Background Observational studies have shown associations between nutritional status and cognition in later life but evidence from intervention studies is unclear. This study systematically reviewed the evidence on the effect of nutrient supplementation on cognitive function in people ≥ 65y.

Methods Databases including MEDLINE and EMBASE were searched up to 1 September 2006. Randomised controlled trials using at least one kind of vitamin, mineral or omega-3 fatty acid, evaluating standardised neuropsychological test(s) were included. There were no restrictions on participants’ baseline nutritional status or cognitive function. Quality assessment and data abstraction was conducted by one author and checked by another.

Results Of 4229 articles retrieved, 22 trials (3442 participants) were identified. Many were small, short duration and poor methodology. Only 16 out of 122 cognitive tests were significantly different between groups. Meta-analysis showed no significant effect of taking B vitamins or antioxidant vitamins on global cognitive function. There was insufficient evidence to evaluate the effect of omega-3 fatty acids on any cognitive domains.
Conclusion There was little evidence of a beneficial effect from taking B vitamins or antioxidant supplements on global cognitive function in later life. Larger scale randomised controlled trials of longer duration in selected age groups are needed.
**Introduction**

Cognitive function declines with age. It ranges from mild cognitive decline to dementia which is one of the most disabling and burdensome health conditions worldwide. It is estimated that 24 million people worldwide had dementia in 2001 and the number of people affected will double every 20 years by 2040 (Ferri et al., 2005). About 60% of dementia is due to Alzheimer’s disease which is characterised by progressive cognitive deterioration, together with declining activities of daily living and behavioural changes (Ferri et al., 2005). Alzheimer’s disease is a neurodegenerative disease complicated by inflammatory reaction in the brain (Pasinetti 1996).

More than 15% of community living people aged 65 years old and over are deficient in one or more micronutrient, rising to over 40% of those living in institutions (Finch et al., 1998). More than 20% of older people in the UK are regular dietary supplement users (Finch et al., 1998), with vitamins, minerals and fatty acids being the most frequently self-administered supplements. However, large randomised controlled trials (RCTs) and systematic reviews have found little positive effect of micronutrients and fatty acids supplements on cancer (Blot, 1997; Bjelakovic et al., 2004), cardiovascular disease (Eidelman et al., 2004; Hooper et al., 2004), infection (Avenell et al., 2005a; El-Kadiki & Sutton, 2005), or fracture, except for very high risk people in nursing homes (Avenell et al., 2005b). The hypothesis of this study was that single or combinations of vitamin, mineral and/or fatty acid supplements, as might be purchased over the counter by older people, might help maintain cognitive function since micronutrients and fatty acids are essential for proper neurological function. B vitamins and folate are methyl donors in the synthesis of neurotransmitters, neuron membrane phospholipids and DNA (Bottiglieri, 1996). Lack of B vitamins can also cause the accumulation of homocysteine, which may damage vascular structure and neurons (Hankey & Eikelboom, 1999). Antioxidant micronutrients such as vitamin C, E and zinc
may protect the nervous system from free-radical-induced oxidative damage (Vatassery, 1998). Omega-3 fatty acids play important roles in neuronal growth, development of synaptic processing for neural cell interaction, and expression of genes regulating cell differentiation and growth (Uauy & Dangour, 2007).

Previous Cochrane reviewers have focused on supplementation with vitamins B₁ (Rodriguez-Martin et al., 2003) and E (Tabet et al., 2000) in people with Alzheimer’s disease. Insufficient evidence was found to assess benefit. This was also the case in previous Cochrane reviews of vitamin B₆ (Malouf & Grimley Evans, 2003), folic acid (Malouf et al., 2003), and omega-3 fatty acids (Lim et al., 2006) in people with or without cognitive impairment; and vitamin B₁₂ with or without folic acid in people having low blood concentrations of vitamin B₁₂ (Malouf & Areosa, 2003). The present review explored the effect of not only single vitamins, minerals, and omega-3 fatty acids on cognitive function but also their combination as might be purchased over the counter. As it was unclear how baseline cognitive ability and nutritional status may have an impact on any supplementation effect, the present review included older people with any level of cognitive ability or nutritional status. Subgroup analysis was predefined to identify the group of people that may be more sensitive to a certain type of nutrient supplementation, where data were available.

**Methods:**

**Search strategy**

Seven electronic databases, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and CAB abstracts up to 1 September 2006 were searched for RCTs on the effect of diet supplementation on cognitive function in people ≥65y. Medical subject headings and text words related to dietary supplements, vitamins, minerals, fatty acids, cognition, ageing, and RCTs were used. Terms were adapted for
BIOSIS, AGRICOLA, PsycINFO up to 1 September 2006, and for official websites for
registered randomised trials in the UK (National Research Register, 2006), USA (The
U.S. National Institutes of Health Clinical Trials Database, 2006), Europe (European
Union Community Research and Development Databases, 2006) and worldwide
(International Standard Randomized Controlled Trial, 2006). Further details are
available from the authors. The titles and abstracts obtained were screened for relevant
articles. Full texts of the relevant articles were checked for inclusion criteria. Secondary
references were checked. Twenty pharmaceutical companies worldwide were contacted
for unidentified trials. No language limits were imposed on the searches.

Study selection criteria

Trials were included if they met the following criteria, otherwise they were excluded:

(1) Standardised neuropsychological test(s) were used to measure cognitive changes, for
e.g., Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) for
measuring global cognitive function (Rosen et al., 1984) and the Rey Auditory Verbal
Learning Test (AVLT) for measuring memory and learning (Rey, 1964).

(2) The supplement contained at least one kind of vitamin, mineral or omega-3 fatty
acid

(4) There was evidence of random allocation and evidence of having a control or
placebo group for comparison

(5) All participants were 65 years old or older

To increase the generalisability of the results, no restrictions were placed on study
setting (community, psychiatric clinic, or hospital), or the treatment received in the
control group (no treatment, placebo, or concomitant routine care) (Gotzsche, 2000).
There were also no restrictions on participants’ baseline nutritional status or cognitive
function. Participants with depression were included because there is evidence that 87% of people with Alzheimer’s disease and 19-27% of people with cardiovascular disease associated dementia also have depression (Fischer et al., 1990). The supplements could be taken by any route with any dose or duration. Trials with any degree of blinding were included.

Types of outcomes

Primary outcomes were changes in cognitive performance. The assessments were categorised into eleven groups: global cognition, attention and concentration, short-term memory, long-term memory, recognition, processing speed, executive function, verbal ability, verbal fluency, and naming. For example, digit span forward and immediate recall from Rey’s Adult Verbal Learning Task were both grouped into short-term memory. Secondary outcomes were changes in nutrient status, homocysteine concentrations, and adverse events.

Data abstraction and quality assessment of RCTs

One author abstracted the data using an in-house data extraction form, and another checked the accuracy. A 10-item quality appraisal form based on that used in a Cochrane review (Avenell & Handoll, 2005) was used to assess the methodological quality of each included trial. The 10 items include the concealment of randomisation, blinding of assessment of outcomes, intention to treat analysis, the specification of inclusion and exclusion criteria, definition of the intervention, the overall duration of the intervention and length of follow up. Each item was given 0-2 (highest) scores according to quality.

Statistics
All the quantitative data were continuous data. Cognitive tests reported by the included trials were grouped into 11 cognitive domains.

For cognitive domains that reported sufficient data (at least three trials reporting mean change and standard deviation, SD), the Cochrane Collaboration’s Review Manager computer program RevMan (v.4.2, 2002) was used. According to the biochemical mechanisms, pre-specified subgroup meta-analysis was used to investigate the effect of B vitamins, antioxidant vitamins, omega-3 fatty acids, and combination of vitamins and minerals. The number of participants in the meta-analysis was the number with both initial and final measurements available, i.e. drop-outs and deaths were excluded by the investigators. Weighted mean difference was used for cognitive domains that tested by the same cognitive test; standardised mean difference was used for domains that tested by different cognitive tests since different scoring methods were used. A random effects model was used because of the diverse interventions (Higgins et al., 2003). Pre-specified sensitivity analyses were not conducted for large trials or longer duration trials since few trials had more than 30 participants and duration longer than six months.

Some trials presented multiple tests for the same cognitive domain. To avoid multiple results from one trial for one cognitive domain being entered into one meta-analysis, only the results of the first test for each domain that appeared in the report was included in the meta-analysis. The first test reported was chosen to avoid bias in the results. For multi-arm trials that used the same control group (Bryan et al., 2002; Seal et al., 2002), to avoid multiple entry of the results from placebo group, the results from supplement groups were combined.

A narrative report is provided for other outcomes such as change in nutrient concentrations, homocysteine concentrations and adverse events.
Authors were contacted for unpublished MMSE data. The MMSE is a widely used tool to screen for cognitive impairment and dementia. MMSE score ranges from 0 to 30. If the number of participants in each group was not reported, it was calculated by dividing the total number of participants by the number of arms, for example Bryan et al. (2000). If the mean change and SD were unavailable but the final mean was available, the mean change was calculated by subtraction of the baseline mean by the final mean. Imputed values were calculated for the missing SDs based on a method provided by Avenell et al. (2004). SD of mean change was available for four trials (Kowk et al., 1998; Seal et al., 2002; Clarke et al., 2003; Petersen et al., 2005). SD of mean change of the other three trials (Nolan et al., 1991; Sano et al., 1997; McMahon et al., 2006) was imputed. The imputed SD was calculated from a formula derived from a linear regression of SDs on the mean change from trials that reported both results. The imputed SDs were:

$$SD\ of\ MMSE = 4.673 + (1.466 \times \text{mean change})$$

Imputed SDs for tests assessing other cognitive domains were not possible, as the number of trials that reported the SDs of mean change was too small (less than half of the trials that reported corresponding outcomes) to meet the assumption of linear regression. Hence meta-analyses were only conducted for global cognitive function tested by MMSE.

**Results**

A total of 4229 articles were found on initial searching of the electronic databases. No pharmaceutical companies replied. Thirty one full text papers were checked for inclusion (Figure 1). Twenty two completed trials (in 22 papers) including thirty three interventions were included in the review. Twenty five interventions used B vitamin(s)
as supplements (Table 1), four used antioxidant vitamin(s) (Table 2), one used
docosahexanoic acid (DHA) (Table 3), and three used combined vitamins and minerals
(Table 4). Four trials on B vitamins were multiple interventions (Bryan et al., 2002;
Seal et al., 2002; Scott et al., 2005; Eussen et al., 2006). One trial on vitamin B12 and
vitamin E used a 2×2×2 factorial design (Clarke et al., 2003). All the trials were
conducted in developed countries, and academic institutes or national organizations
supported all of them. None reported pharmaceutical company funding.

Four trials reported random allocation which did not appear to disclose assignment
(Bryan et al., 2002; Clarke et al., 2003; Scott et al., 2005; McNeill et al., 2007)( Table
5). Only one trial mentioned that the outcome assessment was blinded (Clarke et al.,
2003). Nineteen trials had more than 30 participants. The trial which used a crossover
design (Meador et al., 1993) involved 29 participants.

Another seven trials are on-going (Aisen, 2006; Dangour, 2006; Runyons, 2006;
Smith, 2006; The MEMO study, 2006; van Uffelen et al., 2006; Walker & Christensen,
2006). One study of combined vitamins and minerals (Chandra, 2001), which has
subsequently been withdrawn (Meguid, 2005), was not included.

Baseline characteristics of participants
The 22 included trials involved 3442 participants (male 1490, female 1759, unknown
gender 193). The sample sizes ranged from 11 to 276.

From the 15 trials on B vitamins with 25 different interventions (Table 1), the
participants of six trials were from the community (Deijen et al., 1992; De La Fourniere
et al., 1997; Bryan et al., 2002; Sommer et al., 2003; Lewerin et al., 2005; McMahon et al., 2006) and the other participants were from hospitals or clinics, most of whom had dementia. Nine trials reported the participants’ baseline blood level of B vitamins (Deijen et al., 1992; Passeri et al., 1993; De La Fourniere et al., 1997; Fioravani et al., 1997; Kwok et al., 1998; Seal et al., 2002; Sommer et al., 2003; Eussen et al., 2006; McMahon et al., 2006). Participants in five trials had low blood levels of vitamin B12 (De La Fourniere et al., 1997; Kwok et al., 1998; Seal et al., 2002; Eussen et al., 2006) or folate (Fioravanti et al., 1997). The cut-off used for low vitamin B12 status was different across trials. De La Fourniere et al. (1997) used serum vitamin B12 less than 240 pg/ml, Eussen et al. (2006) used 100-300 pmol/l, Kwok et al. (1998) used less than 120 pmol/l and Seal et al. (2002) used 100-150 pmol/l. The cut-off used for low folate status was serum folate < 3ng/ml (Fioravanti et al., 1997). Ten trials reported that participants had baseline global cognitive decline which ranged from mild cognitive decline through to severe dementia (Nolan et al.; Meador et al., 1993; De La Fourniere et al., 1997; Fioravanti et al., 1997; Kwok et al., 1998; Seal et al., 2002; Clarke et al., 2003; Sommer et al., 2003; Scott et al., 2005; Eussen et al., 2006).

For the four trials on antioxidant vitamins (Table 2), the participants of two trials were from the community (Smith et al., 1999; Petersen et al., 2005) and the others were from hospitals (Sano et al., 1997; Clarke et al., 2003). Three trials reported the baseline cognitive function as having various degrees of cognitive decline (Sano et al., 1997; Clarke et al., 2003; Petersen et al., 2005). None of these trials reported baseline nutritional status.

The participants from the DHA trial were from a home for older people with cardiovascular disease associated dementia (Terano et al., 1999, Table 3). Their nutritional status was not reported.
For the three trials where combinations of vitamins and minerals were used (Table 4), participants from two trials were healthy volunteers from the community (Cockle et al., 2000; McNeill et al., 2007) and the others were from a health centre (De Jong et al., 2001). None reported baseline nutritional status or cognitive function. The MAVIS trial (McNeill et al., 2007) assessed nutritional risk using a simple questionnaire, but did not measure intake or blood levels.

Supplements used in the trials

The nutrient composition, administration route, dose and duration of the supplementation varied widely across trials. Two interventions used vitamin B₁ (Nolan et al., 1991; Meador et al., 1993), one used riboflavin (Scott et al., 2005), three used vitamin B₆ (Deijen et al., 1992; Bryan et al., 2002; Scott et al., 2005), five used vitamin B₁₂ (De La Fourniere et al., 1997; Kwok et al., 1998; Bryan et al., 2002; Seal et al., 2002; Eussen et al., 2006), four used folic acid (Passeri et al., 1993; Fioravanti et al., 1997; Bryan et al., 2002; Sommer et al., 2003), five used combinations of B vitamins (Clarke et al., 2003; Lewerin et al., 2005; Scott et al., 2005; Eussen et al., 2006; McMahon et al., 2006), two used vitamin E alone (Sano et al., 1997; Petersen et al., 2005), two used combinations of antioxidant vitamins (Smith et al., 1999; Clarke et al., 2003), one used DHA (Terano et al., 1999), and three used low dose combinations of vitamins and minerals (Cockle et al., 2000; De Jong et al., 2001; McNeill et al., 2007).

All supplements in the included trials were administered orally daily except two trials that used intramuscular injection of vitamin B₁₂ (De La Fourniere et al., 1997; Kwok et al., 1998). The doses of nutrients were compared with the UK Reference Nutrient Intake (RNI) (Department of Health, 1991). Pharmacological doses of vitamin B₁₂ (more than 300 times RNI) were used in Lewerin et al. (2005) and Clarke et al. (2003) and pharmacological doses of vitamin B₁ (more than 3000 times RNI) were used
in Meador et al. (1993) and Nolan et al. (1991). Nine interventions were for more than
six months (four of B vitamins, three of antioxidant vitamins, one DHA and two of
combinations of vitamin and minerals). Two had no interventions in control groups
(Kwok et al., 1998; Terano et al., 1999). One used regular products without vitamins
and minerals in the control group (same energy content as the intervention group) (De
Jong et al., 2001). The other trials all used a placebo as the control.

Cognitive assessment

122 different psychological assessments were used to measure the cognitive changes but
only twenty three were used in more than one trial. Scores of sixteen assessments
showed significant differences between supplement and control groups with ten
favouring the supplements (Table 6). Five of these ten assessments were from the small
trial by Fioravanti et al. (1997), where 15mg folic acid was given daily to people with
mild to moderate cognitive decline for 60 days.

In short-term memory, two test results for B vitamins which favoured the
treatment group were statistically significant. One of these was a small trial which used
15mg folic acid daily for people with mild to moderate cognitive decline for 60 days
(Fioravanti et al., 1997). The other used 50mg folic acid daily for people with mild to
moderate dementia for eight weeks (Passeri et al., 1993).

There was no other consistent pattern in the significant results in respect of the
kind of nutrient used, baseline nutritional status or cognitive function.

Sufficient data were available for the meta-analysis of global cognitive function
measured by MMSE and short-term memory measured by a variety of tests.
MMSE was used in eight trials with nine interventions with five of B vitamins, three of antioxidant vitamins and one of DHA. Subgroup meta-analysis was therefore not possible for DHA. In the seven trials, all the participants were cognitively impaired except the ones in McMahon et al’s trial (2006). In the subgroup analysis by kind of nutrient (Figure 2), the heterogeneity of effects in both subgroups was zero. B vitamins had a non-significant negative effect (weighted mean difference -0.09, 95% CI -0.97 to 0.78, p=0.84) and antioxidants had a non-significant positive effect (weighted mean difference 0.58, 95% CI -0.17 to 1.33, p=0.13). The results were similar whether trials with assumed SDs were included or excluded.

Sufficient data were available (Kwok et al., 1998; Seal et al., 2002) for the meta-analysis of MMSE in participants with low baseline vitamin B₁₂ status. Vitamin B₁₂ had a non-significant negative effect in these people with effect size -0.52 units of MMSE score (95% CI -1.67 to 0.62, p=0.13).

Changes of nutrients status and homocysteine status

Eight trials measured changes in nutritional and homocysteine status. In the trials where supplements contained vitamin B₁₂ ranging from 1.25µg to 3mg, vitamin B₁₂ status significantly increased and homocysteine also significantly decreased (De Jong et al., 2001; Seal et al., 2002; Clarke et al., 2003; Scott et al., 2005; Eussen et al., 2006; McMahon et al., 2006). Red blood cell folate and serum/plasma folate (Passeri et al., 1993; De Jong et al., 2001; Seal et al., 2002), vitamin B6 (De Jong et al., 2001), beta-carotene, vitamin C, E (Smith et al., 1999) were also increased significantly by supplements with corresponding nutrients. However, in the same trials no significant improvements in cognitive performance were observed.

Adverse effects
Two trials reported adverse events from using vitamin E (Sano et al., 1997; Petersen et al., 2005) including abnormal dreams, arthritis, bronchitis, cataract extraction, diarrhea, loose stools, insomnia, muscle cramps, nausea, vomiting; dental event, falls and syncope. None found a significant increase in adverse events. Data on compliance were rarely presented.

Discussion

The results of the present review suggest that B vitamins and antioxidant vitamins used in the trials were unlikely to have clinically important effects on global cognitive function. Participants with cognitive impairment or dementia with or without low vitamin B status did not appear to benefit from B vitamin supplementation. There was insufficient evidence to evaluate the effect of omega-3 fatty acids or the effect of taking supplements on any specific cognitive domains. These findings are consistent with an earlier review of seven trials of vitamins and minerals (Manders et al., 2004).

Possible reasons for the lack of positive effects from supplementation

The lack of beneficial effect of supplementation is unlikely to be due to inadequate dosage. The lack of effect might be due to insufficient duration of supplementation and inadequately powered studies. The metabolic changes that contribute to cognitive decline may start from young adulthood (Richards et al., 2004); and could be difficult to reverse in later life. It is also possible that particular stages of aging are more sensitive to supplements, such as those people who are very old. In the MAVIS trial there was no effect of multiple micronutrient supplementation in all participants who were 65 years old or over but weak evidence for a beneficial effect in those 75 years old or over (McNeill et al., 2007).
Strength and limitations of the present review

This study included a wide range of populations with all levels of cognitive status and nutritional status, and studied the effects from individual nutrients and combinations. People with depression were also included because the prevalence of depression is very high in cognitively impaired or demented people. Participants’ baseline nutritional status and cognitive status were often not defined or defined by inconsistent criteria.

Grouping of neuropsychological tests was difficult as some tests assessed more than one cognitive domain. For example, the tests of higher cognitive function such as executive function also require attention, concentration, or short-term memory.

‘Case available analysis’ in stead of ‘intention to treat’ was used in this study as a larger proportion of trials provided these data. Little heterogeneity of effects measured by MMSE in meta-analysis suggests consistency amongst the trials.

Excluded trials, on going RCTs

Two RCTs were excluded because not all the participants were over 65 years old and neither trial found significant effects from taking antioxidant vitamin supplements (Heart Protection Study Collaborative Group, 2002) or vitamin B12 supplements (Hvas et al., 2004) on global cognitive function. The other seven RCTs were excluded because vitamin C (Parnetti et al., 1992; Thomas et al., 2001; Carlsson et al., 2002) or niacinamide (Blass et al., 1988) was used as placebo, the outcome measurements were not standardised (Yehuda et al., 1996), baseline cognitive abilities were not measured (Yaffe et al., 2004) or supplements contained energy but the placebo did not (Wouters-Wesseling et al, 2005).

Seven ongoing RCTs were identified, four trials of B vitamins (Aisen, 2006; Smith, 2006; van Uffelen et al., 2006, Walker & Christensen, 2006), two trials using
omega-3 long chain polyunsaturated fatty acids (Dangour, 2006; The MEMO study, 2006), and one trial using vitamin E and/or selenium (Runyons, 2006).

Further research

The methodological quality of the included trials was generally low and sample sizes of most trials were small. Well designed larger scale trials are therefore needed. It may be worth investigating supplements made of naturally occurring forms of nutrients because the synthetic ones, as found in most supplement products, may have less effect (Yeum et al., 1995; Toba et al., 1997).

The results from two double-blind placebo controlled RCTs suggest very high dose folic acid might have significant positive effects on short-term memory in people at an early stage of cognitive impairment (Passeri et al., 1993; Fioravanti et al., 1997). This is supported by the results of a very recently reported three-year RCT in which 800μg folic acid was given orally daily to 818 people with elevated plasma homocysteine (13 - 26 μmol/L) aged 50-70 years (Durga et al., 2007). This trial was outside the timescale for our review. More long-term large trials are needed to confirm the effects.

A separate article on Smith et al’s RCT (1999) reported that a subgroup of their participants who had both low baseline vitamin C status and low mood and cognition were more likely to derive benefits from the increased vitamin C (Smith et al., 1999), so further studies to investigate the response in malnourished subgroups may be justified.

In addition, almost all participants in trials averaged 70 to 80 years old, so it may also be worth investigating cognitive changes in younger adults such as 55-70 years old or very old adults who are more than 80 years old.

Conclusion
The majority of trials did not find statistically significant beneficial effects from taking supplements on later life cognitive function in spite of significant increases in blood vitamin B12 and folate status, or significant decreases in homocysteine levels. There were too few trials to evaluate the effect of taking omega-3 fatty acids. Larger scale RCTs with longer duration in selected age groups are needed.

Word count: 4086
References


<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nolan 1991</td>
<td>Outpatients from Geriatric Evaluation Services of a Rehabilitation Centre, USA.</td>
<td>Sex: 5M, 10F. Age: mean years: 76.3. Mental status: DAT probable or possible. MMSE: mean (SD): (a) 16.6 (5.73), (b) 16.0 (5.7).</td>
<td>(a) Vitamin B1 3g orally daily for 1 year (b) Double-blind placebo made from lactose daily for 1 year.</td>
<td>Follow up: 1 year</td>
</tr>
<tr>
<td>Deijen 1992</td>
<td>Setting: community healthy volunteers, Netherlands.</td>
<td>Sex: 82M Age: mean (SD) years: (a) 73 (3), (b) 73 (3). Nutrient status: 13 marginal vitamin B6 deficiency, (a) 4, (b) 9. IQ &gt; 80, mean (SD): (a) 109 (11), (b) 111 (10).</td>
<td>(a) Vitamin B6 20mg orally daily for 12 weeks. (b) Double-blind placebo for 12 weeks.</td>
<td>Follow up: 12 weeks</td>
</tr>
<tr>
<td>Meador 1993</td>
<td>Setting: patient, living with caretaker who paid particular attention to nutrient intake, USA.</td>
<td>Sex: 5M, 13F. Age: mean years: 71. Mental status: DAT probable MMSE: mean (SD): 18 (7).</td>
<td>Cross-over designed. (a) Vitamin B1 3g orally daily for 1 month, then placebo for 1 month. (b) Double-blind placebo made from lactose orally daily for 1 month, then vitamin B1 for 1 month.</td>
<td>Follow up: 2 months</td>
</tr>
<tr>
<td>Passeri 1993</td>
<td>Setting: 6 Geriatric Centres, Italy.</td>
<td>Sex: 43M, 53F. Age: range: (a) 65-92, (b) 65-94. Nutrient status: normal folate status: RBC folate: 175-700ng/ml Mental status: mild to moderate dementia, 73 Alzheimer’s type, 23 multi-infarction type, with depression</td>
<td>(a) 5'-MTHF 50mg orally daily for 8 weeks. (b) Double-blind Trazadone (atypical antidepressant) 100mg controlled for 8 weeks.</td>
<td>Follow up: 12 weeks</td>
</tr>
<tr>
<td>De La Fourniere 1997</td>
<td>Setting: community dwelling inpatient, France.</td>
<td>Sex: 3M, 8F. Age: mean (range): 84 (78, 89) Nutrient status: serum B12 ≤240 pg/ml, normal folate Mental status: Moderate severity AD, MMSE 11-23</td>
<td>(a) Vitamin B12 1000mg intramuscular injection daily during 5 days, then once monthly for 5 months. (b) Double-blind placebo for 5 months.</td>
<td>Follow up: 5 months</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fioravanti</td>
<td>Setting: volunteers who had complaints in losing memory, Italy.</td>
<td>Sex: 5M, 25F.</td>
<td>(a) Folic acid 15mg orally daily for 60 days.</td>
<td>Follow up: 60 days.</td>
</tr>
<tr>
<td>1997</td>
<td>Age: mean (SD): (a) 80.25 (5.78), (b) 80.21 (5.45).</td>
<td>Nutrient status: Serum folate &lt; 3ng/ml.</td>
<td>(b) Placebo for 60 days</td>
<td>Outcomes: Randt memory test.</td>
</tr>
<tr>
<td></td>
<td>Mental status: very mild to moderate severity of cognitive decline, no dementia.</td>
<td>Allocation: (a) 16, (b) 14.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwok 1998</td>
<td>Setting: hospital medical outpatient clinics or wards, Hong Kong.</td>
<td>Sex: 1M, 51F.</td>
<td>(a) Vitamin B12 1mg intra muscular injection 3 doses in first week, then 1 dose weekly for 3 weeks, then 1 dose monthly for 2-5 m.</td>
<td>Follow up: 3-6 months</td>
</tr>
<tr>
<td></td>
<td>Age: mean (SD) years: (a) 76.6 (6.8), (b) 77.4 (6.4).</td>
<td>Nutrient status: majority vegetarians, serum B12 &lt;120 pmol/l.</td>
<td>(b) No intervention for 2-5 m.</td>
<td>Outcomes: MMSE, WAIS revised: digit span, similarities, block design; Wechsler memory scale revised: logical memory, visual reproduction; Luria-Nebraska neuropsychological battery: motor function scale; IQ: verbal, performance.</td>
</tr>
<tr>
<td></td>
<td>Mental status: 10 dementia, (a) 7, (b) 3.</td>
<td>MMSE: mean (SD): (a) 22.2 (4.7), (b) 23.8 (4.7).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bryan 2002</td>
<td>Setting: community healthy volunteers, Australia.</td>
<td>Sex: 75F.</td>
<td>(a) Vitamin B6 75mg orally daily for 35d.</td>
<td>Follow up: 35d</td>
</tr>
<tr>
<td></td>
<td>Age: mean years: 74.08 (5.75).</td>
<td>Nutrient status: sufficient vitamin B consumption (measured by food frequency questionnaire).</td>
<td>(b) Vitamin B12 15μg orally daily for 35d.</td>
<td>Outcomes: boxes test, WAIS-III: digit-symbol coding, symbol search, digit span backward, letter-number sequencing, vocabulary; spot the word, RAVLT, Stroop test, uses for common objects, the trail making test, verbal fluency (comprising initial letter &amp; excluded letter); CESD.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(c) Folate 750μg orally daily for 35d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(d) Double-blind placebo (Ca, Mg, etc) for 35d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Dropout: (a) 4.2%, (b) 3.6%.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age: mean years: (a) 84.9, (b) 82.0, (c) 77.6.</td>
<td>Nutrient status: Serum vitamin B12 100-150 pmol/l.</td>
<td>(b) Vitamin B12 50μg orally daily for 4 weeks.</td>
<td>Outcomes: MMSE, serum vitamin B12, plasma homocysteine, blood folate status.</td>
</tr>
<tr>
<td></td>
<td>Mental status: 1/3 dementia</td>
<td>MMSE: mean (SD): (a) 15.4 (7.8), (b) 19.6 (6.3), (c) 19.7 (5.3).</td>
<td>(c) Double-blind placebo for 4 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allocation: (a) 10, (b) 10, (c) 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Dropout: (a) 0%, (b) 10%, (c) 27.3%.</td>
<td></td>
</tr>
<tr>
<td>Clarke 2003</td>
<td>Setting: recruited from hospital records, general practice registers,</td>
<td>Age: mean: 75y</td>
<td>(a) Vitamin B12 1mg and folic acid 2mg orally daily for 12 weeks.</td>
<td>Follow up: 12 weeks.</td>
</tr>
<tr>
<td></td>
<td>Age: mean: 75y</td>
<td>MMSE: mean (SD): (a) 20.9 (3.9), (b) 20.1 (3.9)</td>
<td>Allocation: (a) 74, (b) 75.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------</td>
<td>---------------------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Sommer 2003</td>
<td>Community volunteer, USA.</td>
<td>Sex: 4M, 3F (completed study)</td>
<td>(a) Folic acid 20mg orally daily for 10 weeks.</td>
<td>Follow up: 10 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: mean (a) 76.3, (b) 77.3.</td>
<td>(b) Double blind placebo for 10 weeks.</td>
<td>Outcomes: WAIS-R: vocabulary, similarities; Boston naming test, controlled oral world association test, Wechsler memory scale: logic memory, associate learning; Benton visual retention test, trail making test: trail A, B; finger tapping test, adverse events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutrient status: serum folate 2-5mcg/I, RBC folate 127-452mcg/I, B12&gt;200ng/I.</td>
<td>Allocation: (a) 6, (b) 5.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Dropout: (a) 17%, (b) 60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental status: dementia of various types and severity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lewerin 2005</td>
<td>Setting: community, Sweden.</td>
<td>(a) Vitamin B6 3mg, vitamin B12 500μg, and folic acid 800μg, orally daily for 4 months.</td>
<td>Follow up: 4 months.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 78M, 117 F</td>
<td>(b) Double-blind placebo for 4 months.</td>
<td>Outcomes: digit span backward/forward, identical forms, Wechsler memory scales: visual reproduction; synonyms, block design, digit symbol, Thurstone’s picture memory test, figure classification.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: mean (SD): (a) 75.7 (4.7), (b) 75.6 (4.0).</td>
<td>Allocation: (a) 126, (b) 69.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental status: mild cognitive impairment</td>
<td>% Dropout: (a) 13%, (b) 16%.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scott 2005</td>
<td>Setting: 2-centre, hospital based, UK.</td>
<td>(a) Folic acid 2.5mg and vitamin B12 500μg orally daily for 12 weeks.</td>
<td>Follow up: 12 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: mean (SD): (a) 72.9 (6.0), (b) 74.6 (5.3), (c) 74.7 (6.1), (d) 76.5 (8.0), (e) 72.6 (6.4), (f) 74.2 (6.8), (g) 74.0 (6.5), (h) 72.8 (5.4).</td>
<td>(b) Riboflavin 25mg orally daily for 12 weeks.</td>
<td>Outcomes: letter-digit coding test, telephone interview of cognitive status; folate, vitamin B12, riboflavin, vitamin B6, and homocysteine status.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical status: ischemic vascular disease</td>
<td>(c) Vitamin B6 25mg orally daily for 12 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(d) Folic acid 2.5mg, vitamin B12 500μg, and riboflavin 25mg orally daily for 12 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(e) Folic acid 2.5mg, vitamin B12 500μg, and vitamin B6 25mg orally daily for 12 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(f) Riboflavin 25mg and vitamin B6 25mg orally daily for 12 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(g) Folic acid 0.5mg, vitamin B12 500μg, riboflavin 25mg, and vitamin B6 25mg orally daily for 12 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(h) Placebo orally daily for 12 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allocation: (a) 23, (b) 23, (c) 23, (d) 23, (e) 23, (f) 23, (g) 23, (h) 24.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eussen 2006</td>
<td>Setting: free-living or care house –living older persons</td>
<td>(a) Vitamin B12 1000μg for 24 weeks.</td>
<td>Follow up: 24 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 46M, 149F</td>
<td>(b) Vitamin B12 1000μg for 24 weeks.</td>
<td>Outcome: complex figure of Rey, digit span forward, motor planning, finger tapping, trail making test, 15 word learning, digit span backward, stroop test, similarities WAIS, Raven’s progressive matrices, word fluency (animals, letter); vitamin B12 status.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: mean (SD): (a) 82 (5), (b) 83 (6), (c) 82 (5)</td>
<td>(c) Double-blind placebo for 24 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutrient status: serum vitamin B12 100-300 pmol/I (mild deficiency)</td>
<td>Allocation: (a) 64, (b) 66, (c) 65</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental status: MMSE ≥ 19; 14% cognitive impaired (MMSE 19-24)</td>
<td>% Dropouts: (a) 16%, (b) 23%, (c) 12%</td>
<td></td>
</tr>
</tbody>
</table>
McMahon 2006

**Study Participants**
- Setting: community healthy volunteer, New Zealand.
- Sex: 141M, 112F (at 1 year)
- Age: mean (SD): (a) 73.6 (5.8), (b) 73.4 (5.7)
- Nutrient status: plasma homocysteine \( \geq 13 \) umol/l
- MMSE: mean (SD): (a) 29.2 (1.0), (b) 29.2 (1.0)

**Intervention**
- (a) Folate 1000ug, vitamin B12 500ug, and vitamin B6 10mg, orally daily for 2 years.
- (b) Double-blind placebo for 2 years.
- Allocation: (a) 138, (b) 138
- % Dropout: (a) 10%, (b) 10% at 2 years.

**Outcomes**
- Follow up: 2 years
- Outcome: MMSE, Rey auditory verbal learning test, paragraph-recall test from the Wechsler Memory Scales, controlled oral word association test of the multilingual aphasia examination, word fluency (category), trial making test, Raven’s progressive matrices; plasma homocysteine, folate, and vitamin B12 status.

In the meta-analysis (Figure 2), SD of mean change was available for Kwok et al., 1998, Seal et al., 2002, and Clarke et al., 2003, SD of mean change of Nolan et al., 1991 was imputed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age: mean (SD): (a) 73.4 (7.8), (b) 73.5 (8.3).</td>
<td>Mental status: moderate severity of probable AD</td>
<td>Allocation: (a) 84, (b) 85. % Dropout: (a) 5%, (b) 7%.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MMSE: mean (SD): (a) 11.3 (5.7), (b) 13.3 (4.9).</td>
<td></td>
<td>Follow up: 2 years.</td>
<td></td>
</tr>
<tr>
<td>Smith 1999</td>
<td>Setting: volunteers recruited by advertisement, UK.</td>
<td>Sex: 95M, 110F.</td>
<td>(a) β-carotene 12mg, α-tocopherol 400mg and ascorbic acid 500 mg orally daily for 12 months. (b) Double-blind placebo for 12 months.</td>
<td>Follow up: 12 months. Outcomes: Free recall task, Delayed recognition memory task, Logical reasoning task, Simple reaction time task, Repeated-digits vigilance task, Focus attention task, Categorical search task, plasma ascorbic acid, a-carotene, total b-carotene, a-tocopherol.</td>
</tr>
<tr>
<td></td>
<td>Age: mean: (a) 66.8, (b) 66.9.</td>
<td></td>
<td>Allocation: (a) 93, (b) 92. % Dropout: (a) 2.1%, (b) 16.4%.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mental status: Dementia or mild cognitive impairment.</td>
<td>MMSE: mean (SD): (a) 20.2 (3.8), (b) 20.8 (3.9)</td>
<td>Allocation: (a) 75, (b) 74.</td>
<td></td>
</tr>
<tr>
<td>Petersen, 2005</td>
<td>Setting: community, USA</td>
<td>Age: mean (SD): (a) 72.8 (7.3), (b) 72.9 (7.6)</td>
<td>(a) Vitamin E 1000IU (671mg) daily, then 2000IU after six weeks for 3 years. (b) Placebo for 3 years.</td>
<td>Follow up: 3 years. Outcome: MMSE, ADAS-Cog immediate and delayed word recall, global CDR, the global deterioration scale, New York University immediate and delayed paragraph recall scores, digit span backward, symbol digit modalities test, number cancelling test, Boston naming test, verbal fluency (categories), clock drawing test, activities of daily living scale.</td>
</tr>
<tr>
<td></td>
<td>Mental status: amnestic subtype of mild cognitive impairment.</td>
<td>MMSE: mean (SD): (a) 27.20 (1.9), (b) 27.35 (1.8)</td>
<td>Allocation: (a) 257, (b) 259. % Dropout: (a) 28%, (b)26%</td>
<td></td>
</tr>
</tbody>
</table>

ADAS-cog, Cognitive portion of the Alzheimer's Disease Assessment Scale; CDR, Scores for the Clinical Dementia Rating; MMSE, Mini-Mental State Examination; SD, Standard Deviation; TICS-M, Telephone Interview Cognition Scales Modified

In the meta-analysis (Figure 2), SD of mean change was available for Clarke et al., 2003 and Petersen et al., 2005, SD of mean change of Sano et al., 1991 was imputed.
### Table 3. Characteristics of included trials: fatty acids.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terano 1999</td>
<td>Setting: home for the elderly, Japan. Age: mean: 83 years. Mental status: mild to moderate CVD type of dementia. MMSE: mean (SD): (a) 20.1 (5.6), (b) 19.7 (7.1).</td>
<td>(a) Docosahexaenoic acid (DHA) 0.72g orally daily for 1 year. (b) No intervention for 1 year. Allocation: (a) 10, (b) 10.</td>
<td>Follow up: 1 year. Outcomes: MMSE, HDRS-R, serum fatty acid composition.</td>
</tr>
</tbody>
</table>

SD, Standard Deviation; MMSE, Mini-Mental State Examination; CVD, Cardiovascular Disease; HDRS-R, Hasegowa’s Dementia Rating Scale.

### Table 4. Characteristics of included trials: combinations of vitamins and minerals.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocks 2000</td>
<td>Setting: healthy volunteers, Switzerland. Sex: 51M, 88F. Age: mean (SD): (a) 70.7 (5.6), (b) 70.2 (5.4).</td>
<td>(a) 10 vitamins and minerals 1-10 times RDA, USA, for 24 weeks. (b) Double-blind placebo made from rape seed oil for 24 weeks. Allocation: (a) (69), (b) (70). % Dropout: (a) 4.3%, (b) 12.9% at 4 weeks.</td>
<td>Follow up: 24 weeks. Outcomes: Critical Flicker Fusion, Choice Reaction Time, Sternberg Memory Scanning Task, World Scan Task, Profile of Mood Status, blood vitamin B1, B2, B6 status (by gender only).</td>
</tr>
<tr>
<td>De Jong 2001</td>
<td>Setting: freeliving frail elderly from health center, BMI&lt;=25 or had recent weight loss, the Netherlands. Sex: 21M, 45F. Age: mean (SD): (a) 78.8 (4.8), (b) 79.0 (7.2).</td>
<td>(a) 13 vitamins and minerals 0.25 – 1 times RDA, Dutch, enriched product plus a social program for 17 weeks. (b) Regular products (same energy as above) plus a social program for 17 weeks. Allocation: (a) (36), (b) (30).</td>
<td>Follow up: 17 weeks. Outcomes: Block-transfer Test, Reaction Time test, plasma homocysteine, folate, vitamin B6, B12 and RBC folate status.</td>
</tr>
<tr>
<td>McNeill 2007</td>
<td>Setting: 6 health centres, 97% living in the community, UK. Sex: 479M, 431 F. Age: mean (interquartile range): (a) 72 (68, 76), (b) 71 (68, 76).</td>
<td>(a) 16 kinds vitamin and mineral 1-2 times RDA, UK, orally daily for 1 year. (b) Double-blind placebo orally daily for 1 year. Allocation: (a) (456), (b) (454). % Dropout: (a) 12.7%, (b) 17.6%.</td>
<td>Follow up: 1 year. Outcomes: digital span forward, Wechsler Memory Scale: Verbal Fluency (initial letter), risk of nutrient deficiencies.</td>
</tr>
</tbody>
</table>

RDA, Recommended Daily Allowance; SD, Standard Deviation;
<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation concealment¹</th>
<th>Group comparable at entry²</th>
<th>Participants blinding³</th>
<th>Treatment provider blinding⁴</th>
<th>Assessor Blinding⁵</th>
<th>Identical care programs⁶</th>
<th>Withdraws⁵</th>
<th>Entry criteria defined⁷</th>
<th>Intervention defined⁷</th>
<th>Duration⁷</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan et al., 2002</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Clarke et al., 2003</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Cockle et al., 2000</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>de La Fourniere et al., 1997</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>de Jong et al., 2001</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Deijen et al., 1992</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Eussen et al., 2006</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Fioravanti et al., 1997</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Kwok et al., 1998</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Lewerin et al., 2005</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>McMahon et al., 2006</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>McNeill et al., 2007</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Meador et al., 1993</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Nolan et al., 1991</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Passeri et al., 1993</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Petersen et al., 2005</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Sano et al., 1997</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Scott et al., 2005</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Seal et al., 2002</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Smith et al., 1999</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Sommer et al., 2003</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Terano et al., 1999</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

¹² = method did not allow disclosure of assignment, 1 = chance of disclosure of assignment or mentioned concealment but not adjusted for, 0 = quasi-randomised
² = good comparability of groups, or confounding adjusted for in analysis, 1 = confounding possible, mentioned but not adjusted for, 0 = large potential for confounding, or not discussed
³ = effective action taken to blind people, 1 = small or moderate chance of unblinding people, 0 = not mentioned (unless double-blind), or not done
⁴ = care programmes identical, 1 = differences in care programmes but unlikely to influence study outcomes, 0 = not mentioned or differences in care programmes likely to influence study outcomes
⁵ = intention to treat analysis based on all cases randomised possible or carried out, 1 = states number and reason for withdrawal but intention to treat analysis not possible, e.g. because outcomes were not measured, 0 = not mentioned or not possible
⁶ = clearly defined, 1 = inadequately defined, 0 = poorly or not defined
⁷ = optimal duration of surveillance (over 6 months), 1 = adequate duration of surveillance (one up to six months), 0 = not defined, or not adequate.
<table>
<thead>
<tr>
<th>Global cognition</th>
<th>Attention and Concentration</th>
<th>Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog (Meador, 1993)</td>
<td>↑ Randt memory test: attention efficiency (Fioravanti, 1997)</td>
<td>↑ S Associate recognition task (Deijen, 1992)</td>
</tr>
<tr>
<td>MMSE (Meador, 1993)</td>
<td>↑ Categoric search task: accuracy (Smith, 1999)</td>
<td>↑ Delayed recognition memory task (Smith, 1999)</td>
</tr>
<tr>
<td>ADAS-Cog (De La Fourniere, 1997)</td>
<td>→ Focused attention task: accuracy (Smith, 1999)</td>
<td>→ Word scan task: male, female (Cockle, 2000)</td>
</tr>
<tr>
<td>MMSE (Sano, 1997)</td>
<td>→ Repeated-digits vigilance task: total hit rate (Smith, 1999)</td>
<td>→ RAVLT recognition (Bryan, 2002)</td>
</tr>
<tr>
<td>ADAS-Cog (Sano, 1997)</td>
<td>→</td>
<td>15 word learning, recognition (Eussen, 2006)</td>
</tr>
<tr>
<td>MMSE (Kwok, 1998)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Hasegowa’s dementia rating scale (Terano, 1999)</td>
<td>→ Long term memory</td>
<td>Verbal fluency</td>
</tr>
<tr>
<td>MMSE (Terano, 1999)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>MMSE (Seal, 2002)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>MMSE (Clarke, 2003) (B12 + folic acid)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>MMSE (Clarke, 2003) (vitamin C + vitamin E)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>TICS-M (Clarke, 2003)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog (Petersen, 2005)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Global clinical dementia rating (Petersen, 2005)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>The global deterioration scale (Petersen, 2005)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>TICS-M (Scott, 2005)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>MMSE (McMahon, 2006)</td>
<td>→</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short term memory</th>
<th>Processing speed</th>
<th>Verbal ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate learning task (Deijen, 1992)</td>
<td>→ Motor function scale: oral motor (Kwok, 1998)</td>
<td>↑ S Spot the word (Bryan, 2002)</td>
</tr>
<tr>
<td>Digit span test (Kwok, 1998)</td>
<td>→ Categoric search task: response time (Smith, 1999)</td>
<td></td>
</tr>
<tr>
<td>WMS-R: logical memory (Kwok, 1998)</td>
<td>→ Focused attention task: response time (Smith, 1999)</td>
<td></td>
</tr>
<tr>
<td>Free recall task: number of words correctly recalled (Smith, 1999)</td>
<td>↑ Simple reaction time task (Sey, 1999)</td>
<td>↓ Vienna determination unit (Deijen, 1992)</td>
</tr>
<tr>
<td>Digital span backward (Bryan, 2002)</td>
<td>↑ Choice reaction time: recognition reaction time (Cockle, 2000)</td>
<td>↑ Logical reasoning task: number of correctly answered in 3min (Smith, 1999)</td>
</tr>
<tr>
<td>RAVLT immediate recall: list 1-5 (Bryan, 2002)</td>
<td>↑ Block transfer test (De Jong, 2001)</td>
<td>↑ Block design (Bryan, 2002)</td>
</tr>
<tr>
<td>Digit span backward (Eussen, 2006)</td>
<td>↑ Symbol search (Bryan, 2002)</td>
<td>↑ Block design (Lewerin, 2005)</td>
</tr>
<tr>
<td>Digital span backward (Lewerin, 2005)</td>
<td>→ Finger tapping test (Sommer, 2003)</td>
<td>→ Figure classification (Lewerin, 2005)</td>
</tr>
<tr>
<td>Complex figure of Rey, immediate recall (Eussen, 2006)</td>
<td>→ Finger tapping (Eussen, 2006)</td>
<td>↑ Raven’s progressive matrices (McMahon, 2006)</td>
</tr>
<tr>
<td>RAVLT: list 1-5 (McMahon, 2006)</td>
<td>→</td>
<td>↓ S</td>
</tr>
<tr>
<td>Wechsler paragraph recall test (McMahon, 2006)</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Digit span forward (McNeill, 2007)</td>
<td>→ Short version of Boston naming test (Nolan, 1991)</td>
<td></td>
</tr>
<tr>
<td>Boston naming test (Sommer, 2003)</td>
<td>→</td>
<td></td>
</tr>
</tbody>
</table>

*S, Effect favoured supplement significantly; -S, Effect favoured control significantly; ↑, Trend favouring supplement; ↓, Trend favouring control; →, Effect was not different between groups; no significant changes were found in Petersen’s study (Petersen, 2005).
ADAS-cog, Cognitive portion of the Alzheimer's Disease Assessment Scale, with higher scores indicating poorer function; MMSE, Mini-Mental Status Examination, with higher scores indicating better function; RAVLT, Rey-Auditory Verbal Learning Tests; TICS-M, Telephone Interview Cognition Scales Modified, with higher scores indicating better function; WAIS, Wechsler Adult Intelligence Scale; WMS-R, Wechsler Memory Scale-Revised; WMS, Wechsler Memory Scale, with higher scores indicating better function.
Figure 1 Flow diagram for screening process

Potentially relevant reports identified and screened for retrieval (n=4229)

Reports retrieved for more detailed evaluation (n=31):

Excluded reports (n=9):
- Not all the participants aged 65 years or over (n=2)
- Used nutrient as placebo/control (n=4)
- Not used standardised cognitive measurement (n=1)
- Not measured baseline cognitive function (n=1)
- Combined studied nutrient with energy (n=1)

Excluded reports (n=4198): not meeting inclusion criteria, e.g. not a RCT, not all participants aged 65 years or over, or no standardised cognitive measurement used.

RCTs included (n=22)
Figure 2: Effect of dietary supplements on global cognition measured by mini-Mental State Examination (MMSE)

Weighted mean difference (random)

95% CI

01 B Vitamins
- B1 (Nolan, 1991)
- B12 (Seal, 2002)
- B12 (Kwok, 1998)
- B12+folic acid (Clarke, 2003)
- B6+B12+folic acid (McMenon, 2006)
Subtotal (95% CI)
-0.09 (-0.57, 0.70)
Test for heterogeneity: $I^2 = 0$

02 Antioxidant vitamins
- E (Petersen, 2005)
- C+E (Clarke, 2003)
- E (Sano, 1997)
Subtotal (95% CI)
0.58 (-0.17, 1.33)
Test for heterogeneity: $I^2 = 0$

Favours control  Favours supplements

MMSE