Does taking vitamin, mineral and fatty acid supplements prevent cognitive decline? A systematic review of randomized controlled trials?

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Abstract

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 B_1 (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 B_6 (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 B_{12} with or without folic acid in people having low blood concentrations of vitamin B_{12} (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 example, 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) (Gotzshe, 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.

Missing data

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:

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

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.

[Insert table 1, 2, 3, 4]

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.

[Insert table 5]

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 Founiere *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 1991 *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 B_1 (Nolan *et al.*, 1991; Meador *et al.*, 1993), one used riboflavin (Scott *et al.*, 2005), three used vitamin B_6 (Deijen et al., 1992; Bryan et al., 2002; Scot *et al.*, 2005), five used vitamin B_{12} (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 B_{12} (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 B_{12} (more than 300 times RNI) were used in Lewerin *et al.* (2005) and Clarke *et al.* (2003) and pharmacological doses of vitamin B_1 (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.

[Insert table 6]

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 B_{12} status. Vitamin B_{12} 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 B_{12} ranging from 1.25μg to 3mg, vitamin B_{12} 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

Aisen, P. (2006) VITAL – Vitamin to slow Alzheimer's disease (homocysteine study) The U.S. National Institute of Health Clinical Trials Database. Available from: URL: http://www.clinicaltrials.gov/show/NCT00056225 (accessed 1 September 2005)

Anti-oxidant treatment of Alzheimer's disease (2006). The U.S. National Institute of Health Clinical Trial Database. Available from: URL: http://www.clinicaltrials.gov/show/NCT00117403 (accessed 1 September 2005)

Avenell, A., Campbell, M.K., Cook, J.A., Hannaford, P.C., Kilonzo, M.M., McNeill, G., Milne, A.C., Ramsay, C.R., Seymour, D.G., Stephen, A.I. & Vale, L.D. (Writing Group of the MAVIS Trial) (2005a). Effect of multivitamin and multimineral supplements on morbidity from infections in older people (MAVIS Trial): pragmatic, randomised, double blind, placebo controlled trial. *BMJ* **331,** 324-329.

Avenell, A., Gillespie, W.J., Gillespie, L.D. & O'Connell, D.L. (2005b) Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Sys. Rev.* **3**.

Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, Smith WCS, Jung RT, Campbell MK, Grant AM (2004) Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess* **8**(21), 1-458.

Avenell, A. & Handoll, H.H.G. (2005) Nutritional supplementation for hip fracture aftercare in older people. *The Cochrane Database of Sys. Rev.***1**.

Blass, J.P., Gleason, P., Brush, D., DiPonte, P. & Thaler, H. (1988) Thiamine and Alzheimer's disease. A pilot study. *Arch. Neuro.* **45**(8), 833-835.

Blot, W.J. (1997) Vitamin/mineral supplementation and cancer risk: international chemoprevention trials. *P. Soc. Exp. Biol. Med.* **216**(2), 291-296.

Bjelakovic, G., Nikolova, D., Simonetti, R.G. & Gluud, C. (2004) Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet* **364** (9441), 1219-1228.

Bottiglieri, T. (1996) Folate, vitamin B-12, and neuropsychiatric disorders. *Nutr. Rev.* **54**, 382-390.

Bryan, J., Calvaresi, E. & Hughes, D. (2002) Short-Term Folate, Vitamin B-12 or Vitamin B-6 Supplementation Slightly Affects Memory Performance But Not Mood in Women of Various Ages. *J. Nutr.* **132**, 1345-1356.

Carlsson, C.M., Papcke-Benson, K., Carnes, M., McBride, P.E. & Stein, J.H. (2002) Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. *Drug. Aging* **19**(10), 793-805.

Chandra, P. (2001) Effect of vitamin and trace element supplementation on cognitive function in elderly subjects. [retracted in Nutrition 2005; 21: 286]. *Nutrition*. **17**(9), 709-712.

Clarke, R., Harrison, G. & Richard, S. Vital Trial Collaborative Group. (2003) Effect of vitamin and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *J. Intern. Med.* **254** (1), 67-75.

Cockle, S., Haller, J., Kimber, S., Dawe, R. & Hindmarch, I. (2000) The influence of multivitamins on cognitive function and mood in the elderly. Aging Ment. Health **4**(4), 339-353.

De La Fourniere, F., Ferry, M., Cnockaert, X., Cnockaert, X., Chahwakilian, A., Hugonot-Diener, L., Baumann, F., Nedelec, C., Buronfosse, D., Meignan, S. & Fauchier, C. (1997) Vitamin B12 deficiency and dementia: A multicenter epidemiologic and therapeutic study. Preliminary therapeutic trial. *Semaine Des Hopitaux* **73**(5-6), 133-140.

De Jong, N., Chin A Paw, M.J.M., de Groot, L.C.P.G.M., Rutten, R.A.M., Swinkels, D.W., Kok, F.J. & van Staveren, W.A (2001) Nutrient dense foods and exercise in frail elderly effects on B vitamins homocysteine methylmalonic acid and neuropsychological functioning. *Am. J. Clin. Nutr.* **73**, 338-346.

Deijen, J.B., van der Beek, E.J., Orlebeke, J.F. & van den Berg, H. (1992) Vitamin B-6 supplementation in elderly men: effects on mood, memory, performance and mental effort. *Psychopharmacology* **109**(4), 489-496.

Department of Health. (1991) *Dietary reference values for food energy and nutrients for the United Kingdom.* London: H.M.S.O.

Dangour, A., Clemens, F., Elbourne, D., Fasey, N., Fletcher, A.E., Hardy, P., Holder, G.E., Huppert, F.A., Knight, R., Letley, L., Richards, M., Truesdale, A., Vickers, M & Uauy, R. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and renal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol (2006) Nutrition Journal. 5:20; also available Available from: URL: http://www.lshtm.ac.uk/nphiru/research/n3pufas.html (accessed 1 September 2006)

Durga,J., van Boxtel, M.P.J., Schouten, E.G., Kok, F.J., Jolles, J., Katan, M.B. & Verhoef, P. (2007) Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet **369**, 208-216

Eidelman, R.S., Hollar, D., Hebert, P.R., Lamas, G.A. & Hennekens, C.H. (2004) Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. *Arch. Intern. Med.* **164**(14), 1552-1556.

El-Kadiki, A. & Sutton, A.J. (2005) Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials. *BMJ* **330**, 871.

European Union Community Research and Development Databases. Available from: URL: http:// www.cordis.lu/en/home.html (accessed 1 September 2006)

Eussen, S.J., de Groot, L.C., Joosten, L.W., Bloo, R.J. Clarke, R., Ueland, P.M., Schneede, J., Blom, H.J., Hoefnagels, W.H. & van Staveren, W.A. (2006) Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B12 deficiency: a randomized, placebo-controlled trial. *Am. J. Clin. Med.* **84**, 361-370.

Ferri, C., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang, Y., Jorm, A., Mathers, C., Menezes, P.R., Rimmer, E., Scazufca, M., for Alzheimer's Disease International (2005) Global prevalence of dementia: a Delphi consensus study. *Lancet* **366**(9503), 2112-2117

Finch, S., Doyle, W., Lowe, C., Bates, J.C., Prentice, A. & Clarke, C.P. (1998) *National Diet and Nutrition Survey: People Aged 65 Years and Over. Volum 1: Report of the Diet and Nutrition Survey.* London: The Stationery Office.

Fioravanti, M., Ferrario, E., Massaia, M., Cappa, G., Rivolta, G., Grossi, E, & Buckley, A.E. (1997) Low folate levels in the cognitive decline of elderly patients and efficacy of folate as a treatment for improving memory deficies. *Arch. Gerontol. Geriat.* **26** (1), 1-13.

Fischer, P., Simanyi, M. & Danielczyk, W. (1990) Depression in dementia of the Alzheimer type and in multi-infarction dementia. *Am. J. Psychiatry.* **147**, 1484-7.

Gotzshe, P. (2000) *Why we need a broad perspective on meta-analysis. BMJ* **321**, 585-586.

Hankey, G.J. & Eikelboom, J.W. (1999) Homocysteine and vascular disease. *Lancet* **354**, 407-413.

Heart Protection Study Collaborative Group (2002). MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high risk individuals: a randomised placebo controlled trial. *Lancet* **360**, 23-33

Higgins, J.P.T. & Green, S., editors. (2005) *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005].* Available from: URL: http://www.cochrane.org/resources/handbook/hbook.htm (accessed 31st May 2005).

Higgins, J.P.T., Thompson, S.G., Deeks, J.J. & Atman, D.G. (2003) Meausring inconstancy in meta-analyses. *BMJ* **327**, 557-60.

Hooper, L., Thompson, R.L., Harrison, R.A., Summerbell, C.D., Moore, H., Worthington, H.V., Durrington, P.N., Ness, A.R., Capps, N.E., Davey, Smith. G., Riemersma, R.A. & Ebrahim, S.B.J. (2004) Omega 3 fatty acids for prevention and treatment of cardiovascular disease. *Cochrane Database Sys. Rev.* **3**.

Hvas, A.M., Juul, S., Lauritzen, L, Nexo, E & Ellegaard, J. (2004) No effect of vitamin B12 treatment on cognitive function and depression: a randomized placebo controlled study. *J Affect. Disord.* **81**(3), 269-273.

International Standard Randomized Controlled Trials. Available from: URL: http://www.controlled-trials.com/isrctn/ (accessed 1 August 2006)

Kwok, T.C.Y. & Mok, H.L.F. (2006) Can oral vitamin B12 and folate supplementation preserve cognition function of patients with early dementia? The U.S. National Institute of Health Clinical Trial Database. Available from : URL: http://www.clinicaltrials.gov/CT/show/NCT00164970 (accessed 1 September 2006)

Kwok, T., Tang, C., Woo, J., Lai,W.K., Law, L.K. & Pang, C.P. (1998) Randomized trial of the effect of supplementation on the cognitive function of older people with subnormal cobalamin levels. *In. J. Geriatr. Psych.* **13**(9), 611-616.

Lewerin, C., Matousek, M., Steen, G., Johansson, B., Steen, B. & Nilsson-Ehle, H. (2005) 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. *Am. J. Clin. Nutr.* **81**(5), 1155-1162.

Lim, W.S., Gammack, J.K., van Niekerk, J. & Dangour, A.D. (2006) Omega-3 fatty acid for the prevention of dementia. *Cochrane Database Sys. Rev.* **1**.

Malouf, M., Grimley Evans, J. & Areosa, S.A. (2003) Folic acid with or without vitamin B12 for cognition and dementia. *Cochrane Database Sys. Rev.* **1**.

Malouf, R. & Areosa,S.A. (2003) Vitamin B12 for cognition. *Cochrane Database Sys. Rev.* **1**.

Malouf, R. & Grimley Evans, J. (2003) The effect of vitamin B6 on cognition. *Cochrane Database Sys. Rev.* **1**.

Manders, M, de Groot, L.C., van Staveren, W.A. Wouters-Wesseling, W., Mulders, A.J.M.J., Schols, J.M.G.A. & Hoefnagels, W.H.L. (2004) Effectiveness of nutritional supplements on cognitive functioning in elderly persons: a systematic review. *J. Gerontol. A Biol. Sci. Med. Sci.* **59**(10), 1041-1049.

McMahon, J.A., Green, T.J., Skeaff, C.M., Knight, R., Mann, J.I. & Williams, S.M. (2006) A controlled trial of homocysteine lowing and cognitive performance. *N. Eng. J. Med.* **354**(26), 2764-2772.

McNeill, G., Avenell, A., Campbell, M.K., Cook, J.A., Hannaford, P.C., Kilonzo, M.M., Milne, A.C., Ramsay, C.R., Seymour, D.G., Stephen, A.I. & Vale, L.D., the MAVIS Trial Group. (2007) Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial *Nutr. J.* **6**:10

Meador, K., Loring, D., Nichols, M., Zanrini, E., Rivner, M., Posas, H., Thompson, E. & Moore, E. (1993) Preliminary findings of high-dose thiamine in dementia of Alzheimer's type. *J. Geriatr. Psychiat. Neurol.* **6**(4), 222-229.

Meguid, M.M., editor. (2005) Retraction. *Nutrition.* **21**, 286.

National Research Register. (2006) Available at: URL: http://www.update-software.com/national/nrr-frame.html (accessed 1 September 2006)

Nolan, K.A., Black, R.S., Sheu, K.F., Langberg, J. & Blass, J.P. (1991) A trial of thiamine in Alzheimer's disease. *Arch. Neurol.* **48**(1), 81-83.

Parnetti, L., Ambrosoli, L., Abate, G. Azzini, C., Balestreri, R., Bartorelli, L, Bordin, A., Crepaldi, G., Cristianini, G. & Cucinotta, D, et al. (1992) Posatirelin for the treatment of late-onset Alzheimer's disease: A double-blind multicentre study vs citicoline and ascorbic acid. *Acta Neurologica Scandinavica* **92**(2), 135-140.

Pasinetti (1996) Inflammatory mechanisms in neurodegeneration and Alzheimer's disease: the role of the complement system. *Neurobiol Aging* **17**(5),707-16.

Passeri, M., Cucinotta, D., Abate, G., Senin, U. & Ventura, A. (1993) Oral 5'-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. *Aging-Clin. Exp. Res.* **5**(1), 63-71.

Petersen, R.C., Thomas, R.G., Grundman, M., Bennett, D., Doody, R., Ferris, S., Galasko, D., Jin, S., Kaye, J., Levey, A., Pfeiffer, E., Sano, M., van Dyck, C.H. & Thal, L.J. (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. *N. Engl. J. Med.* **352**(23), 2379-2388.

RevMan Analyses [Computer program] Version 1.0 for Windows. (2002) In: Review Manager (RevMan) 4.2. Oxford, England: The Cochrane Collaboration.

Rey, A. (1964) *L'examen clinique en psychologie.* Paris : Presses Universitaries de France.

Richards, M., Shipley, B., Fuhrer, R., Wadsworth, M.E.J. (2004) Cognitive ability in childhood and cognitive decline in mid-life: longitudinal birth cohort study. *BMJ* **328**, 552-554.

Rodriguez-Martin, J.L., Qizilbashm N. & LOpez-Arrieta, J.M. (2003)Thiamine for Alzheimer's disease. *Cochrane Database of Sys. Rev.* **1**.

Rosen, W.G., Mohs, R.C., Davis, K.L. (1984) A new rating scale for Alzheimer's disease. *Am. J. Psychiatr.* **141**, 1356-1364

Runyons, C.R. (2006) Prevention of alzheimer's disease by vitamin E and selenium (PREADVISE). The US National Institutes of Health clinical trials database. Available from: URL: http://clinicaltrials.gov/ct//show/NCT00040378? (accessed 1 September 2005)

Sano, M., Ernesto, C., Thomas, R.G., Klauber, M.R., Schafer, K., Grundman, M., Woodbury, P., Growdon, J., Cotman, C.W., Pfeiffer, E., Schneider, L.S. & Thal L.J. (1997) A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N. Engl. J. Med.* **336**(17), 1216-1222.

Seal, E.C., Metz, J., Flicker, L. & Melny, J. (2002) A randomized, double-blind, placebo-controlled study of oral vitamin B12supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. *J. Am. Geriat. Soc.* **50**(1), 146-151.

Scott, D.J., MacIntosh, G., Lowe, G.D.O, Rurnley, A., McMahon, A.D., Langhorne, P., Tait, R.C., St J O'Reilly, D., Spilg, E.G., MacDonald, J.B., MacFarlance, P.W. & Westendorp, R.G.J. (2005) Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. *Am. J. Clin. Nutr.* **82**,1320-1326.

Smith, A., Clark, R., Nutt, D., Haller, J., Hayward, S. & Perry, K. (1999) Anti-oxidant vitamins and mental performance of the elderly. *Hum. Psychopharmacol. Clin. Exp.* **14**, 459-471.

Smith, A.D. (2006) Homocysteine and B vitamins in cognitive impairment. The International Standard Randomized Controlled Trail. Available from: URL: http://www.controlled-trials.com/ISRCTN94410159/94410159 (accessed 1 September 2006)

Smith, A.P., Clark, R.E., Nutt, D.J., Haller, J., Hayward, S.G. & Perry, K. (1999) Vitamin C, mood and cognitive functioning in the elderly. *Nutr. Neurosci.* **2**, 249-256.

Sommer, B.R., Hoff, A.L. & Costa, M. (2003) Folic acid supplementation in dementia: a preliminary report. *J. Geriat. Psychiat. Neurol.* **16**(3), 156-159.

Tabet, N., Birks, J., Grimley Evans, J., Orrel, M. & Spector, A. (2000)Vitamin E for Alzheimer's disease. *Cochrane Database Sys. Rev.* **4**.

Terano, T., Fujishiro, S., Ban, T. Yamamoto, K., Tanaka, T., Noguchi, Y., Tamura, Y., Yazawa, K. & Hirayama, T. (1999) Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids* **34**(Suppl), S345-6.

The MEMO study. (2006) Mental health in Elderly Maintained with omega-3. Current controlled trials. Available from: URL: http://www.controlled-trials.com/ISRCTN46249783/46249783 (accessed 1 September 2006)

The U.S. National Institutes of Health Clinical Trials Database. Available from: URL: http://clinicaltrials.gov/ct/gui/c/r (accessed 1 August 2006)

Thomas, A., Iacono, D., Bonanni, L., D'Andreamatteo, G. & Onofrj, M. (2001) Donepezil, rivastigmine, and vitamin E in Alzheimer disease: a combined P300 event-related potentials/neuropsychologic evaluation over 6 months. *Clin. Neuropharmacol.* **24**(1), 31-42.

Toba, T., Shidoji, Y., Fujii, J., Moriwaki, H., Muto, Y., Suzuki, T., Ohishi, N. & Yagi, K. (1997) Growth suppression and induction of heat-shock protein-70 by 9-cis beta-carotene in cervical dysplasia-derived cells. *Life Sci.* **61**(8), 839-845.

Uauy, R., Dangour, D. (2007) Nutrition in brain development and aging: role of essential fatty acids. *Nutr. Rev.* **64**(5), S24-33

Van Uffelen, J.G.Z.; Hopman-Rock, M.; Chin A Paw, M.J.M. & van Mechelen, W. (2006) Protocol for project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment. Available from: URL: http://controlled-trials.com/ISRCTN19227688/19227688 , also from: URL: http://www.biomedcentral.com/1471-2318/5/18 (accessed 1 september 2006)

Vatassery, G.T. (1998) Vitamin E and other endogenous antioxidants in the central nervous system. *Geriatrics* **53**(Suppl 1), S25-7.

Walker, J.G. & Christensen, H (2006) Beyond ageing: a study for the prevention of depression, cognitive impairment and the improvement of knowledge about mental health. The U.S. National Institute of Health Clinical Trial Database. Available from: ULR:http://www.clinicaltrials.gov/ct/gui/show/NCT00214682 (accessed 1 September 2006)

Wouters-Wesseling, W., Wagenaar, L.W., Rozendaal, M., Deijen, J.B., de Groot, L.C., Blindels, J.G. & van Staveren, W.A. (2005) Effect of an enriched drink on cognitive function in frail elderly persons. *J. Gerontol. A Biol. Sci. Med. Sci.* **60**, 265-270.

Yaffe, K., Clemons, T.E., McBee, W.L. & Lindblad, A.S., Age-Related Eye Disease Study Research Group. (2004) Impact of antioxidant, zinc, and copper on cognition in the elderly: a randomized, controlled trial. *Neurology* **63**(9), 1705-1707.

Yehuda, S., Rabinovtz, S., Carasso, R.L. & Mostofsky, D.I. (1996) Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life. *Int. J. Neurosci.* **87**(3-4), 141-149.

Yeum, K.J., Zhu, S., Xiao, S., Jiang, S., Mason, J. & Russell, R.M. (1995) Beta-carotene intervention trial in premalignant gastric lesions. *J. Am. Coll. Nutr.* **14**, 536

Table 1. Characteristics of included trials: Vitamin Bs – B1, Riboflavin, B6, B12, folic acid alone or combined

Study	Participants	Intervention	Outcomes
Nolan 1991	Setting: Outpatients from Geriatric Evaluation Services of a Rehabilitation Centre, USA. 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).	(a) Vitamin B1 3g orally daily for 1 year (b) Double-blind placebo made from lactose daily for 1 year. Allocated: (a) 8, (b) 7 % Dropout: (a) 37.5%, (b) 28.6% at 1 year.	Follow up: 1 year Outcomes: CERAD battery: verbal fluency (categories), short version of the Boston naming test, MMSE, constructional praxis test; in addition, 10 item word list learning test, and tests of delayed recall and recognition based on the same 10 word list; adverse events.
Deijen 1992	Setting : community healthy volunteers, Netherlands. Sex: 82M Age: mean (SD) years: (a) 73 (3), (b) 73 (3). Nutrient status: 13 marginal vitamin B6 deficiency, (a) 4, (b) 9. IQ > 80, mean (SD) : (a) 109 (11), (b) 111 (10).	(a) Vitamin B6 20mg orally daily for 12 weeks. (b) Double-blind placebo for 12 weeks. Allocation: (a) 41, (b) 41. % Dropout: (a) 7.3%, (b) 7.3%.	Follow up: 12 weeks Outcomes: Sperling whole report task, associated learning task, associated recognition task, visual memory task, cognitrone, Vienna determination unit.
Meador 1993	Setting: patient, living with caretaker who paid particular attention to nutrient intake, USA. Sex: 5M, 13F. Age: mean years: 71. Mental status: DAT probable MMSE: mean (SD): 18 (7).	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. Allocated: (a) 9, (b) 9.	Follow up: 2 months Outcomes: ADAS-cog, MMSE, adverse events.
Passeri 1993	Setting: 6 Geriatric Centres, Italy. 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	(a) (b) 7 days wash-out period, then 2 weeks placebo run-in. (a) 5'-MTHF 50mg orally daily for 8 weeks. (b) Double-blind Trazodone (atypical antidepressant) 100mg controlled for 8 weeks. (a) (b) 4 weeks drug free follow up Allocation: (a) 47, (b) 49. % Dropout: (a) 0%, (b) 0%.	Follow up: 12 weeks. Outcomes: RVM test: immediate and delayed recall, RBC folate status, depression tested by HDRS, advert events.
De La Fourniere 1997	Setting: community dwelling inpatient, France. Sex: 3M, 8F. Age: mean (range): 84 (78, 89) Nutrient status: serum B12 $\leq$ 240 pg/ml, normal folate Mental status: Moderate severity AD, MMSE 11-23	(a) Vitamin B12 1000mg intramuscular injection daily during 5 days, then once monthly for 5 months. (b) Double-blind placebo for 5 months. Allocation: (a) 6, (b) 5.	Follow up: 5 months. Outcomes: ADAS-Cog.

Study	Participants	Intervention	Outcomes
Fioravanti 1997	Setting: volunteers who had complains in loosing memory, Italy. Sex: 5M, 25F. Age: mean (SD): (a) 80.25 (5.78), (b) 80.21 (5.45). Nutrient status: Serum folate < 3ng/ml. Mental status: very mild to moderate severity of cognitive decline, no dementia.	(a) Folic acid 15mg orally daily for 60 days. (b) Placebo for 60 days Allocation: (a) 16, (b) 14.	Follow up: 60 days. Outcomes: Randt memory test.
Kwok 1998	Setting: hospital medical outpatient clinics or wards, Hong Kong. Sex: 1M, 51F. Age: mean (SD) years: (a) 76.6 (6.8), (b) 77.4 (6.4). Nutrient status: majority vegetarians, serum B12 <120 pmol/l. Mental status: 10 dementia, (a) 7, (b) 3. MMSE: mean (SD): (a) 22.2 (4.7), (b) 23.8 (4.7).	(a) Vitamin B12 1mg intra muscular injection 3 doses in first week, then 1 dose weekly for three weeks, then 1 dose monthly for 2-5 m. (b) No intervention for 2-5 m. Allocation: (a) 24, (b) 28. % Dropout: (a) 4.2%, (b) 3.6%.	Follow up: 3-6 months 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.
Bryan 2002	Setting: community healthy volunteers, Australia. Sex: 75F. Age: mean years: 74.08 (5.75). Nutrient status: sufficient vitamin B consumption (measured by food frequency questionnaire).	(a) Vitamin B6 75mg orally daily for 35d. (b) Vitamin B12 15µg orally daily for 35d. (c) Folate 750µg orally daily for 35d. (d) Double-blind placebo (Ca, Mg, etc) for 35d.	Follow up: 35d 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 & excluded letter); CESD.
Seal 2002	Setting: two geriatric hospitals, Australia. Sex: 14M, 17F. Age: mean years: (a) 84.9, (b) (82.0), (c) (77.6). Nutrient status: Serum vitamin B12 100-150 pmol/l. Mental status: 1/3 dementia MMSE: mean (SD): (a) 15.4 (7.8), (b) 19.6 (6.3), (c) 19.7 (5.3).	(a) Vitamin B12 10µg orally daily for 4 weeks. (b) Vitamin B12 50µg orally daily for 4 weeks. (c) Double-blind placebo for 4 weeks. Allocation: (a) 10, (b) 10, (c) 11 % Dropout: (a) 0%, (b) 10%, (c) 27.3%.	Follow up: 4 weeks. Outcomes: MMSE, serum vitamin B12, plasma homocysteine, blood folate status.
Clarke 2003	Setting: recruited from hospital records, general practice registers, advertisement, UK. Age: mean: 75y Mental status: Dementia or mild cognitive impairment. MMSE: mean (SD): (a) 20.9 (3.9), (b) 20.1 (3.9)	(a) (b) 4 weeks placebo-controlled run-in. (a) Vitamin B12 1mg and folic acid 2mg orally daily for 12 weeks. (b) Double-blind placebo for 12 weeks. Allocation: (a) 74, (b) 75.	Follow up: 12 weeks. Outcomes: MMSE, TICS-M, plasma homocysteine.

Study	Participants	Intervention	Outcomes
Sommer 2003	Setting: community volunteer, USA. Sex: 4M, 3F (completed study) Age: mean: (a) 76.3, (b) 77.3. Nutrient status: serum folate 2-5mcg/l, RBC folate 127-452mcg/l, B12>200ng/l. Mental status: dementia of various types and severity.	(a) Folic acid 20mg orally daily for 10 weeks. (b) Double blind placebo for 10 weeks. Allocation: (a) 6, (b) 5. % Dropout: (a) 17%, (b) 60%	Follow up: 10 weeks. 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.
Lewerin 2005	Setting: community, Sweden. Sex: 78M, 117 F Age: mean (SD): (a) 75.7 (4.7), (b) 75.6 (4.0).	(a) Vitamin B6 3mg, vitamin B12 500µg, and folic acid 800µg, orally daily for 4 months. (b) Double-blind placebo for 4 months. Allocation: (a) 126, (b) 69. % Dropout: (a) 13%, (b) 16%.	Follow up: 4 months. Outcomes: digit span backward/forward, identical forms, Wechsler memory scales: visual reproduction; synonyms, block design, digit symbol, Thurstone's picture memory test, figure classification.
Scott 2005	Setting: 2-centre, hospital based, UK. 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). Mental status: mild cognitive impairment Physical status: ischemic vascular disease	(a) (b) (c) (d) (e) (f) (g) (h) 2-4 weeks placebo run in (a) Folic acid 2.5mg and vitamin B12 500ug orally daily for 12 weeks. (b) Riboflavin 25mg orally daily for 12 weeks. (c) Vitamin B6 25mg orally daily for 12 weeks. (d) Folic acid 2.5mg, vitamin B12 500ug, and riboflavin 25mg orally daily for 12 weeks. (e) Folic acid 2.5mg, vitamin B12 500ug, and vitamin B6 25mg orally daily for 12 weeks. (f) Riboflavin 25mg and vitamin B6 25mg orally daily for 12 weeks. (g) Folic acid 0.5mg, vitamin B12 500ug, riboflavin 25mg, and vitamin B6 25mg orally daily for 12 weeks. (h) Placebo orally daily for 12 weeks. Allocation: (a) 23, (b) 23, (c) 23, (d) 23, (e) 23, (f) 23, (g) 23, (h) 24.	Follow up: 12 weeks. Outcomes: letter-digit coding test, telephone interview of cognitive status; folate, vitamin B12, riboflavin, vitamin B6, and homocysteine status.
Eussen 2006	Setting: free-living or care house –living older persons Sex: 46M, 149F Age: mean (SD): (a) 82 (5), (b) 83 (6), (c) 82 (5) Nutrient status: serum vitamin B12 100-300 pmol/l (mild deficiency) Mental status: MMSE ≥ 19; 14% cognitive impaired (MMSE 19-24)	(a) (b) (c) 2 weeks placebo run-in (a) Vitamin B12 1000µg for 24 weeks. (b) Vitamin B12 1000µg, folic acid 400µg for 24 weeks. (c) Double-blind placebo for 24 weeks. Allocation: (a) 64, (b) 66, (c) 65 % Dropouts: (a) 16%, (b) 23%, (c) 12%	Follow up: 24 weeks. 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.

Study	Participants	Intervention	Outcomes
McMahon 2006	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 ≥ 13 umol/l MMSE: mean (SD): (a) 29.2 (1.0), (b) 29.2 (1.0)	(a) Folate 1000ug, vitamin B12 500µg, 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.	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.

1IU vitamin E, 0.292 mg; AD, Alzheimer's Disease; ADAS-cog, Cognitive portion of the Alzheimer's Disease Assessment Scale; CERAD, Consortium to establish a registry for Alzheimer's Disease; CESD, Center for Epidemiological Studies Depression Scale; DAT, Dementia Alzheimer's Type; HDRS, Hamilton Depression Rating Scale; IQ, Intelligence Quotient; MMSE, Mini-Mental State Examination; PLP, pyridoxal –5'-phosphate; RAVLT – Rey-Auditory Verbal Learning Tests; RBC, Red Blood Cell; RVM test, Rey's Verbal Memory test; SD, Standard Deviation; TICS-M, Telephone Interview Cognition Scales Modified; WAIS, Wechsler Adult Intelligence Scale;

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 2. Characteristics of included trials: Antioxidant vitamins.

Study	Participants	Intervention	Outcomes
Sano 1997	Setting: USA. Sex: 58M, 111F. Age: mean (SD): (a) 73.4 (7.8), (b) 73.5 (8.3). Mental status: moderate severity of probable AD MMSE: mean (SD): (a) 11.3 (5.7), (b) 13.3 (4.9).	(a) Vitamin E 2000 IU for 2 years. (b) Double-blind placebo for 2 years. Allocation: (a) 84, (b) 85. % Dropout: (a) 5%, (b) 7%.	Follow up: 2 years. Outcomes: MMSE, ADAS- Cog, quality of life: dependence scale, behavior rating scale for dementia, institulization, adverse events.
Smith 1999	Setting: volunteers recruited by advertisement, UK. Sex: 95M, 110F. Age: mean: (a) 66.8, (b) 66.9.	(a) (b) 4 weeks placebo run-in (a) β-carotene 12mg, α-tocopherol 400mg and ascorbic acid 500 mg orally daily for 12 months. (b) Double-blind placebo for 12 months. Allocation: (a) 93, (b) 92. % Dropout: (a) 2.1%, (b) 16.4%.	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.
Clarke 2003	Setting: recruited from hospital records, general practice registers, advertisement, England. Age: mean: 75y Mental status: Dementia or mild cognitive impairment. MMSE: mean (SD): (a) 20.2 (3.8), (b) 20.8 (3.9)	(a) (b) 4 weeks placebo-controlled run-in. (a) Vitamin C 200mg and E 500mg orally daily for 12 weeks. (b) Double-blind placebo for 12 weeks. Allocation: (a) 75, (b) 74.	Follow up: 12 weeks. Outcomes: MMSE, TICS-M, plasma homocysteine.
Petersen, 2005	Setting: community, USA Age: mean (SD): (a) 72.8 (7.3), (b) 72.9 (7.6) Mental status: amnestic subtype of mild cognitive impairment. MMSE: mean (SD): (a) 27.20 (1.9), (b) 27.35 (1.8)	(a) Vitamin E 1000IU (671mg) daily, then 2000IU after six weeks for 3 years. (b) Placebo for 3 years. Allocation: (a) 257, (b) 259. % Dropout: (a) 28%, (b)26%	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.

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.

Study	Participants	Intervention	Outcomes
Terano 1999	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).	(a) Docosahexaenoic acid (DHA) 0.72g orally daily for 1 year. (b) No intervention for 1 year. Allocation: (a) 10, (b) 10.	Follow up: 1 year. Outcomes: MMSE, HDRS-R, serum fatty acid composition.

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.

Study	Participants	Intervention	Outcomes
Cockle 2000	Setting: healthy volunteers, Switzerland. Sex: 51M, 88F Age: mean (SD): (a) 70.7 (5.6), (b) 70.2 (5.4).	(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.	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, C status (by gender only).
De Jong 2001	Setting: freeliving frail elderly from health center, BMI<=25 or had recent weight loss, the Netherlands. Sex: 21M, 45F. Age: mean (SD): (a) 78.8 (4.8), (b) 79.0 (7.2).	(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).	Follow up: 17 weeks. Outcomes: Block-transfer Test, Reaction Time test, plasma homocysteine, folate, vitamin B6, B12 and RBC folate status.
McNeill 2007	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).	(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%.	Follow up: 1 year. Outcomes: digital span forward, Wechsler Memory Scale : Verbal Fluency (initial letter), risk of nurient deficiencies.

RDA, Recommended Daily Allowance; SD, Standard Deviation;

Table 5. Quality assessment of included trials

Study	Allocation concealment[1]	Group comparable at entry[2]	Participants blinding[3]	Treatment provider blinding [3]	Assessor Blinding[3]	Identical care programs[4]	Withdraws[5]	Entry criteria defined[6]	Intervention defined[6]	Duration[7]	Total score
Bryan *et al.*, 2002	2	2	2	2	0	0	0	2	2	1	15
Clarke *et al.*, 2003	2	0	2	2	2	0	1	2	2	1	14
Cockle *et al.*, 2000	1	2	1	1	0	0	1	2	2	2	14
de La Fourniere *et al.*, 1997	1	0	1	1	0	0	1	2	2	1	10
de Jong *et al.*, 2001	1	2	0	0	0	0	1	2	2	1	10
Deijen *et al.*, 1992	1	2	2	1	0	0	1	2	2	1	13
Eussen *et al.*, 2006	1	2	2	1	0	0	1	2	2	2	13
Fioravanti *et al.*, 1997	1	2	1	1	0	0	1	2	2	1	11
Kwok *et al.*, 1998	0	1	0	0	0	0	0	1	2	1	7
Lewerin *et al.*, 2005	1	2	1	1	0	0	1	1	2	1	11
McMahon *et al.*, 2006	1	2	2	1	0	0	1	2	2	2	13
McNeill *et al.*, 2007	2	2	2	2	0	0	2	2	2	2	18
Meador *et al.*, 1993	1	2	1	1	0	0	0	2	2	1	11
Nolan *et al.*, 1991	1	2	2	2	0	0	1	2	2	2	16
Passeri *et al.*, 1993	1	2	1	1	0	0	1	2	2	1	11
Petersen *et al.*, 2005	1	2	1	1	0	0	2	2	2	2	13
Sano *et al.*, 1997	1	2	1	1	0	0	2	2	2	2	13
Scott *et al.*, 2005	2	2	2	1	0	0	0	2	2	1	12
Seal *et al.*, 2002	1	2	2	2	0	0	1	2	2	1	15
Smith *et al.*, 1999	1	2	1	1	0	0	1	2	2	2	13
Sommer *et al.*, 2003	1	1	1	1	0	0	1	2	1	1	9
Terano *et al.*, 1999	1	2	0	0	0	1	0	1	1	2	9

[1]2 = method did not allow disclosure of assignment, 1 = chance of disclosure of assignment or mentioned concealment but not adjusted for, 0 = quasi-randomised

[2]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]2 = effective action taken to blind people, 1 = small or moderate chance of unblinding people, 0 = not mentioned (unless double-blind), or not done

[4]2 = care programes 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]2 = 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]2 = clearly defined, 1 = inadequately defined, 0 = poorly or not defined

[7]2 = optimal duration of surveillance (over 6 months), 1 = adequate duration of surveillance (one up to six months), 0 = not defined, or not adequate.

Table 6. Changes in cognitive abilities by supplementation compared with control group, with details of studies providing data

Global cognition		*Attention and Concentration*		*Recognition*	
MMSE (Nolan, 1991)	→	Form perception: cognitrone (Deijen, 1992)	→	10-item word list recognition (Nolan, 1991)	→
ADAS-Cog (Meador, 1993)	↑	Randt memory test: attention efficiency (Fioravanti, 1997)	+ S	Associate recognition task (Deijen, 1992)	→
MMSE (Meador, 1993)	↑	Categoric search task: accuracy (Smith, 1999)	→	Delayed recognition memory task (Smith, 1999)	→
ADAS-Cog (De La Fourniere, 1997)	→	Focused attention task: accuracy (Smith, 1999)	→	Word scan task: male, female (Cockle, 2000)	→
MMSE (Sano, 1997)	→	Repeated-digits vigillance task: total hit rate (Smith, 1999)	→	RAVLT recognition (Bryan, 2002)	→
ADAS-Cog (Sano, 1997)	→			15 word learning, recognition (Eussen, 2006)	→
MMSE (Kwok, 1998)	→				
Hasegowa's dementia rating scale (Terano, 1999)	+S	*Long term memory*		*Verbal fluency*	
MMSE (Terano, 1999)	+S	10-item word list delayed recall (Nolan, 1991)	→	Verbal fluency: categories (Nolan, 1991)	→
MMSE (Seal, 2002)	→	Long-term memory storage (Deijen, 1992)	↑	Verbal fluency: excluded letter (Bryan, 2002)	→
MMSE (Clarke, 2003) (B12 + folic acid)	→	Visual memory task (Deijen, 1992)	→	Verbal fluency: initial letter (Bryan, 2002)	+S
MMSE (Clarke, 2003) (vitamin C + vitamin E)	→	Rey's verbal memory: long-term (Passeri, 1993)	→	Controlled oral word association test (Sommer, 2003)	→
TICS-M (Clarke, 2003)	→	Randt memory test: delayed recall (Fioravanti, 1997)	+S	Verbal fluency: animals, letter (Eussen, 2006)	→
ADAS-Cog (Petersen, 2005)	→	RAVLT delayed recall, list 6 (Bryan, 2002)	→	Controlled oral word association test (McMahon, 2006)	→
Global clinical dementia rating (Petersen, 2005)	→	Thurstone's picture memory task (Lewerin, 2005)	→	Verbal fluency: categories (McMahon, 2006)	→
The global deterioration scale (Petersen, 2005)	→	15 word learning, delayed recall (Eussen, 2006)	→	Verbal fluency: initial letter (McNeill, 2007)	→
TICS-M (Scott, 2005)	→	Complex figure of Rey, delayed recall (Eussen, 2006)	→		
MMSE (McMahon, 2006)	→	RAVLT delayed recall, list 4 (McMahon, 2006)	→		
Short term memory		*Processing speed*		*Verbal ability*	
10-item word list learning test (Nolan, 1991)	→	Randt memory task: encoding (Fioravanti, 1997)	+S	WAIS-R: similarities (Kwok, 1998)	→
Associate learning task (Deijen, 1992)	→	Motor function scale: oral motor (Kwok, 1998)	-S	Spot the word (Bryan, 2002)	→
Sperling whole report task (Deijen, 1992)	→	Motor function scale: drawing (Kwok, 1998)	→	WAIS-III: vocabulary (Bryan, 2002)	→
Rey's verbal memory: short term (Passeri, 1993)	+S	Motor function scale: fine motor (Kwok, 1998)	↓	WAIS-R: information, vocabulary, similarities (Sommer, 2003)	→
Randt memory test: acquisition and recall (Fioravanti, 1997)	+S	Motor function scale: kinestesia-based movement (Kwok, 1998)	↓	Synonyms (Lewerin, 2005)	-S
Randt memory test: memory index (Fioravanti, 1997)	+S	Motor function scale: spatial movement (Kwok, 1998)	→	WAIS: similarities (McMahon, 2006)	→
Digit span test (Kwok, 1998)	→	Categoric search task: response time (Smith, 1999)	→		
WMS-R: logical memory (Kwok, 1998)	→	Focused attention task: response time (Smith, 1999)	→	*Executive function*	
WMS-R: visual reproduction (Kwok, 1998)	→	Repeated-digits vigillance task: total mean reaction time (Smith, 1999)	→	Construction praxis test (Nolan, 1991)	→
Free recall task: number of words correctly recalled (Smith, 1999)	→	Simple reaction time task (Smith, 1999)	→	Vienna determination unit (Deijen, 1992)	→
Sternberg memory scanning task: male, female (Cockle, 2000)	→	Choice reaction time: motor reaction time (Cockle, 2000)	→	WAIS-R: block design (Kwok, 1998)	→
Digital span backward (Bryan, 2002)	→	Choice reaction time: recognition reaction time (Cockle, 2000)	→	Logical reasoning task: number of correctly answered in 3min (Smith, 1999)	→
Letter number sequencing (Bryan, 2002)	→	Choice reaction time: total reaction time (Cockle, 2000)	+S	Critical flicker fusion: male, female (Cockle, 2000)	→
RAVLT immediate recall: list 1-5 (Bryan, 2002)	→	Block transfer test (De Jong, 2001)	→	Stroop (Bryan, 2002)	→
Benton visual retention test (Sommer, 2003)	→	Reaction time (De Jong, 2001)	→	Trial making test: A/B (Bryan, 2002)	→
WMS: Associate learning (Sommer, 2003)	-S	Boxes test (Bryan, 2002)	→	Uses of objects (Bryan, 2002)	→
WMS: logical memory (Sommer, 2003)	→	Digit symbol coding (Bryan, 2002)	→	Trial making test: A/B (Sommer, 2003)	↓
Digit span backward (Eussen, 2006)	-S	Symbol search (Bryan, 2002)	→	Block design (Lewerin, 2005)	→
Digital span backward (Lewerin, 2005)	→	Finger tapping test (Sommer, 2003)	→	Figure classification (Lewerin, 2005)	→
Digit span forward (Lewerin, 2005)	→	Digit symbol (Lewerin, 2005)	→	Motor planning (Eussen, 2006)	→
WMS: visual reproduction (Lewerin, 2005)	→	Identical forms (Lewerin, 2005)	-S	Stroop test (Eussen, 2006)	→
15 word learning, immediate recall (Eussen, 2006)	→	Letter-digit coding test (Scott, 2005)	→	Trial making test (Eussen, 2006)	→
Complex figure of Rey, immediate recall (Eussen, 2006)	→	Finger tapping (Eussen, 2006)	→	Raven's progressive matrices (McMahon, 2006)	→
Digit span forward (Eussen, 2006)	→	Motor planning (Eussen, 2006)	→	Trial making test (McMahon, 2006)	-S
RAVLT: list 1-5 (McMahon, 2006)	→				
Wechsler paragraph recall test (McMahon, 2006)	→	*Naming*			
Digit span forward (McNeill, 2007)	→	Short version of Boston naming test (Nolan, 1991)	→		
		Boston naming test (Sommer, 2003)	→		

+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

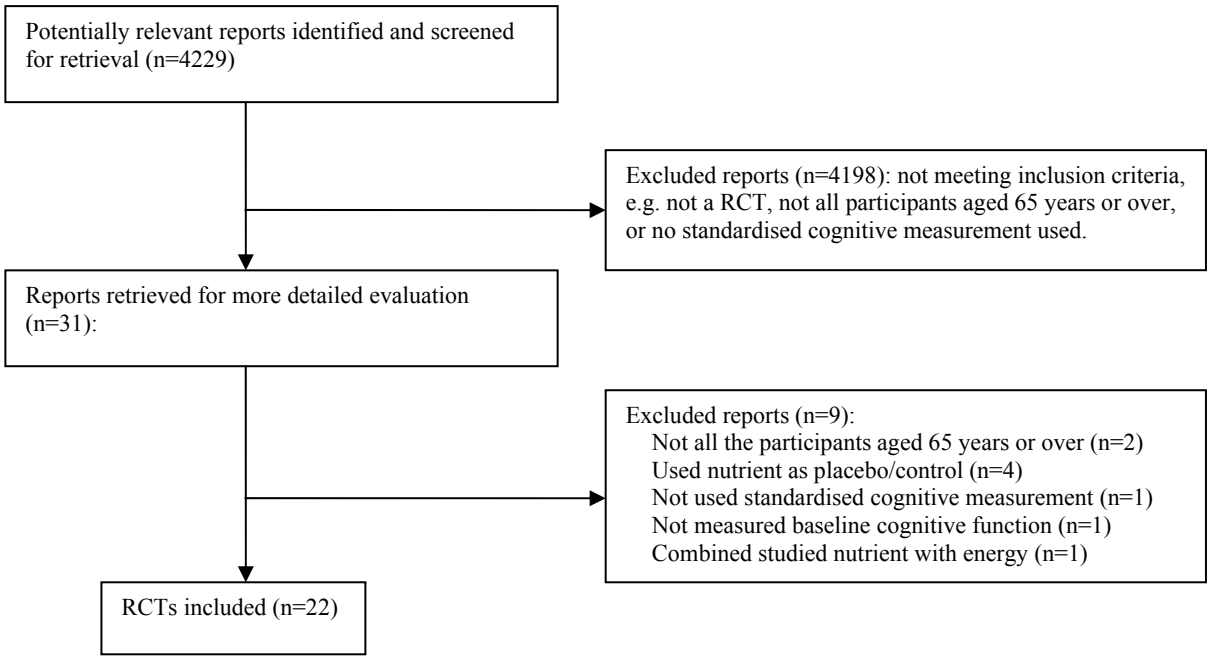

Figure 2 Effect of dietary supplements on global cognition measured by mini-Mental State Examination (MMSE)