemiology Biomarkers and Prevention* 2007;**16**:1325–9.

Mayer 1996
Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. *Journal of the American College of Cardiology* 1996;**27**:517.

McCaddon 1998
McCaddon A, Davis G, Hudson P, Tandy S, Cattell H. Total serum homocysteine in senile dementia of Alzheimer type. *International Journal of Geriatric Psychiatry* 1998;**13**: 235–9.

McKhann 1984
McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 1984;**4**:939–44.

McNair 1971
McNair PM. *Profile of mood states manual.* San Diego, CA: Education and Industrial Testing Service, 1971.

Meindok 1970
Meindok H, Dvorsky R. Serum folate and vitamin B12 levels in the elderly. *Journal of the American Geriatrics Society* 1970;**18**:317–26.

Morris 2005
Morris MC, Evans DA, Bienias JL, et al.Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. *Archives of Neurology* 2005;**62**:641–5.

Morris 2007
Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *American Journal of Clinical Nutrition* 2007;**85**:193–200.

NICE 2006a
NICE. Donepezil, galantamine, revastigmine and memantine for the treatment of Alzheimer's disease. www.nice.org/uk 2006.

Nygard 1997
Nygard O, Nordrehauge JE, Refsum H. Plasma homocysteine levels and mortality in patients with coronary artery disease. *New England Journal of Medicine* 1997;**337**: 230.

Ortega 1996
Ortega RM, Manas LR, Andres P, Gaspar MJ, Agudo FR, et al.Functional and psychic deterioration in elderly people may be aggravated by folate deficiency. *Journal of Nutrition* 1996;**126**:1992–9.

Perry 1995
Perrt IJ, Refsum H, Morris RW. Protictive study of serum total homocysteine concentaration and risk of stroke in middle aged British men. *The Lancet* 1995;**346**:1395.

Petrides 1982
Petrides M, Milner B. Deficts on subject ordered tasks after frontal and temporal lobe lesions in man. *Neuropsychologia* 1982;**20**:249–62.

Prince 1999
Prince M, MacDonald AM, Sham PC, Richards M, Quraishi S, Horn I. The development and validation of a telephone administered cognitive test battery (TACT). *The International Journal of Methods in Psychiatric Research* 1999; **8**:49–57.

Radloff 1977
Radloff LS. The CES-D scale a self report depression scale for research in the general population. *Applied Psychological Measurement* 1977;**1**(3):385–401.

Randt 1983
Randt CT, Brown ER. *Randt memory test administration manual.* Bayport, NY: Life Science Associates, 1983.

Ravaglia 2005
Ravaglia G, Forti P, Maioli F, et al.Homocysteine and folate as risk factors for dementia and Alzheimer disease. *American Journal of Clinical Nutrition* 2005;**82**:636–43.

Reisberg 1982
Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for the assessment of primary degenerative dementia. *American Journal of Psychiatry* 1982; **139**:1136–39.

Reitan 1974
Reitan RM, Davidson LA. *Clinical neuropsychology: Current status and applications*. New York: Hemisphere, 1974.

Reitan 1985
Reitan RM, Wolfson D. *The Halstead Reitan Neuropsychological Test Battery*. Tucson, AZ: Neuropsychology Press, 1985.

Reitan 1992
Reitan RM. *Trial making test : Manual for administration and scoring.* Tucson: Reitan Neuropsychological Laboratory, 1992.

Renvall 1989
Renvall MJ, Spindler AA, Ramsdell JW. Nutritional status of free living Alzheimer's patients. *American Journal of Medical Science* 1989;**298**:20–7.

Rey 1964
Rey A. Psychological clinical examination. *L'examen clinique en psychologie*. Paris, France: Presses Universitaires de France, 1964.

Reynolds 1976
Reynolds EH. Neurological aspects of folate and vitamin B12 metabolism. *Clinics in Haematology* 1976;**5**:661–96.

Rosen 1984
Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *American Journal of Psychiatry* 1984; **141**:1356–64.

Rosenberg 1985
Rosenberg IH, Zimmerman J, Selhub J. Folate transport. *Chemioterapia* 1985;**4**:354.

Schulz 1995
Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. *Journal of the American Medical Association* 1995;**273**:408–12.

Selhub 1993
Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *Journal of the American Medical Association* 1993;**270**(22):2693–8.

Senti 1985
Snti. Analysis of folate data from the second national health examination study (NHANESII). *Journal of Niutrition* 1985;**115**(11):1398–402.

Seshadri 2002
Seshadri S, Beiser A, Selhub J, Jacques P, Jacques PF, Rosenberg IH. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *The New Engalnd Journal of Medicine* 2002;**346**:476–83.

Shane 1985
Shane B, Stokstad ELB. Vitamin B12 folate interrelationships. *Annual Review of Nutrition* 1985;**5**: 115–41.

Small 1997
Small GW, Rabins PV, Barry PP. Diagnosis and treatment of Alzheimer disease and related disorders. *Journal of the American Medical Association* 1997;**278**:1363–71.

Smith 2002
Smith PG. *Clinical Pharmacology and Drug Therapy*. 3rd Edition. Oxford Textbook, 2002.

Smith 2008
Smith DA. The worldwide challenge of the dementias: a role for B vitamins and homocysteine?. *Food and Nutrition Bulletin* 2008;**29**(2):S143–72.

Sneath 1973
Sneath P, Chanarin I, Hodkinson HM, McPherson CK, Reynolds EH. Folate status in a geriatric population and its relation to dementia. *Age and Ageing* 1973;**2**:177–82.

Snowdon 2000
Snowdon DA, Tully CL, Smith CD, Riley KP, Markesbery WR. Serum folate and the severity of atrophy of the neocortex in Alzheimer disease finding from the nun study. *American Journal of Clinical Nutrition* 2000;**71**(4):993–8.

Spiegel 1991
Spiegel R, Brunner C, Ermini-Funfschilling D, et al.A new behavioural assessment scale for geriatric out and in patients the NOSGER (Nurses' Observation scale for geriatric patients). *Journal of The American Geriatrics Society* 1991; **39**(4):339–47.

Spreen 1998
Spreen O, Strauss E. *A compendium of neuropsychological test administration*. 2nd Edition. New York: Oxford University Press, 1998.

Stabler 1986
Stabler SP, Marcell PD, Podell ER. Assay of methylmalonic acid in the serum of patients with cobalamin deficiency using capillary gas chromatography mass spectrometry. *Journal of Clinical Investigation* 1986;**77**(5):1606–12.

Stabler 1988
Stabler SP, Marcell PD, Podell ER. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography mass spectrometry. *Journal of Clinical Investigation* 1988; **81**:466.

Stehouwer 1998
Stehouwer CDA, Weijenberg MP, Van den Berg M. Serum homocysteine and risk of coronary heart disease and cerebrovascular disease in elderly men a ten year follow up. *Arteriosclerosis Thrombosis and Vascular Biology* 1998;**18**: 1895–901.

Ueland 1993
Ueland PM, Refsum H, Stabler SP, Malinow MR, Anderson A, Allen RH. Total homocysteine in plasma or serum methods and clinical applications. *Clinical Chemistry* 1993; **39**:1764–79.

Van der Elst 2006 a
Van der Elst W, van Boxtel Mp, Van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants ages 24-81 years and the influence of age, sex, education and mood of presentation. *Journal of the International Neuropsychological Society* 2005;**11**:290–301.

Van der Elst 2006 b
Van der Elst W, Boxtel MP, Breukelen GJ, Jolles J. The concept shifting test: adult normative data. *Psychological Assessment* 2006;**18**:424–32.

Wahlin 1996
Wahlin A, Hill RD, Winblad B. Effects of serum vitamin B12 and folate status on episodic memeory performance in very old age a population based study. *Psychology and Aging* 1996;**11**:487–96.

Wang 2001
Wang HX, Wahlin A, Basun H, Fastbom J, Winblad B, Fratiglioni L. Vitamin B12 and folate in relation to the development of Alzheimer's disease. *Neurology* 2001;**56**(9): 1188–94.

Wechsler 1955
Wechsler D, Stone CP. *Wechsler Memory Scale manual*. New York: The Psychological Corporation, Harcourt, Brace and Jovanovich, 1955.

Wechsler 1997
Wechsler D. *Wechsler adult intelligence scale*. 3rd Edition. San Antonio, TX: The Psychological Corporation/Harcourt Brace, 1997.

Wecshler 1981
Wecshler D. *Wecshler Adult Intelligence Scale Revised*. New York: The psychological Corporation, 1981.

Welchsler 1982
Wechsler D. *Wechsler Adult Intelligence Scale-Revised manual*. New-York: The Psychological Corporation, Harcourt, Brace and Jovanovich, 1982.

Whitehead 1995
Whitehead AS, Gallagher PM, Mills JM, Kirke P, Burke H, Molloy AM, Weir DG, Shields DC, Scott JM. A genetic defect in 5,10 methylenetetrahydrofolate reductase in neural tube defects. *Quarterly Journal of Medicine* 1995;**88**:763–5.

References to other published versions of this review

Malouf 2003 b
Malouf R, Grimley Evans J, Areosa Sastre A. Folic acid with or without vitamin B12 for cognition and dementia. *Cochrane Database of Systematic Reviews* 2003, Issue 4.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bryan 2002

Methods	35 days, randomized, double-blind, placebo-controlled study
Participants	Country: Australia 221 women were enrolled 75 elderly participants aged 65-92 years 40 of the elderly group assigned randomly 19 to folic group and 21 to placebo group. Selection criteria: healthy women and English as a first language. Exclusion criteria: * Smoking *On hormone replacement therapy (HRT). * On medication that could affect mental performance.
Interventions	1- placebo 2- 750 microgram of folate /day
Outcomes	* Speed of processing: 1-Boxes test 2-Digit Symbol Coding 3-Symbol Search *Working Memory: 1-Digit Span Backwards 2-Letter Number Sequencing *Free Recall: 1-Immediate Recall 2-Delayed Recall 3-Recognition *Incidental Recall: 1-Digit Symbol 2-Symbol Position 3-Activity *Verbal ability
Notes	One participant dropped from the folic acid group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	randomized
Blinding? All outcomes	Yes	Identical capsules in colour and shape were administrated.

Clarke 2003

Methods	12 weeks 2x2x2 factorial design randomized, double-blind, placebo-controlled trial
Participants	Country: England 149 participants Aged 56-89 Inclusion criteria: 1-Clinical diagnosis of dementia using DSM IV and MMSE score between 12 and 26 or 2-MIC with TICS-M score below 27 Exclusion criteria: 1-Frontal lobe dementia, Huntington's disease, normal pressure hydrocephalus 2-Taken any of the study treatments.
Interventions	1-placebo 2-81 mg aspirin 3-2 mg folic acid 4-1 mg B12 5-500 mg vitamin E 6-200 mg vitamin C
Outcomes	1-MMSE 2-DSM IV 3-TICS-M 4-Homocysteine levels 5-Folate levels
Notes	seven participants dropped from the study

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Using a telephone randomization system.
Blinding? All outcomes	Yes	Identical blister packs for each participant for both placebo and treatment

Connelly 2008

Methods	6 months randomized, double-blind placebo-controlled trial
Participants	Country: Scotland 75 patients with AD Inclusion criteria: 1-Unable to perform significantly in the study protocol 2-Cerebrovascular comorbid condition 3-conditions that interacts with folate or B12 metabolism 4-Usage of ChI primarily for hallucination or delusion 5-Taking folic acid or B12

Connelly 2008 (*Continued*)

	6-AD based on NINCDS-ADRDA criteria 7-Were treated according to NICE 2001 8-Scoring 0 or 1 on MHI scale
Interventions	1-placebo 2-1 mg folic acid/day
Outcomes	1-MMSE 2-DSST 3-IADL 4-SB of NOSGER 5-HCy level
Notes	All patients were on ChI

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Allocation sequence generated by using a computer programme.
Blinding? All outcomes	Yes	Identical capsules were supplied.

Durga 2007

Methods	3-year randomized, double-blind, placebo controlled trial
Participants	Country: The Netherlands 818 elderly aged 50-70 years Exclusion criteria: 1-total plasma homocysteine < 13 mcm/l 2-homocysteine level > 26 mcm/l 3-serum B12 < 200pmol/l 3-renal or theroid disease 4-use of medications that interact with folic acid 5-intestinal disease 6-using vitamin B supplements
Interventions	1-placebo 2-800 mcg/day folic acid
Outcomes	1-word learning test 2-concept shifting test 3-stroop colour-word test 4-verbal fluency test 5-letter digit substitution test

Durga 2007 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Allocation to treatment or placebo using blocks of sizes of four and six
Blinding? All outcomes	Yes	capsules were indistinguishable in appearance.

Eussen 2006

Methods	6 months randomized double-blind trial
Participants	Country: The Netherlands 195 elderly were enrolled Inclusion criteria: 1-Free-living or in elderly homes 2- Age < 70 years Exclusion criteria: 1-Current use of B12 injection 2-current use of high-dose multivitamins 3-gastrointestinal surgery 4-suffering from stoma, anaemia, dementia, life-threatening disease, visual/hearing problems
Interventions	1-placebo 2-1000 mcg B12 3-1000 mcg B12 + 400 mcg folic acid
Outcomes	1-MMSE 2-CRD 3-GDS 4-tHcy 5-MMA
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Randomization was stratified according to MMA concentration at screening, age, sex, and MMSE score
Blinding? All outcomes	Yes	Double-blind. The capsules were identical in appearance, smell, and taste

Fioravanti 1997

Methods	60 days, randomized, double-blind, placebo-controlled study
Participants	Country: Italy 30 participants Aged 70-90 16 in the treatment group 14 in the placebo group Inclusion criteria: 1-Low folate level < 3 ng/ml 2-Very mild to moderate severity cognitive decline according to the (GDS) and MMSE score Exclusion criteria: 1-Gastrointestinal, endocrinal, cardiovascular, renal disorders 2-Depression 3-24<MMSE<16 4-Vitamin supplement 5-Alcohol consumption less than 55 g/d of alcohol
Interventions	1-placebo 2-15 mg/day of folic acid
Outcomes	1-Randt Memory Test (RMT) 2-Acquisition and recall 3-Delayed Recall 4-Memory Index 5-Encoding 6-Cognitive Efficiency 7-Attention Efficiency
Notes	One patient dropped from the placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	The randomization method was not stated.
Blinding? All outcomes	Yes	Double-blind.

Pathansali 2006

Methods	4-week randomized double-blind placebo controlled trial
Participants	Country: UK 24 healthy participants were enrolled Inclusion criteria: 1-age>65 years 2-no previous history of vascular disease, hypertension, diabetes or smoking 3-MMSE > 27

Pathansali 2006 (*Continued*)

	4-no folic acid or vitamin B12 deficiency 5-normal renal function 6-not on vitamin supplement or any medication that affects folic acid levels
Interventions	1-placebo 2-5 mg/day folic acid/day
Outcomes	1-CAT 2-FCRT 3-DSS 4-SMS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Allocation sequence was generated by using a computer program
Blinding? All outcomes	Yes	Double-blind.

Sommer 2003

Methods	Randomized controlled trial
Participants	11 patients with (AD, vascular and frontotemporal, and other dementia) Inclusion criteria: 1-Age 65 years and over 2-Demented based on DSM-III-R 3-Serum folates between 2 and 5 mcg/L, red blood cell folic acid levels between 127 and 452 mcg/L, and normal vitamin B12 levels (above 200 ng/L) Exclusion criteria: 1-Patients with seizure disorder 2-Patients with major depression or need for antidepressant medication 3-On oral multivitamins supplements refrained for at least 1 month prior to the study
Interventions	1-placebo 2-10 mg folic acid for10 weeks
Outcomes	1-Prorated Verbal IQ 2-Boston Naming Test 3-Controlled Oral Word Association Test 4-Logical Memory and Associate Learning subtests 5-Benton Visual Retention Test 6-Trail Making Test (Trails A and B)

Sommer 2003 (*Continued*)

	7-Finger Tapping Test
Notes	Folic acid group performed worse on the Learning associated Task

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Randomized method was not reported
Blinding? All outcomes	Yes	Double-blind

GDS: Global Deterioration Scale
MMSE: Mini Mental State Examination
RMT: Randt Memory Test
DSST: Digit Symbol Substitution Test
SB: Social behaviour
NOSGER: Nurses Observation Scale for Geriatric Patients
CDR: Clinical Dementia Rating
tHcy: total homocysteine
MMA: Methylmalonic acid
holo TC: holotranscobalamin
CAT: Continuous Attention Test
FCRT: Four-Choice Reaction Time
SMS: Scanning Memory Sets

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

Study	Reason for exclusion
Brouwer 2000	Younger age participants
Cockle 2000	Multivitamin intervention study
Jong 2001	Multivitamin intervention study
Lewerin 2005	Intervention confounded by cyanocobalamin and vitamin B6
McMahon 2006	Intervention confounded with vitamins B12 and B6
Passeri 1993	Not placebo-controlled
Ralph 1974	The intervention is the combination of vitamin B1, B6, B12 and vitamin C

(*Continued*)

Stott 2005	The intervention is fortified cereal with folic acid, vitamin B12, vitamin B6 and riboflavin
Tucker 2004	The intervention is fortified cereal with folic acid, vitamin B12 and vitamin B6

DATA AND ANALYSES

Comparison 1. Folic acid (1mg/day) vs placebo for cognitive impairment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mini Mental State Examination MMSE (changes from baseline at week 24)	1	41	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-1.96, 1.70]
2 DDST (changes from baseline at week 24)	1	41	Mean Difference (IV, Fixed, 95% CI)	0.26 [-4.12, 4.64]
3 IADL (changes from baseline at week 24)	1	41	Mean Difference (IV, Fixed, 95% CI)	2.67 [0.25, 5.09]
4 SB (changes from baseline at week 24)	1	41	Mean Difference (IV, Fixed, 95% CI)	1.38 [-1.13, 3.89]
5 IADL/SB (changes from baseline at week 24)	1	41	Mean Difference (IV, Fixed, 95% CI)	4.01 [0.50, 7.52]
6 Completers	1	49	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.91]
7 Treatment responders	1	49	Odds Ratio (M-H, Fixed, 95% CI)	4.06 [1.22, 13.53]

Comparison 2. Folic acid (10mg/day) vs placebo for cognitive impairment and dementia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Language: WAIS-R:Pro-rated Verbal IQ (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Boston Naming Test (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Controlled Oral Word Association Test (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 WMS:Logical Memory Subtest (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 WMS: Associated Learning Subtest (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Speed/Concentration:Trial A (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Speed/Concentration: Trial B (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

8 Fingger Tapping Test (changes from baseline at week 10)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3. Folic acid (15mg/day) vs placebo for cognitive impairment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Randt Memory Test - acquisition and recall (change from baseline at 9 weeks)	1	29	Mean Difference (IV, Fixed, 95% CI)	5.47 [-10.05, 20.99]
2 Randt Memory Test - delayed recall (change from baseline at 9 weeks)	1	29	Mean Difference (IV, Fixed, 95% CI)	7.38 [-8.58, 23.34]
3 Randt Memory Test - memory index (change from baseline at 9 weeks)	1	29	Mean Difference (IV, Fixed, 95% CI)	7.34 [-9.67, 24.35]
4 Randt Memory Test - encoding (change from baseline at 9 weeks)	1	29	Mean Difference (IV, Fixed, 95% CI)	0.67 [-1.89, 3.23]
5 Randt Memory Test - cognitive efficiency (change from baseline at 9 weeks)	1	29	Mean Difference (IV, Fixed, 95% CI)	0.57 [-1.97, 3.11]
6 Randt Memory Test - attention efficiency (change from baseline at 9 weeks)	1	29	Mean Difference (IV, Fixed, 95% CI)	1.05 [-0.17, 2.27]

Comparison 4. Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MMSE (change from baseline at 12 weeks)	1	138	Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.43, 1.21]
2 ADAS-Cog (change from baseline at 12 weeks)	1	133	Mean Difference (IV, Fixed, 95% CI)	0.41 [-1.25, 2.07]
3 BADL (change from baseline at 12 weeks)	1	134	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.95, 0.81]

Comparison 5. Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Constuction complex figure of Rey (change from baseline at week 24)	1	97	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-5.33, 4.33]
2 Attention digit span forward (change from baseline at week 24)	1	107	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
3 Sensomotor speed motor planning (change from baseline at week 24)	1	94	Mean Difference (IV, Fixed, 95% CI)	84.0 [-80.38, 248. 38]
4 Sensomotor speed, finger tapping (change from baseline at week 24)	1	94	Mean Difference (IV, Fixed, 95% CI)	3.0 [-119.50, 125. 50]
5 Sensomotor speed trial making test (change from baseline at week 24)	1	104	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-34.41, 16.41]
6 Memory 15 words learning, immediate recall (change from baseline at week 24)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.5 [-5.25, 6.25]
7 Memory, delayed recall (change from baseline at week 24)	1	105	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.42, 2.62]
8 Memory 15 learning word, recognition (change from baseline at week 24)	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.87, 1.07]
9 Memory, complex figure of Rey, immediate recall (change from baseline at week 24)	1	95	Mean Difference (IV, Fixed, 95% CI)	0.20 [-3.92, 4.32]
10 Memory, complex figure of Rey, delayed recall (change from baseline at week 24)	1	92	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-4.60, 3.60]
11 Memory, digit span backward (change from baseline at week 24)	1	107	Mean Difference (IV, Fixed, 95% CI)	-0.8 [-1.62, 0.02]
12 Executive function, motor planing (change from baseline at week 24)	1	92	Mean Difference (IV, Fixed, 95% CI)	35.0 [-247.33, 317. 33]
13 Excutive function, trial making test (change from baseline at week 24)	1	100	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.20, 1.20]
14 Excutive function, stroop test (change from baseline at week 24)	1	97	Mean Difference (IV, Fixed, 95% CI)	Not estimable
15 Excutive function , similarities (change from baseline at week 24)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.50 [-1.02, 2.02]

16 Excutive function, Raven (change from baseline at week 24)	1	103	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.55, 2.55]
17 Executive function, word fluency, animals, numbers of nouns (changes from baselien at week 24)	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.55, 2.35]
18 Executive function, word fluency, letters, numbers of nouns (changes from baselien at week 24)	1	105	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-5.91, 2.31]
19 Homocysteine (mcmo/L) (changes from baseline at week 12)	1	103	Mean Difference (IV, Fixed, 95% CI)	-4.5 [-7.05, -1.95]
20 Homocysteine (mcmol/L) (change from baseline at week 24)	1	105	Mean Difference (IV, Fixed, 95% CI)	-5.90 [-8.43, -3.37]

Comparison 6. Folic acid (800 mcg/day) vs placebo in healthy elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global cognitive function (changes from baseline to 3-year)	1	818	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.00, 0.10]
2 Memory (change from baseline to 3-year)	1	818	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.04, 0.24]
3 Sensorimotor speed (change from baseline at 3-year)	1	818	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.00, 0.12]
4 Complex speed (change from baseline at 3-year)	1	818	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.05, 0.13]
5 Information processing (change from baseline at 3-year)	1	818	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.02, 0.16]
6 Word fluency (change from baseline at 3-year)	1	818	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.19, 0.05]

Comparison 7. Folic acid (0.75 mg/day) vs placebo in healthy older women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognitive processing (change from baseline at 5 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Speed of processing - boxes	1	39	Mean Difference (IV, Fixed, 95% CI)	2.12 [-11.28, 15.52]

1.2 Speed of processing - digit symbol coding	1	39	Mean Difference (IV, Fixed, 95% CI)	2.19 [-7.40, 11.78]
1.3 Speed of processing - symbol search	1	39	Mean Difference (IV, Fixed, 95% CI)	1.59 [-1.55, 4.73]
1.4 Working memory - digit span backwards	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-2.66, 2.04]
1.5 Working memory - letter number sequencing	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.78, 1.78]
2 Memory (change from baseline at 5 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Immediate recall - RAVLT 1-5	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-6.87, 6.75]
2.2 Immediate recall - RAVLT B	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-2.05, 0.97]
2.3 Delayed recall - RAVLT 6	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-2.28, 2.14]
2.4 Delayed recall - RAVLT 7	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-2.85, 2.17]
2.5 Recognition - RAVLT A	1	39	Mean Difference (IV, Fixed, 95% CI)	1.42 [-0.24, 3.08]
2.6 Recognition - RAVLT B	1	39	Mean Difference (IV, Fixed, 95% CI)	1.59 [-1.35, 4.53]
3 Executive function (change from baseline at 5 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Stroop	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.44, 0.26]
3.2 Trail making test : Test A	1	39	Mean Difference (IV, Fixed, 95% CI)	2.29 [-11.40, 15.98]
3.3 Trail making test: Test B	1	39	Mean Difference (IV, Fixed, 95% CI)	-5.21 [-37.01, 26.59]
3.4 Verbal fluency - initial letter	1	39	Mean Difference (IV, Fixed, 95% CI)	-3.44 [-11.20, 4.32]
3.5 Verbal fluency - excluded letter	1	39	Mean Difference (IV, Fixed, 95% CI)	0.57 [-6.76, 7.90]
4 Verbal ability (change from baseline at 5 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Vocabulary	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-4.87, 4.61]
4.2 Spot the word	1	39	Mean Difference (IV, Fixed, 95% CI)	0.87 [-7.92, 9.66]
5 Mood Measures (change from baseline at 5 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 CESD - depression	1	39	Mean Difference (IV, Fixed, 95% CI)	-1.11 [-7.31, 5.09]
5.2 POMS: total	1	39	Mean Difference (IV, Fixed, 95% CI)	-3.14 [-23.56, 17.28]
5.3 POMS - Tension/anxiety	1	39	Mean Difference (IV, Fixed, 95% CI)	0.3 [-3.93, 4.53]
5.4 POMS - Depression/dejection	1	39	Mean Difference (IV, Fixed, 95% CI)	0.59 [-5.45, 6.63]
5.5 POMS - Anger/hostility	1	39	Mean Difference (IV, Fixed, 95% CI)	0.97 [-3.29, 5.23]
5.6 POMS - Vigour/activity	1	39	Mean Difference (IV, Fixed, 95% CI)	3.13 [-2.26, 8.52]
5.7 POMS - Fatigue/inertia	1	39	Mean Difference (IV, Fixed, 95% CI)	-1.83 [-5.85, 2.19]
5.8 POMS - Confusion/bewilderment	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-3.05, 2.95]

Comparison 8. Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Four-Choice Reaction Time (FCRT) fixed correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-16.29, 4.29]
2 Four-Choice Reaction Time (FCRT) fixed incorrect (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Four-Choice Reaction Time (FCRT) fixed reaction time (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.06, 0.12]
4 Four-Choice Reaction Time (FCRT) random correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	6.75 [-3.70, 17.20]
5 Four-Choice Reaction Time (FCRT) random incorrect (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.82, 0.32]
6 Four-Choice Reaction Time (FCRT) random reaction time (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.11, 0.07]
7 Four-Choice Reaction Time (FCRT) transform correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Four-Choice Reaction Time (FCRT) transform reaction time (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.15, 0.31]
9 Four-Choice Reaction Time (FCRT) transform incorrect (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 Continuous Attention Test (CAT) correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	1.94 [1.00, 4.88]
11 Countinous Attention Test (CAT) incorrect (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-1.55, 1.17]
12 Countinous Attention Test (CAT) error index (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.11, 0.03]

13 Digit-symbol substitution (DSS) correct (change from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.66 [-0.49, 1.81]
14 Digit-symbol substitution (DSS) reaction time correct (change from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.21 [0.01, 0.41]
15 Digit-symbol substitution (DSS) incorrect (change from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.81, 0.49]
16 Scanning Memory Sets (SMS) three digits correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-1.60, 0.44]
17 Scanning Memory Sets (SMS) three digits reaction time correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.05, 0.13]
18 Scanning Memory Sets (SMS) four digits correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-1.69, 1.67]
19 Scanning Memory Sets (SMS) four digits reaction time (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.14, 0.12]
20 Scanning Memory Sets (SMS) five digits correct (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.15 [-1.97, 2.27]
21 Scanning Memory Sets (SMS) five digits reaction time (changes from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable
22 Homocysteine level mcom/L (change from baseline at week 4)	1	24	Mean Difference (IV, Fixed, 95% CI)	-1.6 [-4.28, 1.08]

Comparison 9. Folic acid with or without vitamin B12 in healthy people

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Memory, immediate recall	2	145	Mean Difference (IV, Fixed, 95% CI)	0.27 [-4.14, 4.67]
2 Memory, delayed recall	2	145	Mean Difference (IV, Fixed, 95% CI)	0.23 [-1.34, 1.80]
3 Memory, word recognition	2	144	Mean Difference (IV, Fixed, 95% CI)	0.46 [-0.81, 1.73]
4 Verbal ability	3	963	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.18, 0.06]

Comparison 10. Folic acid with or without vitamin B12 for cognitive impairment and dementia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MMSE	2	179	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.45, 1.05]

Analysis 1.1. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 1 Mini Mental State Examination MMSE (changes from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

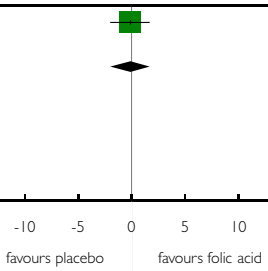
Outcome: 1 Mini Mental State Examination MMSE (changes from baseline at week 24)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Connelly 2008	23	0.09 (3.3)	18	0.22 (2.67)		100.0 %	-0.13 [-1.96, 1.70]
Total (95% CI)	**23**		**18**			**100.0 %**	**-0.13 [-1.96, 1.70]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 2 DDST (changes from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

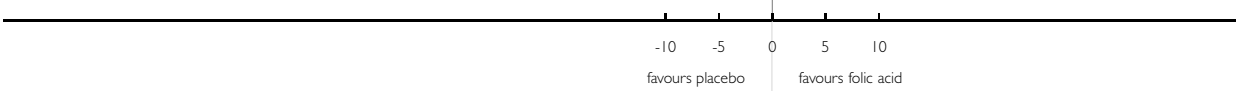
Outcome: 2 DDST (changes from baseline at week 24)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Connelly 2008	23	3.26 (7.89)	18	3 (6.42)		100.0 %	0.26 [-4.12, 4.64]
Total (95% CI)	**23**		**18**			**100.0 %**	**0.26 [-4.12, 4.64]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.12 (P = 0.91)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 3 IADL (changes from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

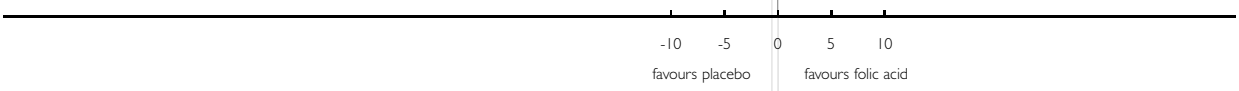
Outcome: 3 IADL (changes from baseline at week 24)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Connelly 2008	23	0.61 (3.6)	18	-2.06 (4.17)		100.0 %	2.67 [0.25, 5.09]
Total (95% CI)	**23**		**18**			**100.0 %**	**2.67 [0.25, 5.09]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.16 (P = 0.031)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 4 SB (changes from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

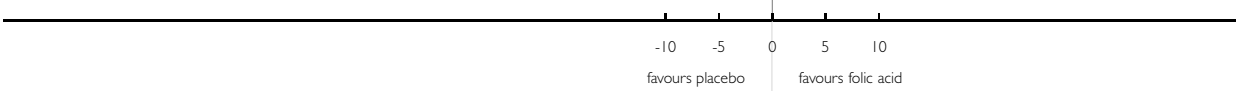
Outcome: 4 SB (changes from baseline at week 24)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Connelly 2008	23	0.82 (3.52)	18	-0.56 (4.46)		100.0 %	1.38 [-1.13, 3.89]
Total (95% CI)	**23**		**18**			**100.0 %**	**1.38 [-1.13, 3.89]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 5 IADL/SB (changes from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

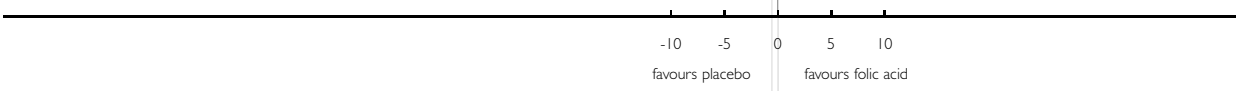
Outcome: 5 IADL/SB (changes from baseline at week 24)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Connelly 2008	23	1.4 (5.34)	18	-2.61 (5.94)		100.0 %	4.01 [0.50, 7.52]
Total (95% CI)	**23**		**18**			**100.0 %**	**4.01 [0.50, 7.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.24 (P = 0.025)

Test for subgroup differences: Not applicable



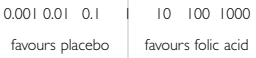
Analysis 1.6. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 6 Completers.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

Outcome: 6 Completers

Study or subgroup	folic acid n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Connelly 2008	23/28	21/21		100.0 %	0.10 [0.01, 1.91]
Total (95% CI)	**28**	**21**		**100.0 %**	**0.10 [0.01, 1.91]**
Total events: 23 (folic acid), 21 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					



Analysis 1.7. Comparison 1 Folic acid (1mg/day) vs placebo for cognitive impairment, Outcome 7 Treatment responders.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 1 Folic acid (1mg/day) vs placebo for cognitive impairment

Outcome: 7 Treatment responders

Study or subgroup	1mg/day folic acid n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Connelly 2008	20/28	8/21		100.0 %	4.06 [1.22, 13.53]
Total (95% CI)	**28**	**21**		**100.0 %**	**4.06 [1.22, 13.53]**
Total events: 20 (1mg/day folic acid), 8 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.28 (P = 0.022)					

Analysis 3.1. Comparison 3 Folic acid (15mg/day) vs placebo for cognitive impairment, Outcome 1 Randt Memory Test - acquisition and recall (change from baseline at 9 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 3 Folic acid (15mg/day) vs placebo for cognitive impairment

Outcome: 1 Randt Memory Test - acquisition and recall (change from baseline at 9 weeks)

Study or subgroup	Folic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fioravanti 1997	16	4.25 (17.39)	13	-1.22 (23.87)		100.0 %	5.47 [-10.05, 20.99]
Total (95% CI)	**16**		**13**			**100.0 %**	**5.47 [-10.05, 20.99]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Folic acid (15mg/day) vs placebo for cognitive impairment, Outcome 2 Randt Memory Test - delayed recall (change from baseline at 9 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 3 Folic acid (15mg/day) vs placebo for cognitive impairment

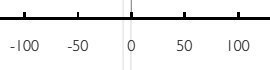
Outcome: 2 Randt Memory Test - delayed recall (change from baseline at 9 weeks)

Study or subgroup	Folic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fioravanti 1997	16	7.38 (17.83)	13	0 (24.56)		100.0 %	7.38 [-8.58, 23.34]
Total (95% CI)	**16**		**13**			**100.0 %**	**7.38 [-8.58, 23.34]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Folic acid (15mg/day) vs placebo for cognitive impairment, Outcome 3 Randt Memory Test - memory index (change from baseline at 9 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 3 Folic acid (15mg/day) vs placebo for cognitive impairment

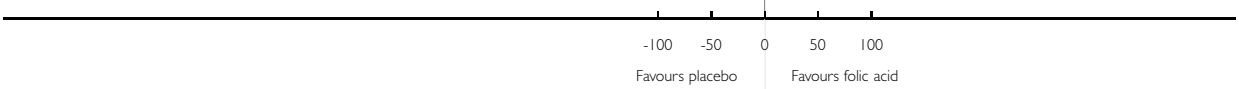
Outcome: 3 Randt Memory Test - memory index (change from baseline at 9 weeks)

Study or subgroup	Folic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fioravanti 1997	16	6.81 (18.53)	13	-0.53 (26.46)		100.0 %	7.34 [-9.67, 24.35]
Total (95% CI)	**16**		**13**			**100.0 %**	**7.34 [-9.67, 24.35]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.85 (P = 0.40)

Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3 Folic acid (15mg/day) vs placebo for cognitive impairment, Outcome 4 Randt Memory Test - encoding (change from baseline at 9 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 3 Folic acid (15mg/day) vs placebo for cognitive impairment

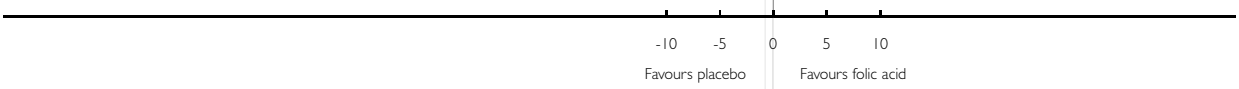
Outcome: 4 Randt Memory Test - encoding (change from baseline at 9 weeks)

Study or subgroup	Folic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fioravanti 1997	16	0.46 (2.72)	13	-0.21 (4.03)		100.0 %	0.67 [-1.89, 3.23]
Total (95% CI)	**16**		**13**			**100.0 %**	**0.67 [-1.89, 3.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3 Folic acid (15mg/day) vs placebo for cognitive impairment, Outcome 5 Randt Memory Test - cognitive efficiency (change from baseline at 9 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 3 Folic acid (15mg/day) vs placebo for cognitive impairment

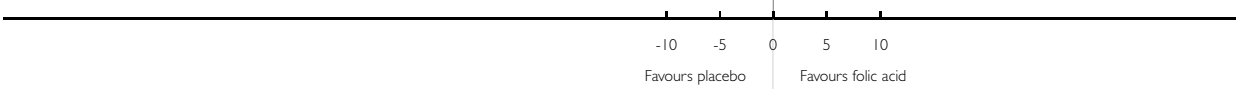
Outcome: 5 Randt Memory Test - cognitive efficiency (change from baseline at 9 weeks)

Study or subgroup	Folic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fioravanti 1997	16	0.63 (3.16)	13	0.06 (3.7)		100.0 %	0.57 [-1.97, 3.11]
Total (95% CI)	**16**		**13**			**100.0 %**	**0.57 [-1.97, 3.11]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3 Folic acid (15mg/day) vs placebo for cognitive impairment, Outcome 6 Randt Memory Test - attention efficiency (change from baseline at 9 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 3 Folic acid (15mg/day) vs placebo for cognitive impairment

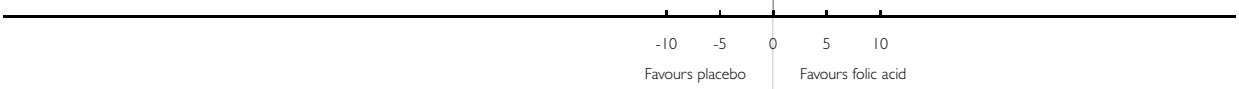
Outcome: 6 Randt Memory Test - attention efficiency (change from baseline at 9 weeks)

Study or subgroup	Folic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fioravanti 1997	16	1.12 (1.67)	13	0.07 (1.66)		100.0 %	1.05 [-0.17, 2.27]
Total (95% CI)	**16**		**13**			**100.0 %**	**1.05 [-0.17, 2.27]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.69 (P = 0.091)

Test for subgroup differences: Not applicable

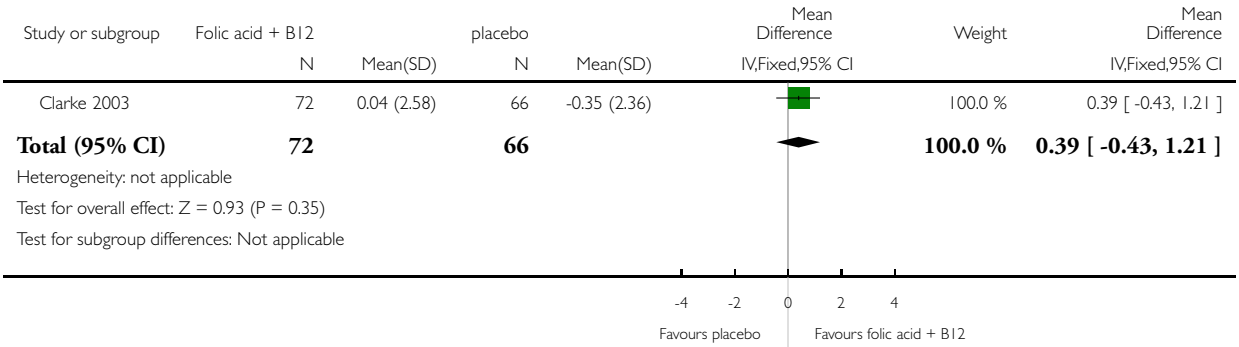


Analysis 4.1. Comparison 4 Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia, Outcome 1 MMSE (change from baseline at 12 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 4 Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia

Outcome: 1 MMSE (change from baseline at 12 weeks)

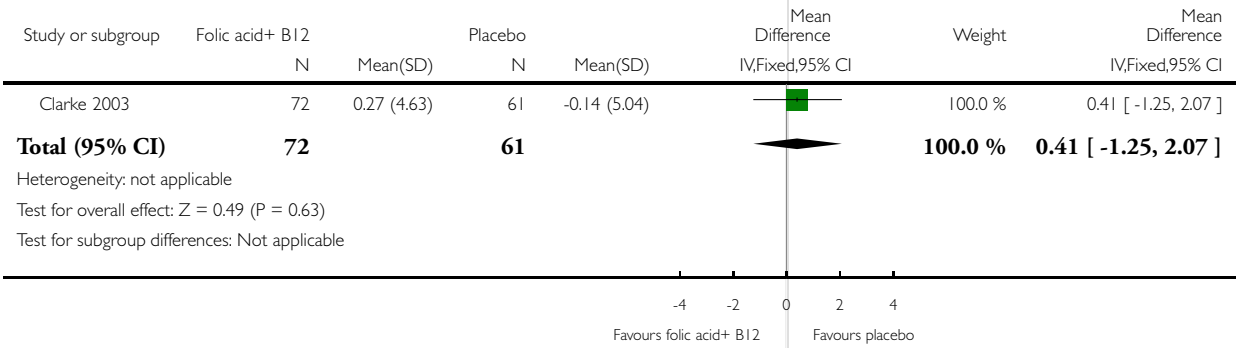


Analysis 4.2. Comparison 4 Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia, Outcome 2 ADAS-Cog (change from baseline at 12 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 4 Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia

Outcome: 2 ADAS-Cog (change from baseline at 12 weeks)

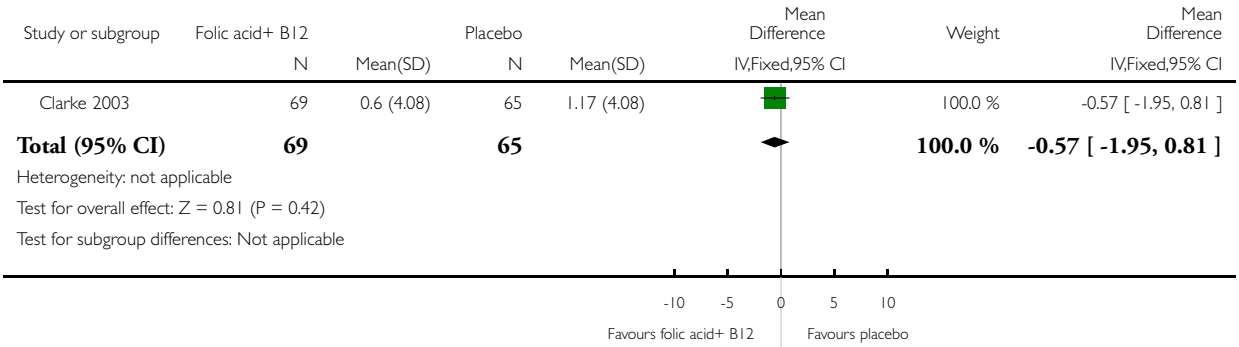


Analysis 4.3. Comparison 4 Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia, Outcome 3 BADL (change from baseline at 12 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 4 Folic acid (2 mg/day) + vitamin B12 (1mg/day) for mild cognitive impairment or dementia

Outcome: 3 BADL (change from baseline at 12 weeks)

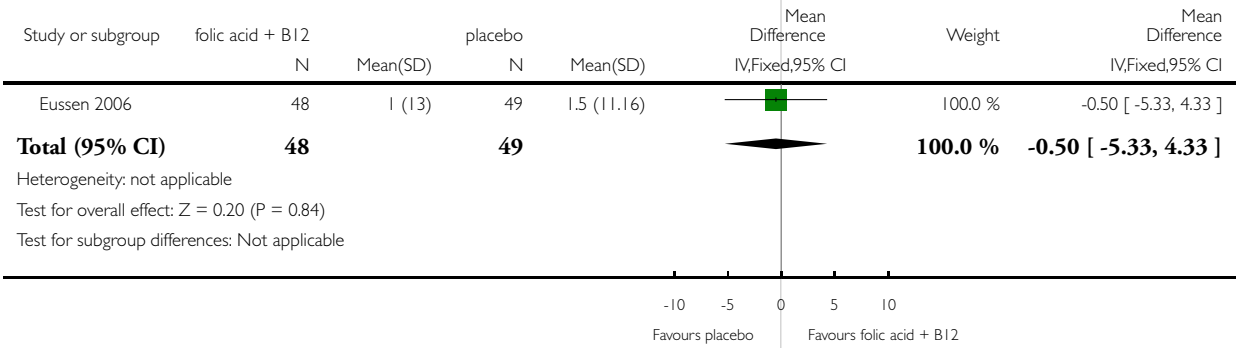


Analysis 5.1. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 1 Constuction complex figure of Rey (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 1 Constuction complex figure of Rey (change from baseline at week 24)



Analysis 5.2. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 2 Attention digit span forward (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 2 Attention digit span forward (change from baseline at week 24)

Study or subgroup	folic acid + B12 N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	51	-0.1 (2.26)	56	0.2 (2.33)		100.0 %	-0.30 [-1.17, 0.57]
Total (95% CI)	**51**		**56**			**100.0 %**	**-0.30 [-1.17, 0.57]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 3 Sensomotor speed motor planning (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

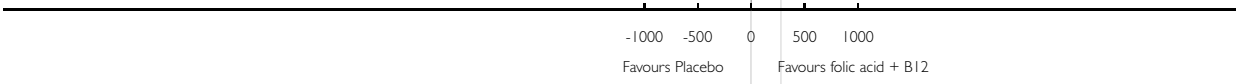
Outcome: 3 Sensomotor speed motor planning (change from baseline at week 24)

Study or subgroup	folic acid + B12 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	44	29 (375.9)	50	-55 (437.17)		100.0 %	84.00 [-80.38, 248.38]
Total (95% CI)	**44**		**50**			**100.0 %**	**84.00 [-80.38, 248.38]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.00 (P = 0.32)

Test for subgroup differences: Not applicable

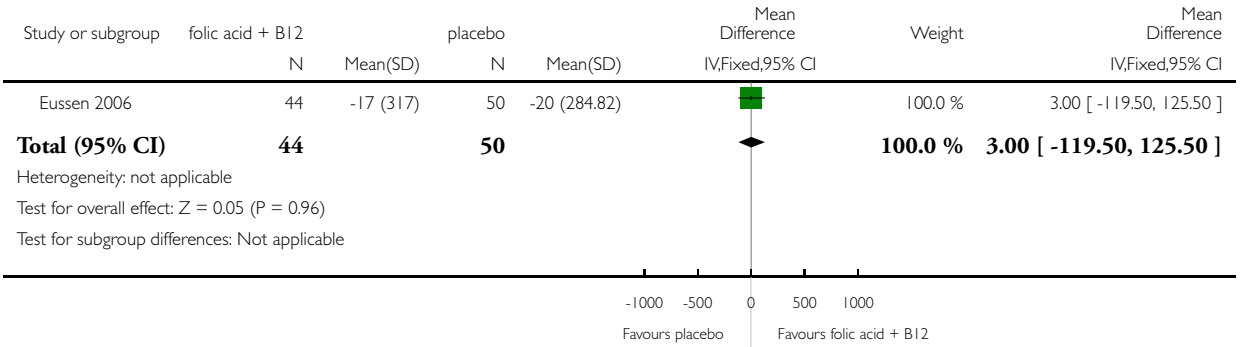


Analysis 5.4. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 4 Sensomotor speed, finger tapping (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 4 Sensomotor speed, finger tapping (change from baseline at week 24)

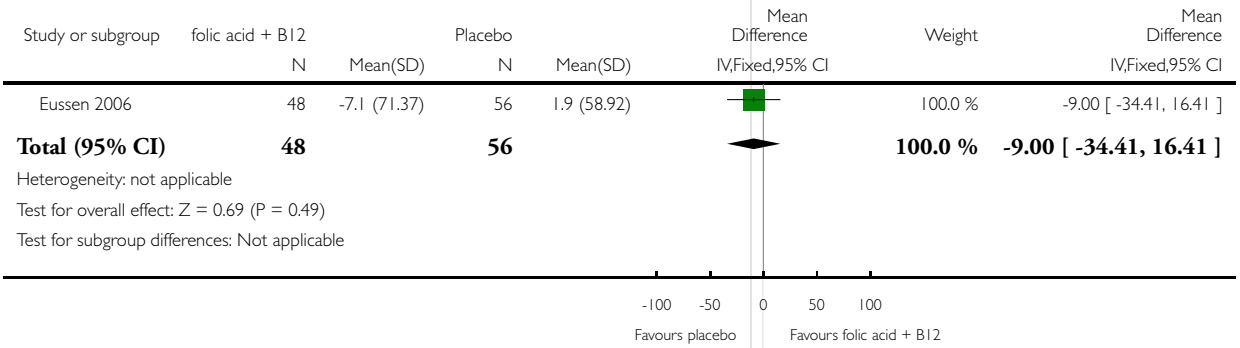


Analysis 5.5. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 5 Sensomotor speed trial making test (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 5 Sensomotor speed trial making test (change from baseline at week 24)



Analysis 5.6. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 6 Memory 15 words learning, immediate recall (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 6 Memory 15 words learning, immediate recall (change from baseline at week 24)

Study or subgroup	folic acid +B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	50	6.2 (15)	56	5.7 (15.14)		100.0 %	0.50 [-5.25, 6.25]
Total (95% CI)	**50**		**56**			**100.0 %**	**0.50 [-5.25, 6.25]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Not applicable

Analysis 5.7. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 7 Memory, delayed recall (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 7 Memory, delayed recall (change from baseline at week 24)

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	50	1.6 (5.6)	55	1 (4.9)		100.0 %	0.60 [-1.42, 2.62]
Total (95% CI)	**50**		**55**			**100.0 %**	**0.60 [-1.42, 2.62]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable

Analysis 5.8. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 8 Memory 15 learning word, recognition (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 8 Memory 15 learning word, recognition (change from baseline at week 24)

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	50	0.8 (4.6)	55	1.7 (5.68)		100.0 %	-0.90 [-2.87, 1.07]
Total (95% CI)	**50**		**55**			**100.0 %**	**-0.90 [-2.87, 1.07]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable

Analysis 5.9. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 9 Memory, complex figure of Rey, immediate recall (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 9 Memory, complex figure of Rey, immediate recall (change from baseline at week 24)

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	43	3.2 (10.32)	52	3 (10.04)		100.0 %	0.20 [-3.92, 4.32]
Total (95% CI)	**43**		**52**			**100.0 %**	**0.20 [-3.92, 4.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

Analysis 5.10. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 10 Memory, complex figure of Rey, delayed recall (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 10 Memory, complex figure of Rey, delayed recall (change from baseline at week 24)

Study or subgroup	folica acid + B12 N	Mean(SD)	placebol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	43	1.9 (10.33)	49	2.4 (9.64)		100.0 %	-0.50 [-4.60, 3.60]
Total (95% CI)	**43**		**49**			**100.0 %**	**-0.50 [-4.60, 3.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable

Analysis 5.11. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 11 Memory, digit span backward (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

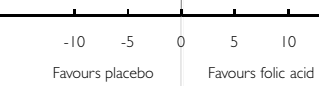
Outcome: 11 Memory, digit span backward (change from baseline at week 24)

Study or subgroup	folic acid + B12 N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	51	-0.2 (1.83)	56	0.6 (2.47)		100.0 %	-0.80 [-1.62, 0.02]
Total (95% CI)	**51**		**56**			**100.0 %**	**-0.80 [-1.62, 0.02]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.91 (P = 0.056)

Test for subgroup differences: Not applicable

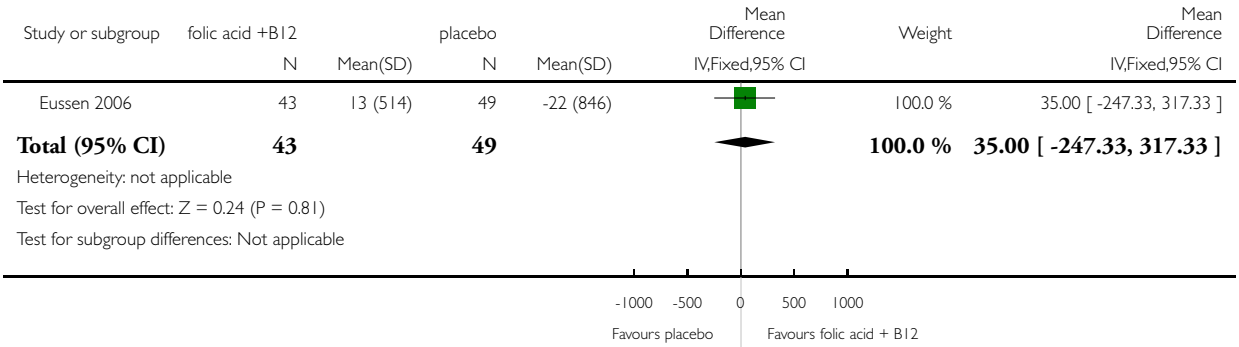


Analysis 5.12. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 12 Executive function, motor planing (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 12 Executive function, motor planing (change from baseline at week 24)

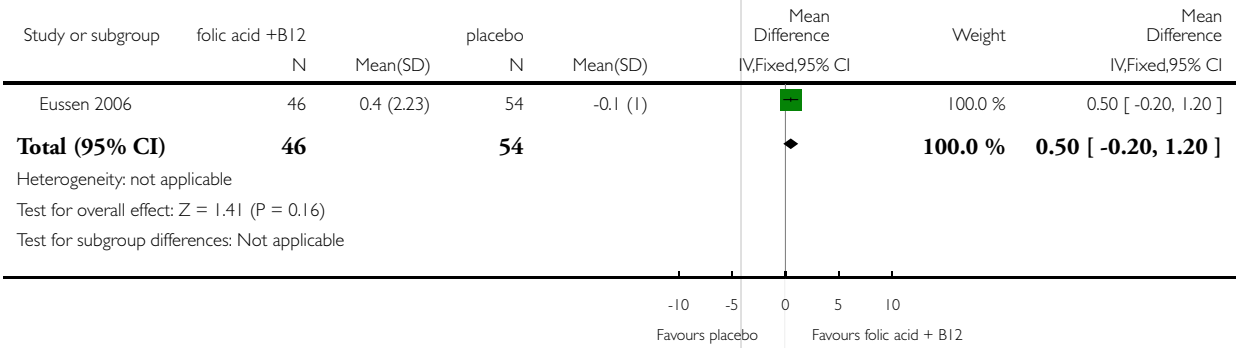


Analysis 5.13. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 13 Excutive function, trial making test (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 13 Excutive function, trial making test (change from baseline at week 24)



Analysis 5.14. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 14 Excutive function, stroop test (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

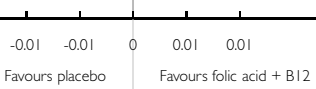
Outcome: 14 Excutive function, stroop test (change from baseline at week 24)

Study or subgroup	folic acid + B12 N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	43	0 (0)	54	0.7 (1.16)			Not estimable
Total (95% CI)	**43**		**54**				**Not estimable**

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



Analysis 5.15. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 15 Excutive function , similarities (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

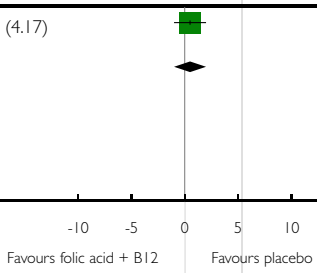
Outcome: 15 Excutive function , similarities (change from baseline at week 24)

Study or subgroup	folic acid + B12 N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	50	1.1 (3.82)	56	0.6 (4.17)		100.0 %	0.50 [-1.02, 2.02]
Total (95% CI)	**50**		**56**			**100.0 %**	**0.50 [-1.02, 2.02]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable



Analysis 5.16. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 16 Excutive function, Raven (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

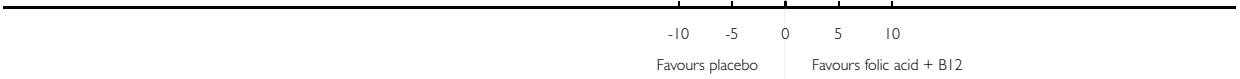
Outcome: 16 Excutive function, Raven (change from baseline at week 24)

Study or subgroup	folic acid+ B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	47	1.5 (4.96)	56	1 (5.65)		100.0 %	0.50 [-1.55, 2.55]
Total (95% CI)	**47**		**56**			**100.0 %**	**0.50 [-1.55, 2.55]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 5.17. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 17 Executive function, word fluency, animals, numbers of nouns (changes from baselien at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 17 Executive function, word fluency, animals, numbers of nouns (changes from baselien at week 24)

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	50	0.3 (7.63)	56	0.9 (7.85)		100.0 %	-0.60 [-3.55, 2.35]
Total (95% CI)	**50**		**56**			**100.0 %**	**-0.60 [-3.55, 2.35]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

Analysis 5.18. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 18 Executive function, word fluency, letters, numbers of nouns (changes from baselien at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 18 Executive function, word fluency, letters, numbers of nouns (changes from baselien at week 24)

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	50	0.5 (10.2)	55	2.3 (11.3)		100.0 %	-1.80 [-5.91, 2.31]
Total (95% CI)	**50**		**55**			**100.0 %**	**-1.80 [-5.91, 2.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable

Analysis 5.19. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 19 Homocysteine (mcmo/L) (changes from baseline at week 12).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 19 Homocysteine (mcmo/L) (changes from baseline at week 12)

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Eussen 2006	49	-4.8 (5.16)	54	-0.3 (7.9)		100.0 %	-4.50 [-7.05, -1.95]
Total (95% CI)	**49**		**54**			**100.0 %**	**-4.50 [-7.05, -1.95]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.45 (P = 0.00056)

Test for subgroup differences: Not applicable

Analysis 5.20. Comparison 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency, Outcome 20 Homocysteine (mcmol/L) (change from baseline at week 24).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 5 Folic acid(400 mcg/day) + vitamin B12 (1000 mcg/day) in healthy elderly with mild B12 deficiency

Outcome: 20 Homocysteine (mcmol/L) (change from baseline at week 24)

Study or subgroup	folic acid + B12 N	Mean(SD)	placebol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Eussen 2006	51	-5.6 (3.46)	54	0.3 (8.8)		100.0 %	-5.90 [-8.43, -3.37]
Total (95% CI)	**51**		**54**			**100.0 %**	**-5.90 [-8.43, -3.37]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.57 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 6.1. Comparison 6 Folic acid (800 mcg/day) vs placebo in healthy elderly, Outcome 1 Global cognitive function (changes from baseline to 3-year).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 6 Folic acid (800 mcg/day) vs placebo in healthy elderly

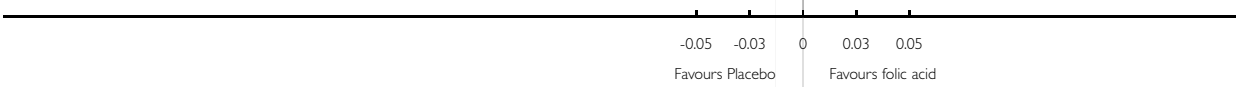
Outcome: 1 Global cognitive function (changes from baseline to 3-year)

Study or subgroup	800 mcg/d folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Durga 2007	405	0.067 (0.338)	413	0.02 (0.33)		100.0 %	0.05 [0.00, 0.10]
Total (95% CI)	**405**		**413**			**100.0 %**	**0.05 [0.00, 0.10]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.14 (P = 0.032)

Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6 Folic acid (800 mcg/day) vs placebo in healthy elderly, Outcome 2 Memory (change from baseline to 3-year).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 6 Folic acid (800 mcg/day) vs placebo in healthy elderly

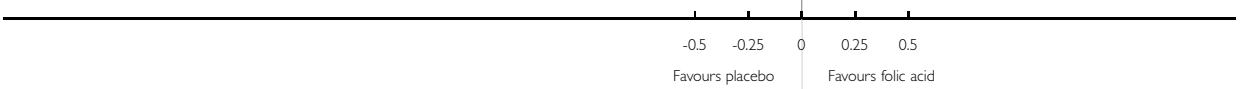
Outcome: 2 Memory (change from baseline to 3-year)

Study or subgroup	800 mcg/d folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Durga 2007	405	0.48 (0.72)	413	0.34 (0.73)		100.0 %	0.14 [0.04, 0.24]
Total (95% CI)	**405**		**413**			**100.0 %**	**0.14 [0.04, 0.24]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.76 (P = 0.0058)

Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6 Folic acid (800 mcg/day) vs placebo in healthy elderly, Outcome 3 Sensorimotor speed (change from baseline at 3-year).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 6 Folic acid (800 mcg/day) vs placebo in healthy elderly

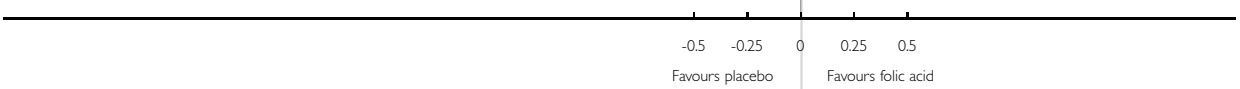
Outcome: 3 Sensorimotor speed (change from baseline at 3-year)

Study or subgroup	800 mcg/d folc acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Durga 2007	405	-0.04 (0.45)	413	-0.1 (0.49)		100.0 %	0.06 [0.00, 0.12]
Total (95% CI)	**405**		**413**			**100.0 %**	**0.06 [0.00, 0.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.82 (P = 0.068)

Test for subgroup differences: Not applicable

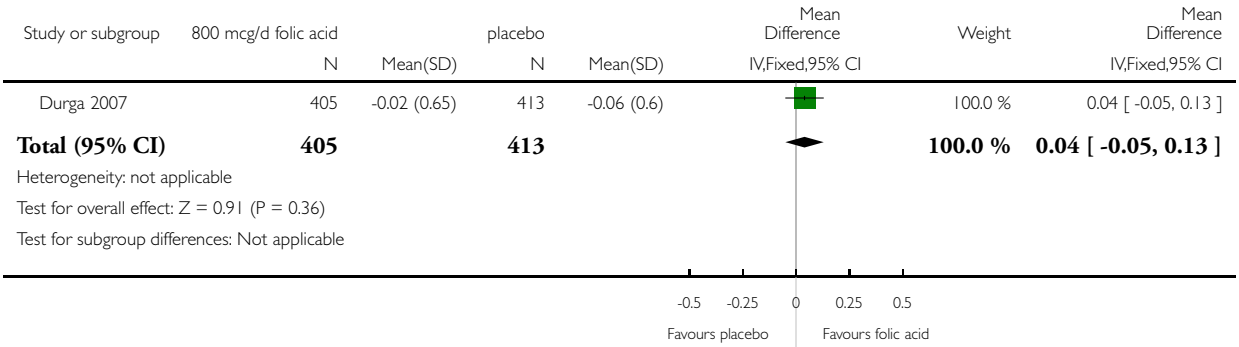


Analysis 6.4. Comparison 6 Folic acid (800 mcg/day) vs placebo in healthy elderly, Outcome 4 Complex speed (change from baseline at 3-year).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 6 Folic acid (800 mcg/day) vs placebo in healthy elderly

Outcome: 4 Complex speed (change from baseline at 3-year)

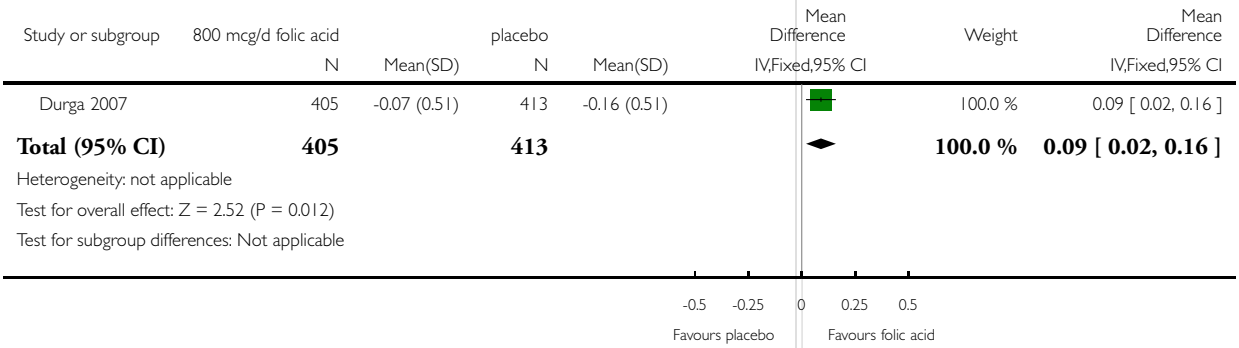


Analysis 6.5. Comparison 6 Folic acid (800 mcg/day) vs placebo in healthy elderly, Outcome 5 Information processing (change from baseline at 3-year).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 6 Folic acid (800 mcg/day) vs placebo in healthy elderly

Outcome: 5 Information processing (change from baseline at 3-year)



Analysis 6.6. Comparison 6 Folic acid (800 mcg/day) vs placebo in healthy elderly, Outcome 6 Word fluency (change from baseline at 3-year).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 6 Folic acid (800 mcg/day) vs placebo in healthy elderly

Outcome: 6 Word fluency (change from baseline at 3-year)

Study or subgroup	800mcg/d folic cid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Durga 2007	405	-0.002 (0.864)	413	0.07 (0.86)		100.0 %	-0.07 [-0.19, 0.05]
Total (95% CI)	**405**		**413**			**100.0 %**	**-0.07 [-0.19, 0.05]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.16 (P = 0.25)

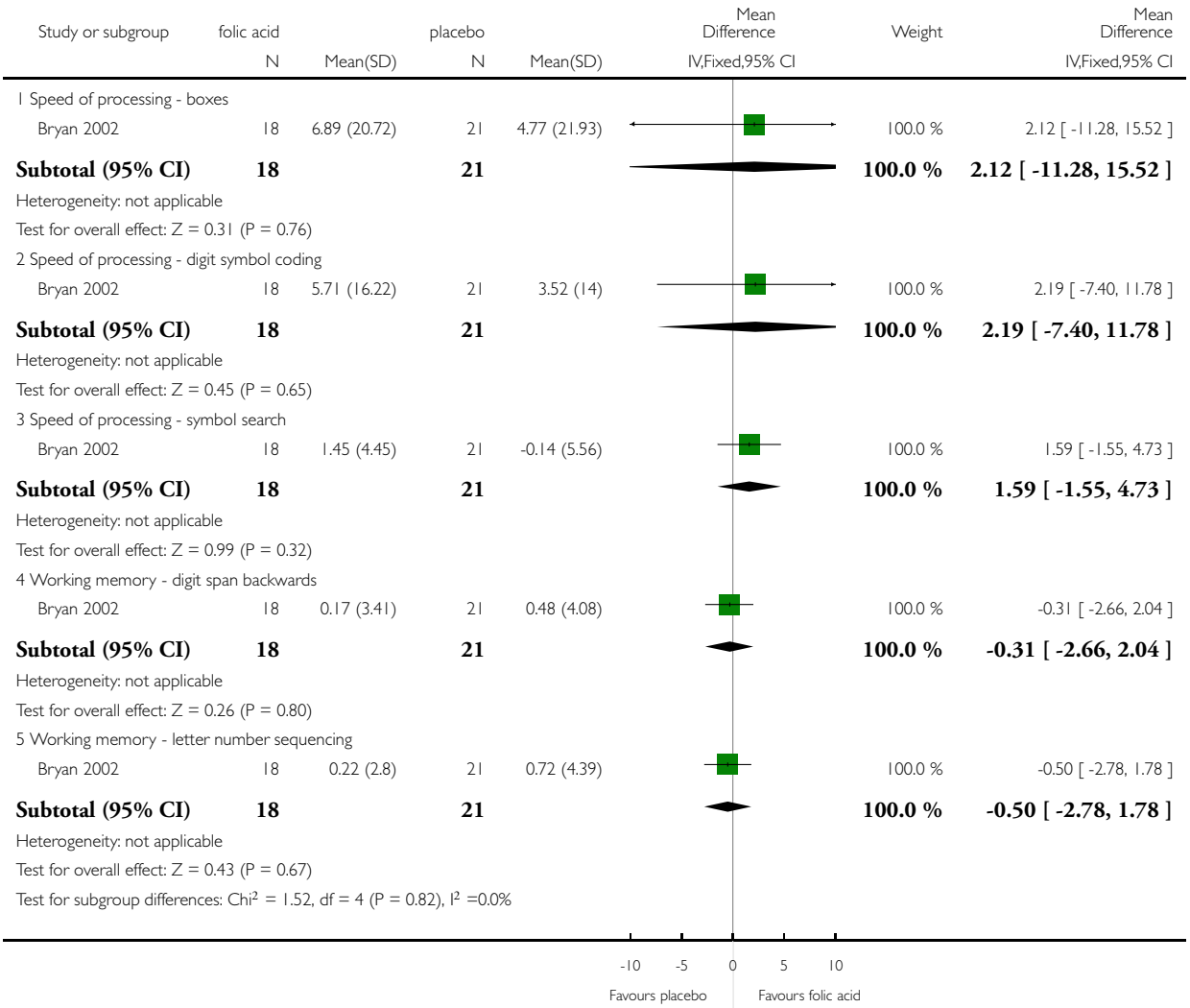
Test for subgroup differences: Not applicable

Analysis 7.1. Comparison 7 Folic acid (0.75 mg/day) vs placebo in healthy older women, Outcome 1 Cognitive processing (change from baseline at 5 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 7 Folic acid (0.75 mg/day) vs placebo in healthy older women

Outcome: 1 Cognitive processing (change from baseline at 5 weeks)

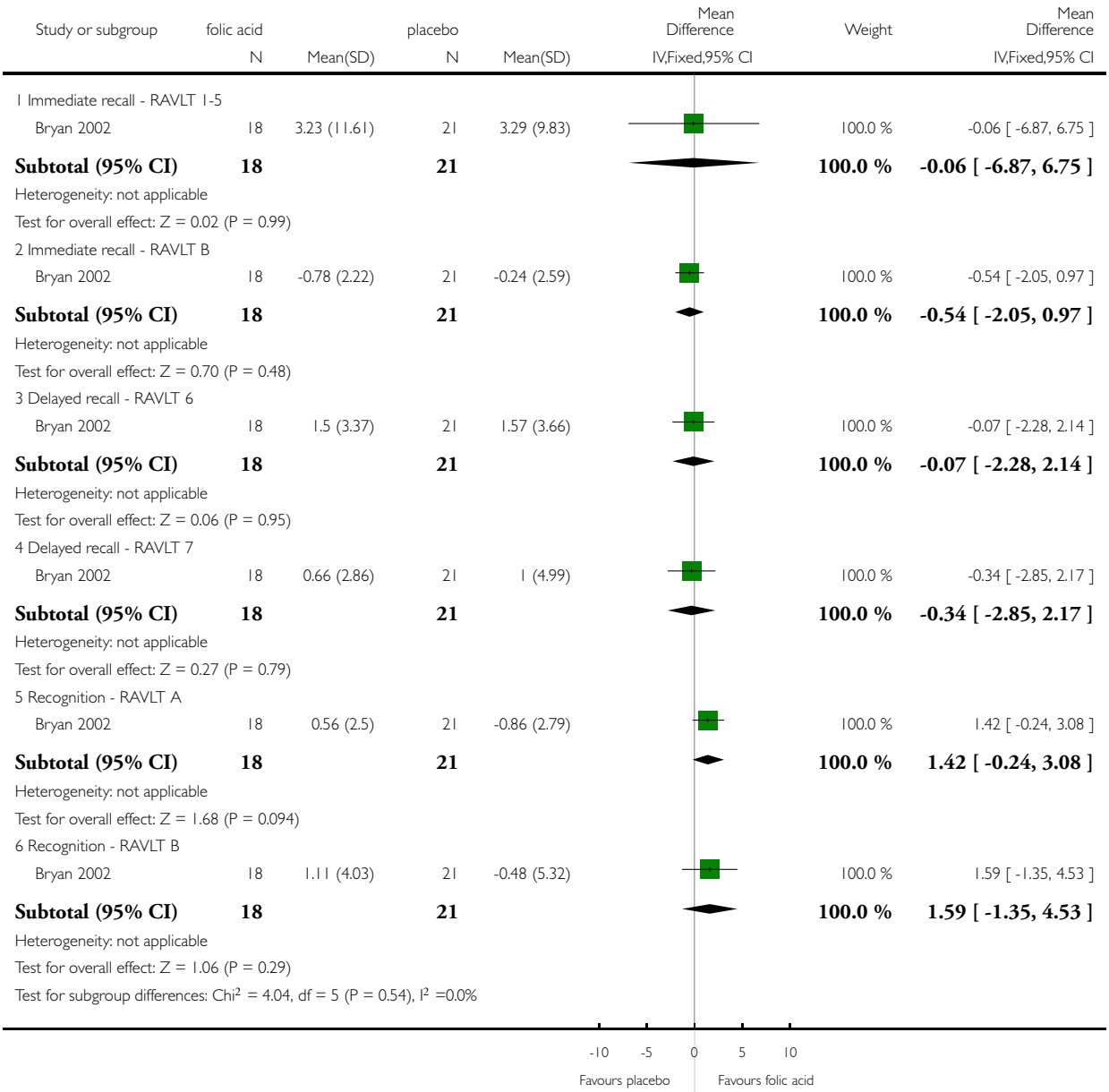


Analysis 7.2. Comparison 7 Folic acid (0.75 mg/day) vs placebo in healthy older women, Outcome 2 Memory (change from baseline at 5 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 7 Folic acid (0.75 mg/day) vs placebo in healthy older women

Outcome: 2 Memory (change from baseline at 5 weeks)

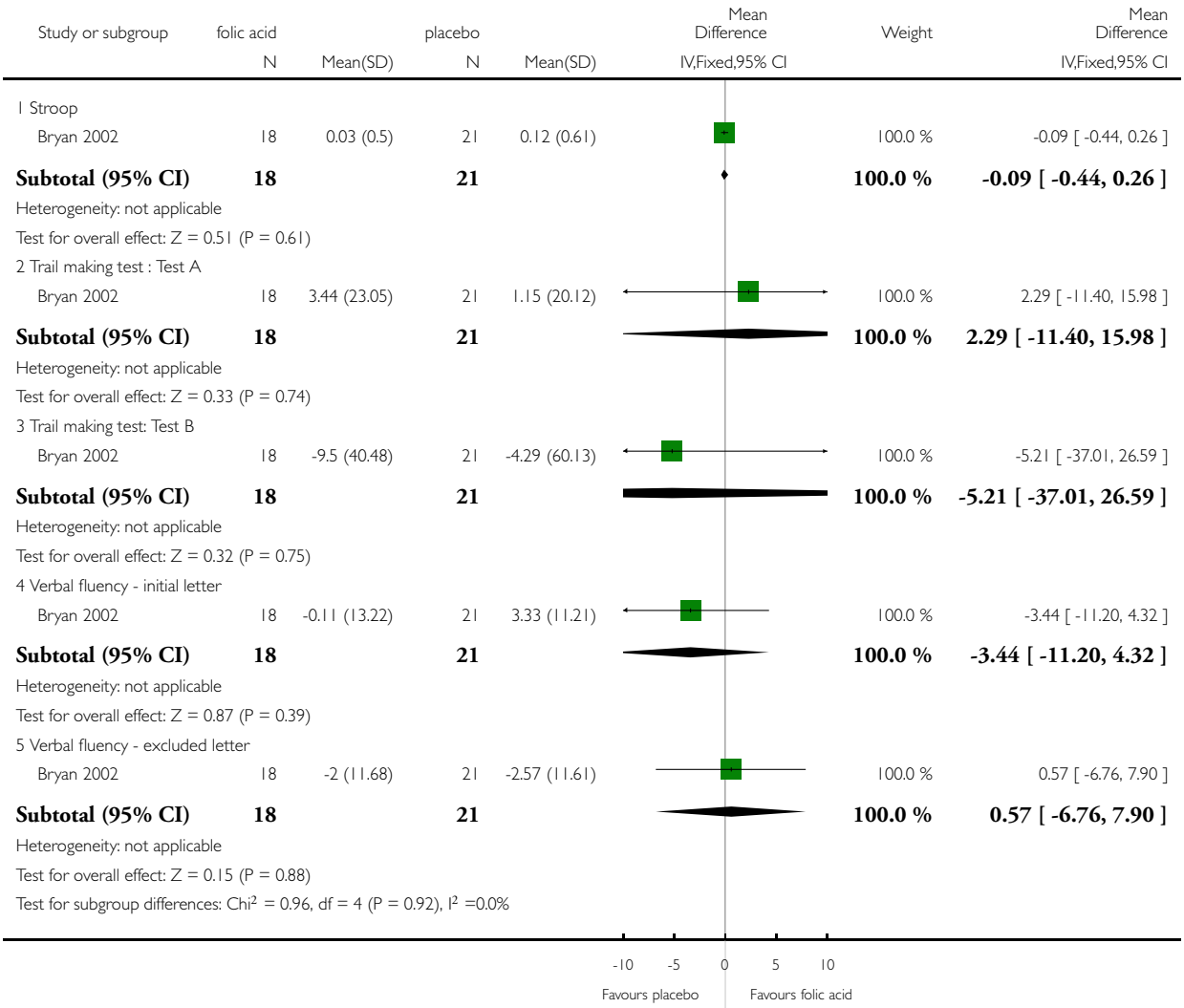


Analysis 7.3. Comparison 7 Folic acid (0.75 mg/day) vs placebo in healthy older women, Outcome 3 Executive function (change from baseline at 5 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 7 Folic acid (0.75 mg/day) vs placebo in healthy older women

Outcome: 3 Executive function (change from baseline at 5 weeks)



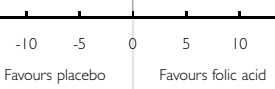
Analysis 7.4. Comparison 7 Folic acid (0.75 mg/day) vs placebo in healthy older women, Outcome 4 Verbal ability (change from baseline at 5 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 7 Folic acid (0.75 mg/day) vs placebo in healthy older women

Outcome: 4 Verbal ability (change from baseline at 5 weeks)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Vocabulary							
Bryan 2002	18	-0.28 (7.56)	21	-0.15 (7.48)		100.0 %	-0.13 [-4.87, 4.61]
Subtotal (95% CI)	**18**		**21**			**100.0 %**	**-0.13 [-4.87, 4.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.05 (P = 0.96)							
2 Spot the word							
Bryan 2002	18	1.44 (14.95)	21	0.57 (12.7)		100.0 %	0.87 [-7.92, 9.66]
Subtotal (95% CI)	**18**		**21**			**100.0 %**	**0.87 [-7.92, 9.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.19 (P = 0.85)							
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 =0.0%							

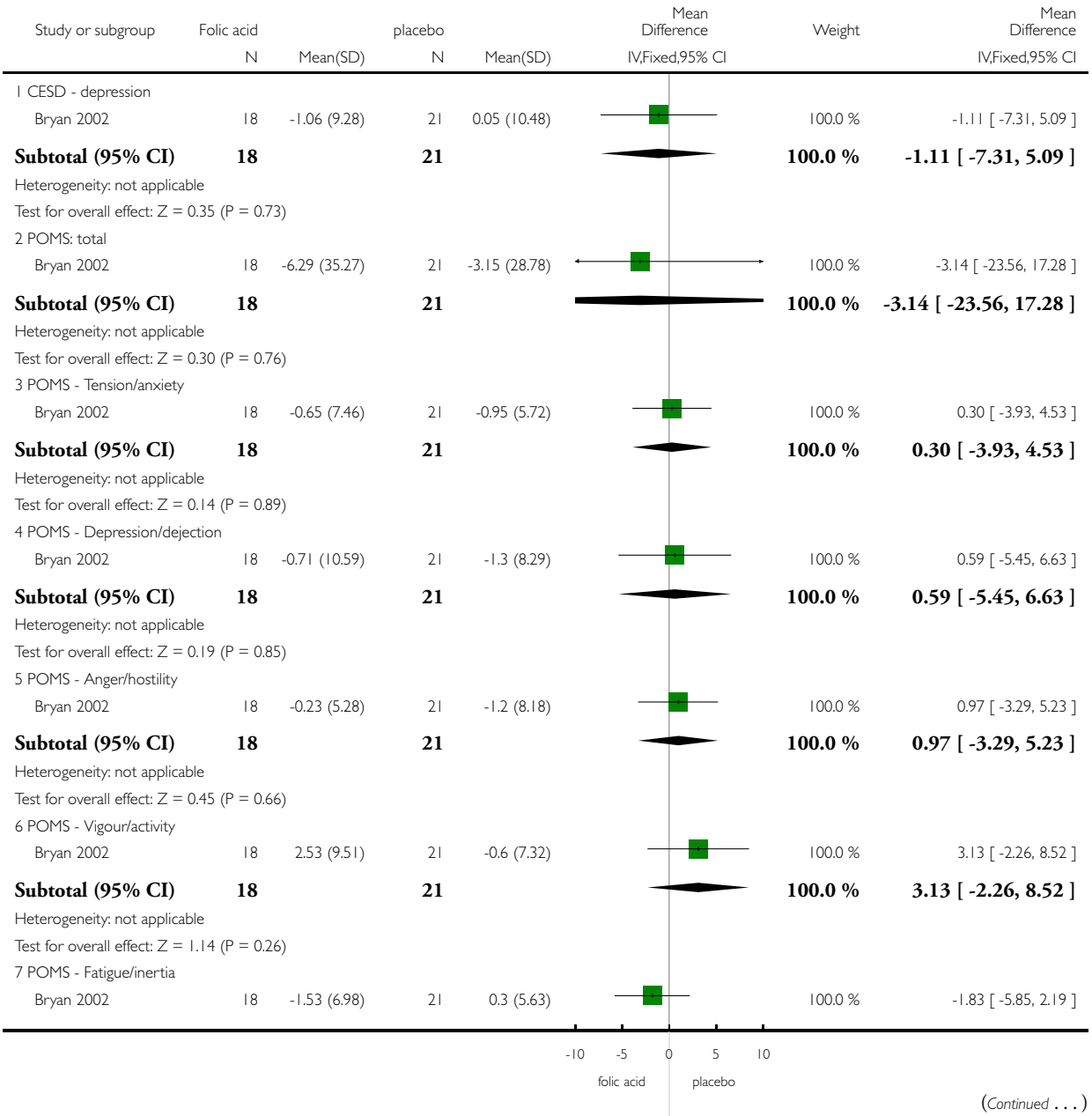


Analysis 7.5. Comparison 7 Folic acid (0.75 mg/day) vs placebo in healthy older women, Outcome 5 Mood Measures (change from baseline at 5 weeks).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 7 Folic acid (0.75 mg/day) vs placebo in healthy older women

Outcome: 5 Mood Measures (change from baseline at 5 weeks)



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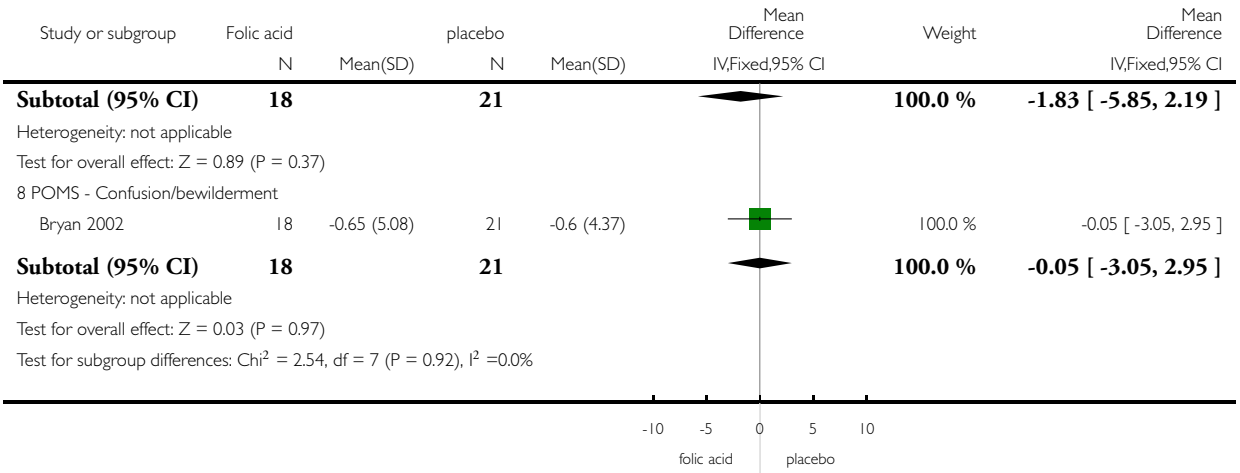
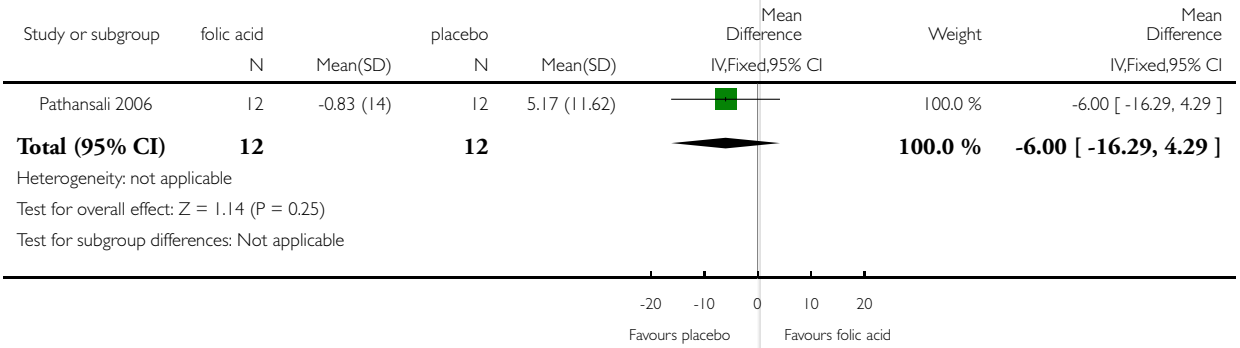


Analysis 8.1. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 1 Four-Choice Reaction Time (FCRT) fixed correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 1 Four-Choice Reaction Time (FCRT) fixed correct (changes from baseline at week 4)



Analysis 8.2. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 2 Four-Choice Reaction Time (FCRT) fixed incorrect (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 2 Four-Choice Reaction Time (FCRT) fixed incorrect (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.17 (0.39)	12	0.17 (0.39)		100.0 %	0.0 [-0.31, 0.31]
Total (95% CI)	**12**		**12**			**100.0 %**	**0.0 [-0.31, 0.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

Analysis 8.3. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 3 Four-Choice Reaction Time (FCRT) fixed reaction time (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

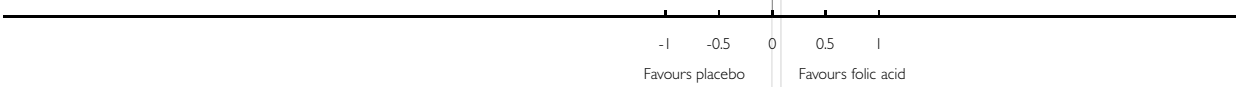
Outcome: 3 Four-Choice Reaction Time (FCRT) fixed reaction time (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0 (0.05)	12	-0.03 (0.15)		100.0 %	0.03 [-0.06, 0.12]
Total (95% CI)	**12**		**12**			**100.0 %**	**0.03 [-0.06, 0.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 4 Four-Choice Reaction Time (FCRT) random correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

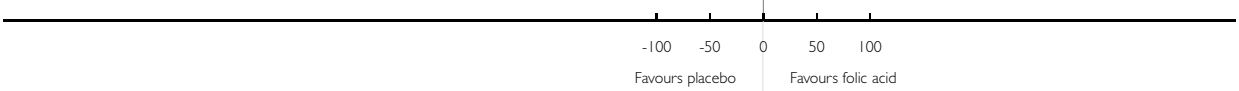
Outcome: 4 Four-Choice Reaction Time (FCRT) random correct (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	1.17 (14.6)	12	-5.58 (11.3)		100.0 %	6.75 [-3.70, 17.20]
Total (95% CI)	**12**		**12**			**100.0 %**	**6.75 [-3.70, 17.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.27 (P = 0.21)

Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 5 Four-Choice Reaction Time (FCRT) random incorrect (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

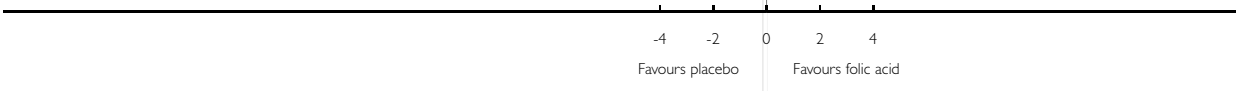
Outcome: 5 Four-Choice Reaction Time (FCRT) random incorrect (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	-0.5 (0.8)	12	0.25 (1.71)		100.0 %	-0.75 [-1.82, 0.32]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.75 [-1.82, 0.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.38 (P = 0.17)

Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 6 Four-Choice Reaction Time (FCRT) random reaction time (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

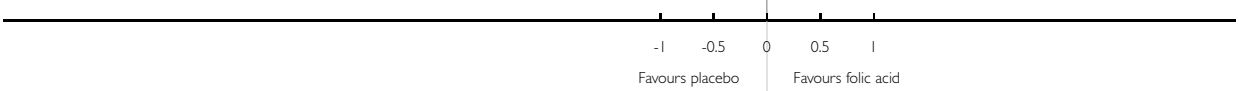
Outcome: 6 Four-Choice Reaction Time (FCRT) random reaction time (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	-0.002 (0.05)	12	0.02 (0.15)		100.0 %	-0.02 [-0.11, 0.07]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.02 [-0.11, 0.07]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 8.7. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 7 Four-Choice Reaction Time (FCRT) transform correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

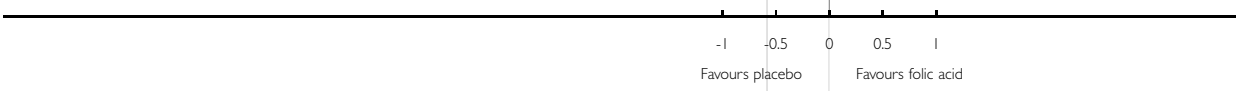
Outcome: 7 Four-Choice Reaction Time (FCRT) transform correct (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.08 (0.28)	12	0 (0)			Not estimable
Total (95% CI)	**12**		**12**				**Not estimable**

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



Analysis 8.8. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 8 Four-Choice Reaction Time (FCRT) transform reaction time (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 8 Four-Choice Reaction Time (FCRT) transform reaction time (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.06 (0.25)	12	-0.02 (0.31)		100.0 %	0.08 [-0.15, 0.31]
Total (95% CI)	**12**		**12**			**100.0 %**	**0.08 [-0.15, 0.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.70 (P = 0.49)

Test for subgroup differences: Not applicable

Analysis 8.9. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 9 Four-Choice Reaction Time (FCRT) transform incorrect (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

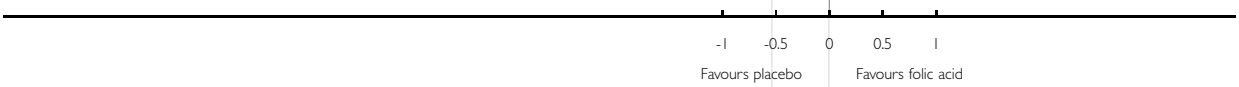
Outcome: 9 Four-Choice Reaction Time (FCRT) transform incorrect (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	-0.8 (0.29)	12	0 (0)			Not estimable
Total (95% CI)	**12**		**12**				**Not estimable**

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



Analysis 8.10. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 10 Continuous Attention Test (CAT) correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

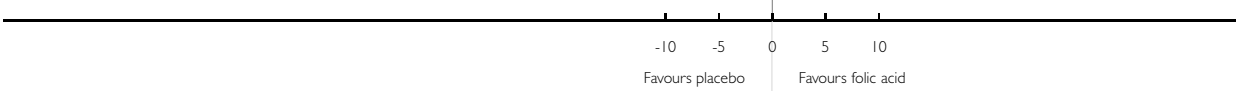
Outcome: 10 Continuous Attention Test (CAT) correct (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.67 (2.15)	12	-1.27 (4.73)		100.0 %	1.94 [-1.00, 4.88]
Total (95% CI)	**12**		**12**			**100.0 %**	**1.94 [-1.00, 4.88]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable



Analysis 8.11. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 11 Countinous Attention Test (CAT) incorrect (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

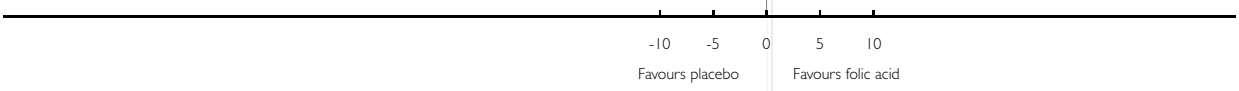
Outcome: 11 Countinous Attention Test (CAT) incorrect (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	-1 (2.01)	12	-0.81 (1.32)		100.0 %	-0.19 [-1.55, 1.17]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.19 [-1.55, 1.17]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.27 (P = 0.78)

Test for subgroup differences: Not applicable



Analysis 8.12. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 12 Countinous Attention Test (CAT) error index (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 12 Countinous Attention Test (CAT) error index (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	-0.02 (0.06)	12	0.02 (0.11)		100.0 %	-0.04 [-0.11, 0.03]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.04 [-0.11, 0.03]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable

Analysis 8.13. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 13 Digit-symbol substitution (DSS) correct (change from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

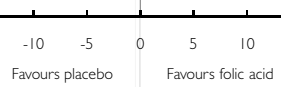
Outcome: 13 Digit-symbol substitution (DSS) correct (change from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.33 (1.61)	12	-0.33 (1.23)		100.0 %	0.66 [-0.49, 1.81]
Total (95% CI)	**12**		**12**			**100.0 %**	**0.66 [-0.49, 1.81]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 8.14. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 14 Digit-symbol substitution (DSS) reaction time correct (change from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 14 Digit-symbol substitution (DSS) reaction time correct (change from baseline at week 4)

Study or subgroup	folic acid		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Pathansali 2006	12	0.05 (0.2)	12	-0.16 (0.3)		100.0 %	0.21 [0.01, 0.41]
Total (95% CI)	**12**		**12**			**100.0 %**	**0.21 [0.01, 0.41]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.02 (P = 0.044)

Test for subgroup differences: Not applicable

Analysis 8.15. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 15 Digit-symbol substitution (DSS) incorrect (change from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 15 Digit-symbol substitution (DSS) incorrect (change from baseline at week 4)

Study or subgroup	folic acid		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Pathansali 2006	12	-0.33 (1.61)	12	0.33 (1.23)		100.0 %	-0.66 [-1.81, 0.49]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.66 [-1.81, 0.49]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 8.16. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 16 Scanning Memory Sets (SMS) three digits correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 16 Scanning Memory Sets (SMS) three digits correct (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	-0.08 (1.08)	12	0.5 (1.44)		100.0 %	-0.58 [-1.60, 0.44]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.58 [-1.60, 0.44]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 8.17. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 17 Scanning Memory Sets (SMS) three digits reaction time correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

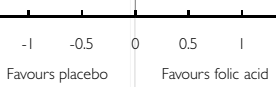
Outcome: 17 Scanning Memory Sets (SMS) three digits reaction time correct (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.02 (0.1)	12	-0.02 (0.13)		100.0 %	0.04 [-0.05, 0.13]
Total (95% CI)	**12**		**12**			**100.0 %**	**0.04 [-0.05, 0.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.84 (P = 0.40)

Test for subgroup differences: Not applicable



Analysis 8.18. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 18 Scanning Memory Sets (SMS) four digits correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 18 Scanning Memory Sets (SMS) four digits correct (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0.08 (2.27)	12	0.09 (1.92)		100.0 %	-0.01 [-1.69, 1.67]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.01 [-1.69, 1.67]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

Analysis 8.19. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 19 Scanning Memory Sets (SMS) four digits reaction time (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

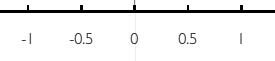
Outcome: 19 Scanning Memory Sets (SMS) four digits reaction time (changes from baseline at week 4)

Study or subgroup	folic acid N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pathansali 2006	12	0 (0.18)	12	0.01 (0.13)		100.0 %	-0.01 [-0.14, 0.12]
Total (95% CI)	**12**		**12**			**100.0 %**	**-0.01 [-0.14, 0.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.16 (P = 0.88)

Test for subgroup differences: Not applicable

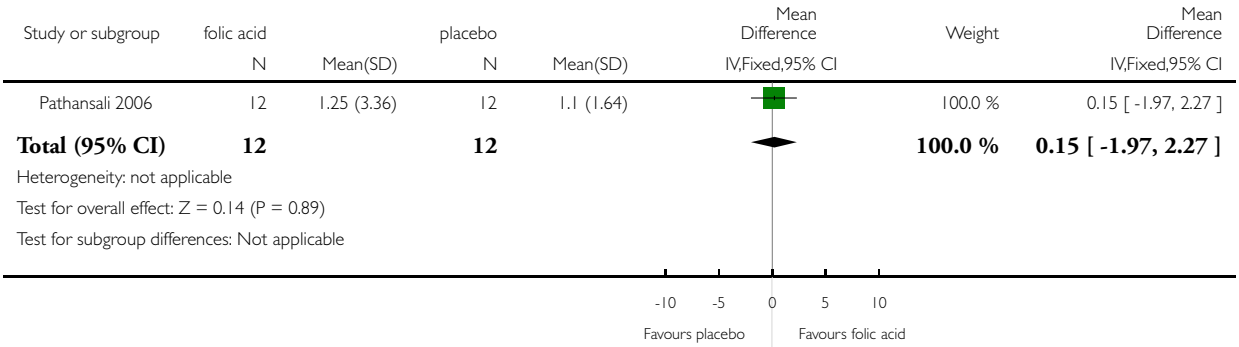


Analysis 8.20. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 20 Scanning Memory Sets (SMS) five digits correct (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 20 Scanning Memory Sets (SMS) five digits correct (changes from baseline at week 4)

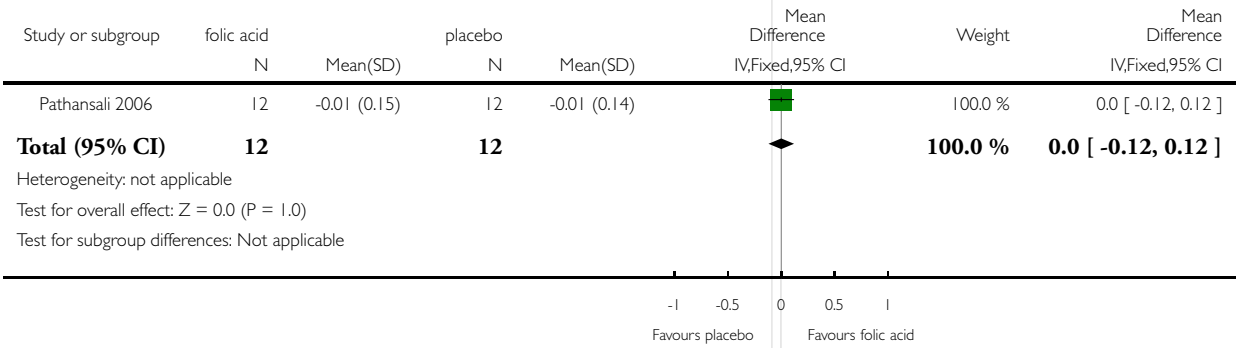


Analysis 8.21. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 21 Scanning Memory Sets (SMS) five digits reaction time (changes from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 21 Scanning Memory Sets (SMS) five digits reaction time (changes from baseline at week 4)

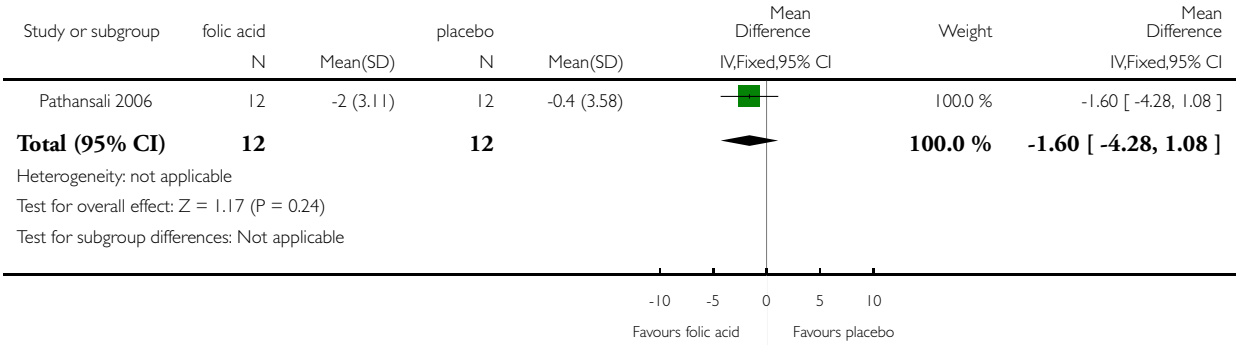


Analysis 8.22. Comparison 8 Folic acid (5 mg/day) vs placebo in healthy elderly, Outcome 22 Homocysteine level mcom/L (change from baseline at week 4).

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 8 Folic acid (5 mg/day) vs placebo in healthy elderly

Outcome: 22 Homocysteine level mcom/L (change from baseline at week 4)

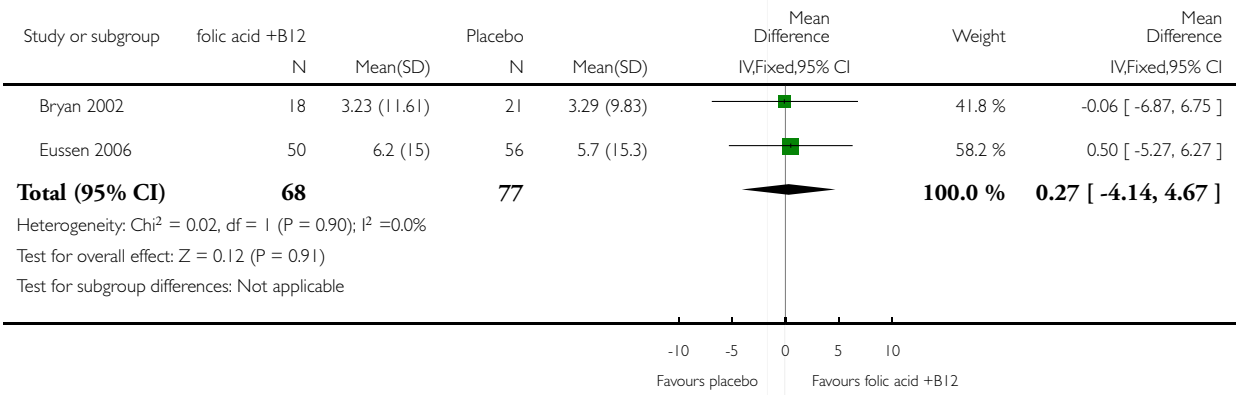


Analysis 9.1. Comparison 9 Folic acid with or without vitamin B12 in healthy people, Outcome 1 Memory, immediate recall.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 9 Folic acid with or without vitamin B12 in healthy people

Outcome: 1 Memory, immediate recall



Analysis 9.2. Comparison 9 Folic acid with or without vitamin B12 in healthy people, Outcome 2 Memory, delayed recall.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 9 Folic acid with or without vitamin B12 in healthy people

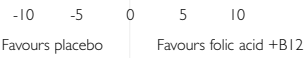
Outcome: 2 Memory, delayed recall

Study or subgroup	folic acid +B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bryan 2002	18	0.66 (2.86)	21	1 (4.99)		39.2 %	-0.34 [-2.85, 2.17]
Eussen 2006	50	1.6 (5.6)	56	1 (4.9)		60.8 %	0.60 [-1.41, 2.61]
Total (95% CI)	**68**		**77**			**100.0 %**	**0.23 [-1.34, 1.80]**

Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² =0.0%

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9 Folic acid with or without vitamin B12 in healthy people, Outcome 3 Memory, word recognition.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 9 Folic acid with or without vitamin B12 in healthy people

Outcome: 3 Memory, word recognition

Study or subgroup	folic acid +B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bryan 2002	18	0.56 (2.5)	21	-0.86 (2.79)		58.4 %	1.42 [-0.24, 3.08]
Eussen 2006	50	0.8 (4.6)	55	1.7 (5.68)		41.6 %	-0.90 [-2.87, 1.07]
Total (95% CI)	**68**		**76**			**100.0 %**	**0.46 [-0.81, 1.73]**

Heterogeneity: Chi² = 3.12, df = 1 (P = 0.08); I² =68%

Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Not applicable

Analysis 9.4. Comparison 9 Folic acid with or without vitamin B12 in healthy people, Outcome 4 Verbal ability.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 9 Folic acid with or without vitamin B12 in healthy people

Outcome: 4 Verbal ability

Study or subgroup	folic acid + B12		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bryan 2002	18	0.28 (7.56)	21	-0.15 (7.48)		0.1 %	0.43 [-4.31, 5.17]
Durga 2007	405	0 (0.86)	413	0.06 (0.86)		99.8 %	-0.06 [-0.18, 0.06]
Eussen 2006	50	0.3 (7.63)	56	0.9 (7.85)		0.2 %	-0.60 [-3.55, 2.35]
Total (95% CI)	**473**		**490**			**100.0 %**	**-0.06 [-0.18, 0.06]**

Heterogeneity: $Chi^2 = 0.17$, df = 2 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 1.01 (P = 0.31)

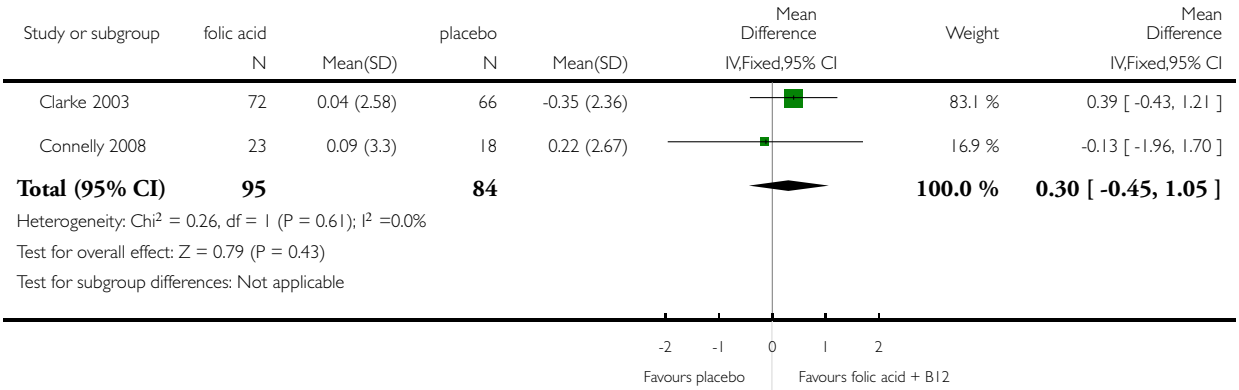
Test for subgroup differences: Not applicable

Analysis 10.1. Comparison 10 Folic acid with or without vitamin B12 for cognitive impairment and dementia, Outcome 1 MMSE.

Review: Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Comparison: 10 Folic acid with or without vitamin B12 for cognitive impairment and dementia

Outcome: 1 MMSE



ADDITIONAL TABLES

Table 1. Baseline characteristics of included studies

Study	Participant number	Age range	Females proportion	Diagnosis	MMSE range	ADAS-Cog range	Homocysteine levels	Folic acid levels
Bryan 2002	40	65-92	100%	healthy	Not assessed	Not assessed	Not assessed	Not assessed
Connelly 2008	41	Mean 76.27 (SD = 6.23)	29%	AD patients	Mean 23.49 (SD = 3.53)	Not assessed	Mean 18.39 (SD = 4.62)	Not assessed
Durga 2007	818	50-70	28%	healthy	28-30	Not assessed	13.0 (11.2-14.7) µmol/L	12 (10-15) nmol/L
Eussen 2006	195	>70	76%	healthy, with vitamin B12 deficiency	Mean 26.7± 3	Not assessed	15.3 ± 5.5 µmol/L	RBC 616 ± 218 nmol/L
Fioravanti 1997	39	70-90	83%	mild to moderate cognitive impairment,	16-24	Not assessed	Not assessed	Blood folate 2.28 (0.6) ng/ml

Table 1. Baseline characteristics of included studies (*Continued*)

				not demented with folic acid <3 ng/ml				
Pathansali 2006	24	73 (5.6)	87%	healthy	<27	Not assessed	11.2±2 µmol/L	6.3 ± 2.5 µmol/
Sommer 1998	11	76.7±4.1	15%	Demented	16-27	Not assessed	Not assessed	127-452 mcg/L (RBC)
VITAL 2003	149	56-89	not reported	84 AD,11 mixed dementia, 47 MCI, 4 unclassified	10-26	5-55	5.7-130.2 µmol/ (range)	1.7-30.5 nmol/l (range)

WHAT'S NEW

Last assessed as up-to-date: 21 July 2008.

Date	Event	Description
1 December 2008	Amended	Published note added

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2003

Date	Event	Description
19 March 2008	New citation required and conclusions have changed	March 2008 update: Five new trials were included. Three conducted among healthy older people, one in Alzheimer's patients, and one in mixed dementia. There is no adequate evidence of folic acid supplementation alone or with vitamin B12, on cognition function in both normal people or those with impaired cognitive function One trial showed a benefit of folic acid in cognition

(*Continued*)

		function after three years in healthy elderly with high homocysteine levels
25 January 2006	New search has been performed	minor update
15 February 2005	Feedback has been incorporated	reply to feedback added
4 December 2004	Feedback has been incorporated	feedback added

CONTRIBUTIONS OF AUTHORS

-RM- contact author, collection of studies, assessment of studies, data extraction and input into Revman, writing the review

-JGE- co-reviewer, assessment of studies, co-drafting of text

-Dymphna Hermans: original search and update searches; Vittoria Lutje, 2008 update search

-The review was peer reviewed anonymously in April 2008

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Division of Clinical Geratology, Nuffield Department of Clinical Medicine, University of Oxford, UK.
- Alzheimer's Society, UK.

External sources

- National Health Service, Research and Development, UK.
- Alzheimer's Society, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

NOTES

This review and the following review on Vitamin B12 for cognition will be combined into a single review on Folate and B vitamins for the prevention and treatment of dementia. New searches will be run, and the reviewers anticipate completion of the combined updated review for issue 3/2009.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Cognition [drug effects]; Cognition Disorders [*drug therapy; etiology]; Dementia [*drug therapy; etiology]; Drug Therapy, Combination; Folic Acid [*therapeutic use]; Folic Acid Deficiency [complications]; Randomized Controlled Trials as Topic; Vitamin B 12 [*therapeutic use]

MeSH check words

Humans