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Vitamin E for Alzheimer's dementia and mild cognitive impairment.
Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD002854.
DOI: 10.1002/14651858.CD002854.pub3.

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[Intervention Review]

Vitamin E for Alzheimer's dementia and mild cognitive impairment

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: Edited (conclusions changed), published in Issue 11, 2012.
Review content assessed as up-to-date: 25 June 2012.

Citation: Farina N, Isaac MGEKN, Clark AR, Rusted J, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD002854. DOI: 10.1002/14651858.CD002854.pub3.

ABSTRACT

Background

Vitamin E is a dietary compound that functions as an antioxidant scavenging toxic free radicals. Evidence that free radicals may contribute to the pathological processes of cognitive impairment including Alzheimer's disease has led to interest in the use of vitamin E in the treatment of mild cognitive impairment (MCI) and Alzheimer's dementia (AD).

Objectives

To assess the efficacy of vitamin E in the treatment of AD and prevention of progression of MCI to dementia.

Search methods

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (ALOIS), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS as well as many trials databases and grey literature sources were searched on 25 June 2012 using the terms: "Vitamin E", vitamin-E, alpha-tocopherol.

Selection criteria

All unconfounded, double-blind, randomised trials in which treatment with vitamin E at any dose was compared with placebo for patients with AD and MCI.

Data collection and analysis

Two review authors independently applied the selection criteria and assessed study quality and extracted and analysed the data. For each outcome measure data were sought on every patient randomised. Where such data were not available an analysis of patients who completed treatment was conducted. It was not possible to pool data between studies owing to a lack of comparable outcome measure.

Main results

Only three studies met the inclusion criteria: two in an AD population and one in an MCI population. In the first of the AD studies (Sano 1996) the authors reported some benefit from vitamin E (2000 IU/day) with fewer participants reaching an end point of death, institutionalisation, change to a Clinical Dementia Rating (CDR) of three, or loss of two basic activities of daily living within two years. Of patients completing treatment, 58% (45/77) on vitamin E compared with 74% (58/78) on placebo reached one of the end

points (odds ratio (OR) 0.49; 95% confidence interval (CI) 0.25 to 0.96). The second AD treatment study (Lloret 2009) explored the effects of vitamin E (800 IU/day) on cognitive progression in relation to oxidative stress levels. Patients whose oxidative stress markers were lowered by vitamin E showed no significant difference in the percentage change in Mini-Mental State Examination (MMSE) score, between baseline and six months, compared to the placebo group. The primary aim of the MCI study (Petersen 2005) was to investigate the effect of vitamin E (2000 IU/day) on the time to progression from MCI to possible or probable AD. A total of 214 of the 769 participants progressed to dementia, with 212 being classified as having possible or probable AD. There was no significant difference in the probability of progression from MCI to AD between the vitamin E group and the placebo group (hazard ratio 1.02; 95% CI 0.74 to 1.41; P = 0.91).

Authors' conclusions

No convincing evidence that vitamin E is of benefit in the treatment of AD or MCI. Future trials assessing vitamin E treatment in AD should not be restricted to alpha-tocopherol.

PLAIN LANGUAGE SUMMARY

Vitamin E should not be used for the treatment of mild cognitive impairment (MCI) and Alzheimer's dementia (AD)

Vitamin E is a dietary compound that has strong antioxidant properties. Vitamin E has been shown to act on some toxic chemicals that may contribute to the damage seen in AD. Many laboratory, animal and epidemiological studies have pointed towards a possible beneficial role for vitamin E in the prevention and treatment of AD. However, to date very limited evidence exists in humans to support the routine use of vitamin E. Further, in recent years evidence has come to light implicating vitamin E with potentially serious side effects and even increased mortality. In this review three studies were identified and these demonstrated no or limited benefit for vitamin E in MCI and AD. Therefore, vitamin E should not be used in the treatment of MCI or AD. More trials are still needed but these should include different forms of vitamin E.

BACKGROUND

Description of the condition

Alzheimer's dementia (AD) is a progressive neurodegenerative disease resulting in deficits in multiple cognitive domains, including memory, language and executive functioning, as well as a variety of emotional and behavioural symptoms. This subsequently leads to progressive functional impairment. AD causes huge emotional and financial burden to patients, carers, and health and social care systems. Current treatments for AD have limited efficacy and cannot prevent progression of the condition. It is projected that one in 85 people will suffer from the disease by 2050, equating to a worldwide prevalence of 106.2 million cases (Brookmeyer 2007). Mild cognitive impairment (MCI) is a condition that results in cognitive deficits but does not meet the diagnostic criteria for dementia. There has been much controversy over the status of MCI; whether it is a discrete disorder, a continuation of normal ageing or precursor to dementia. Regardless, what is known is that those with MCI are at a greater risk of developing dementia (Ganguli 2011). It is currently estimated that between 10% and 20% of people over the age of 65 years suffer from MCI (Petersen 2011), which is expected to increase along with the increasing prevalence rates of AD.

Description of the intervention

Vitamin E is a generic term for a group of eight naturally occurring, fat-soluble chemical derivatives of tocopherol and tocotrienol. Until very recently, alpha-tocopherol was the most commonly studied compound. Vitamin E occurs in a variety of food substances including vegetable oils and fats, and in nuts and seeds, such as almonds and sunflower seeds. However, alpha-tocopherol has been the sole form of supplements used in clinical trials in AD. According to the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies (US) the recommended daily allowance for men and women over 14 years of age is 22.4 IU (15 mg of alpha-tocopherol) (National Academy of Sciences 2000).

Vitamin E functions biologically as a scavenger of different free

radicals by working as an antioxidant (Uneri 2006). Oxygen free radicals contain oxygen atoms with unpaired electrons and are highly reactive, damaging proteins, deoxyribonucleic acid (DNA) and cell membranes unless rapidly 'quenched' by antioxidants. They are produced as by-products of the body's metabolism as well as by radiation. As vitamin E is lipophilic, it is able to protect cell membranes and plasma lipoproteins from peroxyl radicals, which react with vitamin E preferentially (Traber 2011). In particular vitamin E is thought to inhibit the process of lipid peroxidation, which damages the polyunsaturated fatty acids essential to the integrity of cell membranes. Vitamin E activities in protecting against the deleterious effects of free radicals may be measured indirectly by assessing the state of the antioxidant-oxidant system. Endogenous antioxidants such as glutathione provide an indication of the antioxidant status while the oxidised form of glutathione, glutathione disulphide (GSSG), and malondialdehyde (MDA) may provide an indication of the oxidative stress status and in particular lipid peroxidation.

High doses of vitamin E (over 3000 IU/day) are considered toxic, and have been implicated in a variety of symptoms including fatigue, gastrointestinal cramps and diarrhoea. Further, there is an increasing body of evidence that vitamin E supplementation can cause adverse effects, even at therapeutic doses. For example, vitamin E increases bleeding tendency and can potentiate the effect of aspirin (Steiner 1995). One meta-analysis found that vitamin E supplementation, while reducing risk of ischaemic stroke by 10%, increased the risk of haemorrhagic stroke by 22% (Schurks 2010). Evidence from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) suggests that daily supplementation with 400 IU vitamin E in healthy men may significantly increase the risk of prostate cancer (Klein 2011) and there is evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial that vitamin E supplementation increases the risk of heart failure and hospitalisation for heart failure in patients over 55 years of age with diabetes mellitus and vascular disease (Lonn 2005). Miller 2005 carried out a meta-analysis of 19 clinical trials testing vitamin E alone or in combination with other supplements. The median dose of vitamin E in these trials was 400 IU/day although the maximum dose range was up to 2000 IU/day. The authors reported a statistically significant dose-dependent relationship between vitamin E intake and all-cause mortality. One Cochrane meta-analysis also found that vitamin E given singly or combined significantly increased mortality in 26 trials (risk ratio (RR) 1.04) (Bjelakovic 2010).

How the intervention might work

As summarised by Grundman 2000, there are both theoretical reasons and empirical findings to suggest that free radical damage may be one of the mechanisms causing neuronal degeneration in a range of conditions including ageing, MCI and AD. Many studies have found evidence of increased level of oxidative damage to neurons and mitochondrial DNA in AD and MCI (Butterfield 2002; Hensley 1995; Mecocci 1994; Mecocci 2004; Marcus 1998; Wang 2005; Wang 2006). Antioxidants, including vitamin E, improve cognitive functioning of aged rodents (Socci 1995), and protect against the effects of brain ischaemia (Hara 1990) and of some neurotoxins (Wortwein 1994).Transgenic mice over-expressing the amyloid precursor protein (APP), implicated in AD, show accelerated age-associated brain degeneration (Hsiao 1995). Vitamin E can delay this deterioration (Behl 1992; Koppal 1998; Zhou 1996) and decrease oxidative DNA damage (Boothby 2005).

Central nervous tissue contains a high proportion of fatty material (lipid), and since vitamin E is fat-soluble it can readily enter the brain (Vatassery 1988). In humans, there have been reports of an association between low blood levels of vitamin E and impaired cognitive function (Ichitani 1992; Perrig 1997). However, the studies of plasma and serum biomarkers including vitamin E as an antioxidant are not conclusive or consistent for the treatment of cognitive impairment (Irizarry 2004). Average levels of Vitamin E in the blood and cerebrospinal fluid of patients with AD were reported to be lower than normal in several reports (Jeandel 1989; Jimenez-Jimenez 1997; Polidori 2002; Tohgi 1994; Zaman 1992) though not in all (Ahlskog 1995). Lower levels of both forms of vitamin E - tocotrienols and tocopherols - have been observed in plasma of AD and MCI patients (Mangialasche 2012). However, reported lower levels of vitamin E in AD may be due in part to an overall decreased general dietary intake especially as the disease advances (Tabet 2001; Tabet 2002). Hence, lower vitamin E blood levels in AD may be a consequence of the disease rather than a cause of it.

Results from clinical trials of vitamin E in non-AD neurodegenerative disorders have not been promising. For example, neither patients with Parkinson's disease (Parkinson's SG 1993, Pham 2005) nor Huntington's disease (Peyser 1995) have shown a significant overall effect for vitamin E. In this review we focus specifically on the role of vitamin E in the treatment of AD and MCI.

OBJECTIVES

To assess the efficacy of vitamin E in the treatment of AD and MCI.

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded, randomised, double-blind trials identified in the search in which vitamin E was compared with placebo in the treatment of patients with MCI or AD, or both, were studied. Trials in which allocations to treatment were not randomised, or in which treatment allocations were not concealed were excluded.

Types of participants

Participants for treatment of AD in included trials were diagnosed with probable AD according to internationally accepted diagnostic criteria including NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann 1984), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA 1994) and International Statistical Classification of Diseases and Related Health Problem, Tenth Revision (ICD 10). Participants in trials for prevention of progression to AD should have MCI. In the absence of consensus on accepted criteria, this could be defined either according to published criteria such as those by Petersen 2005, or any other criterion with face validity.

Types of interventions

Any dosage of vitamin E or any of its constituent tocopherols or tocotrienols. Co-administration of another drug with vitamin E was permitted if the same drug was also taken by the placebo group.

Types of outcome measures

All outcome measures had to derive from validated, published scales.

Primary outcomes

- Development of, or time to development of, possible AD from MCI.
- Cognitive function.
- Adverse events.
- Death.

Secondary outcomes

- Global measure of severity and deterioration.
- Behavioural disturbance.
- Mood.
- Activities of daily living.
- Carer burden.
- Quality of life.
- Permanent physical disability.
- Institutionalisation.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 26 June 2012. The search terms used were: "Vitamin E", vitamin-E, alpha-tocopherol.

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
3. quarterly searches of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

Data collection and analysis

Selection of studies

Three review authors (NF, MI, and NT) independently examined the title and abstract of the papers identified by the search and selected them for their relevance to the review. The selected citations were retrieved. All disagreements concerning inclusion were resolved by discussion. Inclusion criteria were clearly defined.

Data extraction and management

Data were extracted by one review author (NT for Sano study, MI for Petersen study, and NF for Lloret study). An attempt was made to collect the following data:

- report - author, year and source of publication;
- study - study setting;
- patients - demographics, diagnostic criteria for AD or MCI, exclusion criteria, other concomitant medical conditions or medications that may affect cognition;
- research design and features - sampling mechanism, treatment assignment mechanism, blinding, drop-out rates, length of follow-up, pertinent design features (e.g. cross-over design);
- intervention - type, duration, dose, timing, mode of delivery;
- outcome measures;
- results - number of patients randomised, outcome data.

For each outcome measure, data were sought on every patient randomised. Intention-to-treat data were preferred. If these were not available, data were extracted on patients who completed treatment. Data were not extracted for any non-randomised titration periods or any open-label follow-on phases.

For continuous data the means, standard deviation (SD) and number of participants in each treatment group at each time point were extracted. Change from baseline data were extracted if end-point data were unavailable.

For binary data, the data extracted was the number of patients with each outcome in each treatment group at each time point.

For ordinal data, there were two possible approaches. If ordinal scale data appeared to be approximately normally distributed or if the analysis that the investigators performed suggested that parametric tests were appropriate, then the outcome measures were treated as continuous data. The second approach, which may not exclude the first, was to concatenate into two categories that best represent the contrasting states of interest, and to treat the variable as binary.

For time-to-event data, a hazard ratio (HR) was sought.

Assessment of risk of bias in included studies

Risk of bias was assessed by NF and MI for each included study was assessed based upon the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following criteria were assessed:

- sequence generation;
- allocation concealment;
- blinding (participants);
- blinding (investigators);
- incomplete outcome reporting;
- selective outcome reporting.

For each study, a risk of bias rating ('Low risk', 'Unclear risk' or 'High risk') was given for each of the above criteria. Empirical research has shown that lack of adequate allocation concealment may be associated with bias. Trials with unclear concealment measures have been shown to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but less pronounced than inadequately concealed trials (Chalmers 1983; Schulz 1995). Thus trials were included if they conform to 'Low risk' or 'Unclear risk' allocation risk categories, while those falling into 'High risk' category were excluded.

Measures of treatment effect

For studies with continuous outcome measures, mean differences or standardised mean differences were calculated. For binary outcome measures odds ratio (OR) were calculated. For time-to-event outcome measures, HRs were calculated.

Unit of analysis issues

The participant was the unit of analysis. No cross-over studies were identified.

Dealing with missing data

An intention-to-treat analysis was carried out where possible. In cases where only completers' data were available the impact of the missing data on the findings was explored, where possible. A sensitivity analysis was carried out in one study (Petersen 2005) to investigate the impact of a high drop-out rate.

Assessment of heterogeneity

Owing to the significant clinical and methodological heterogeneity between studies, results were not synthesised and no statistical tests for heterogeneity were performed.

Assessment of reporting biases

There was an insufficient number of studies identified to make any quantitative assessment.

Data synthesis

It was not possible to synthesise and compare data across studies as there were no comparable outcome measures.

Subgroup analysis and investigation of heterogeneity

Although not specified in the protocol, data were extracted and reported for a subgroup analysis carried out in one included study. The subgroups were participants who did or did not show a decline in markers of oxidative stress in response to vitamin E treatment. This subgroup was considered important to include as a reduction

of oxidative stress is thought to be the mechanism by which vitamin E may affect cognition.

RESULTS

Description of studies

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

Only three trials met the inclusion criteria: Lloret 2009, Petersen 2005 and Sano 1996. Two (Lloret 2009; Sano 1996) were trials of alpha-tocopherol (vitamin E) for the treatment of AD and one (Petersen 2005) was a trial of alpha-tocopherol to delay progression from amnestic MCI to dementia.

Treatment of Alzheimer's dementia

The primary purpose of the first treatment study by Sano 1996 was to determine whether selegiline (a monoamine oxidase inhibitor), alpha-tocopherol (vitamin E) or a combination of the two agents would slow the clinical deterioration associated with AD. Both selegiline and vitamin E were tested using a factorial 2x2 design, with four groups: placebo, selegiline (10 mg total daily dose divided into two doses), vitamin E (2000 IU total daily dose divided into two doses) and selegiline (10 mg total daily dose divided into two doses) plus vitamin E (2000 IU total daily dose divided into two doses). A total of 341 subjects with a diagnosis of probable AD and with moderate severity (Clinical Dementia Rating (CDR) 2) (Berg 1988), were recruited from 23 centres in the US. For further details about the study refer to the Characteristics of included studies.

Assessments were conducted one month after enrolment and at three-monthly intervals for two years. The primary outcome was the survival time to any one of four end points; death, institutionalisation, change in severity of dementia to a CDR of three or loss of two basic activities of daily living. After the primary end point was reached, every effort was made to continue further assessment of the secondary outcomes if possible. The secondary outcomes were; the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen 1984), Mini-Mental State Examination (MMSE) (Folstein 1975), Blessed Dementia Scale (BDS) (Blessed 1968), function was also measured using the Dependence Scale (DS) (Stern 1994) and Behavior Rating Scale for Dementia (BRSD) (Tariot 1995). The primary analysis compared survival to end point for each of the three treatment groups in comparison with the placebo group, using Kaplan-Meier estimation and log-rank tests with no correction for other factors or variables, and the Cox proportional hazards model including covariates. A small number of patients did not complete to the primary end point (placebo 6/84, selegiline 4/87, vitamin E 8/85, selegiline plus vitamin E 5/85). The secondary outcomes were assessed at one month, and then every three months until two years.

The purpose of the second treatment study (Lloret 2009) was to explore the effects of vitamin E on AD progression and markers of oxidative stress. Vitamin E (800 IU) or placebo was given daily for six months. There were 57 participants diagnosed with probable AD. All AD participants were taking a cholinesterase inhibitor and were not on any other antioxidant medication. Assessments were conducted on the first day of enrolment and six months after. Oxidative stress was assessed in two ways. The first method used blood concentrations of the oxidised glutathione molecule, GSSG, with greater levels indicating greater oxidative stress. GSSG was also assessed as a ratio with the antioxidant molecule glutathione. Further the blood marker MDA was measured as a marker of lipid peroxidation, which is a strong indicator of oxidative damage. AD progression was measured by the Clock drawing test (Sunderland 1989), the BDS (Blessed 1968) and MMSE (Folstein 1975). For further details about the study refer to the Characteristics of included studies.

The primary analysis was to compare performance on the cognitive tasks in relation to the effects of vitamin E on oxidative stress. Vitamin E-treated participants were divided into responders and non-responders according to whether vitamin E was effective or not in reducing markers of oxidative stress. The responder, non-responder and placebo group means were compared using a Kruskal-Wallis test. Comparison between groups was also undertaken following removal of participants with cerebrovascular disease. To determine the effect of modifying oxidative stress on cognitive performance - the relationship between MMSE change and GSSG change in patients treated with vitamin E was assessed using Spearman's coefficient of correlation. The effects of vitamin E on oxidative stress markers were investigated using a Mann-Whitney test to compare GSSG and MDA values at the beginning of the study and the end of the study in both the placebo and active treatment conditions.

Prevention of progression of cognitive impairment

The primary purpose of the MCI study (Petersen 2005) was to determine whether treatment with vitamin E (2000 IU/day) or donepezil in subjects with the amnestic form of MCI decreased the conversion rate into AD. There were three treatment groups: vitamin E, donepezil and placebo. All participants were also taking a multivitamin. This review includes the vitamin E and the placebo groups only. Out of a total of 769 subjects enrolled from 69 sites in the US and Canada, 516 received either placebo or vitamin E intervention. The secondary outcomes were scores on various measures: the MMSE (Folstein 1975), ADAS-Cog (Rosen 1984), CDR (sum of boxes), the Alzheimer's Disease Assessment Scale Mild Cognitive Impairment Activities of Daily Living Scale, the Global Deterioration Scale, a neuropsychological battery, and adverse events. For further details about the study design refer to

the Characteristics of included studies.

The primary analysis was conducted according to an intention-to-treat principle to determine whether there was a significant reduction in time to progression to AD among subjects treated with either vitamin E or donepezil as compared with those given placebo. The Cox proportional-hazards model was used, and the baseline variables were included in the analysis as covariates. Two primary analyses were conducted, one comparing the vitamin E and placebo groups, which was the main interest of this review, and one comparing the donepezil and placebo groups. The Hochberg method (Hochberg 1988) was used to adjust the two P values for multiple comparisons. The Schoenfeld residuals test was used to test for non-proportional hazards (Schoenfeld 1982). A z test was used to compare estimated survival rates at various points on the Kaplan-Meier curves (at 6, 12, 18, 24 and 36 months). The Hochberg method was used to adjust the six P values for multiple comparisons. Subgroup analysis for apolipoprotein E4 (ApoE4) carriers was conducted using HRs derived from the Cox analysis. The secondary outcomes were examined with the use of covariance for the change in the scores without correction for multiple comparisons, and missing values were input with the use of a projection method appropriate for assessing responses among subjects with neurodegenerative diseases.

Risk of bias in included studies

Random sequence generation (selection bias)

We judged that all three studies had a low risk of bias.

Allocation (selection bias)

Concealment of participant allocation according to the randomisation sequence was unclear in the three studies as they did not clearly refer to how the ensured allocation concealment.

Blinding of participants and personnel (performance bias)

All studies had an unclear risk of bias as they did not report what steps were taken to ensure that participants and personnel remained blinded to treatment allocation.

Blinding of outcome assessment (detection bias)

Only the Petersen 2005 study reported evidence that assessors were blinded to the outcomes. There were unclear risks of bias in the Lloret 2009 and Sano 1996 studies as they did not refer to blinding during outcome assessment.

Incomplete outcome data (attrition bias)

Only Petersen 2005 investigated the impact of the drop-out. Sano 1996 reported the attrition rate but did not give reasons, and hence is judged as an unclear risk of bias. Lloret 2009 reported a very high attrition rates and did not give reasons, as such it was judged as a high risk of bias.

Selective reporting (reporting bias)

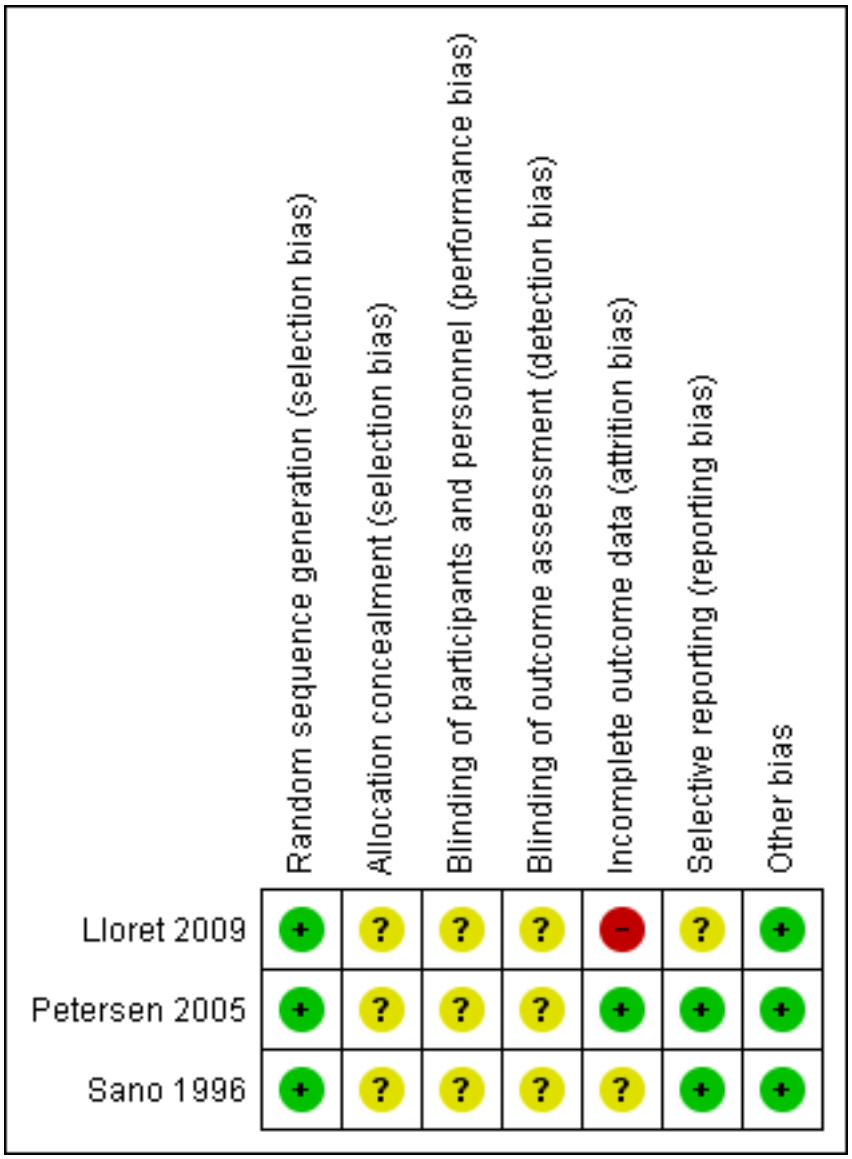
All studies reported outcomes stated in their protocol.

Other potential sources of bias

No other sources of bias were found.

See Figure 1 for the summary of the risk of bias.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

Treatment of Alzheimer's dementia

The treatment study (Sano 1996) had four treatment groups, but data from only two of the groups were evaluated. These were the groups receiving placebo only and vitamin E only. The selegiline and selegiline plus vitamin E groups were excluded because there was no placebo control for the vitamin E.

Sano 1996 reported the number in each outcome group who reached the primary end point within two years for the completers only. The analysis of data of those reaching end point showed benefit associated with vitamin E (58% (45/77) of patients in the vitamin E group reached end point compared with 74% (58/78) in the placebo group; OR 0.49; 95% confidence interval (CI) 0.25 to 0.96). Because the trial was limited in time, this analysis, comparing a count of events without taking into account the timing of events, should still be valid but is less precise than the survival analysis reported by Sano 1996. Using Kaplan-Meier estimation and log-rank testing in their primary analysis, Sano 1996 found no significant difference in survival time to one of the four end points between the vitamin E and placebo groups (RR 0.70; P = 0.08). However, the study groups differed in baseline MMSE scores and these were correlated with clinical course. The vitamin E group began with a mean MMSE of 11.3 (SD 5.7) and the placebo group with a mean of 13.3 (SD 4.9). When the analysis was repeated using the Cox proportional hazards model and controlling for baseline MMSE a significant difference favouring vitamin E emerged (RR 0.47; P = 0.001). No statistical analysis was performed on secondary outcome measures data as only mean change scores to the time point where a patient was last assessed were reported and patients had been assessed over varying and unidentified time spans.

Six patients from the placebo group and eight from the vitamin E group were lost to follow-up before reaching an end point, but there is no information on the time points at which these patients were lost. A total of 49 categories of adverse events were defined but the only results initially reported were for three categories, in which significant differences between one or more of the treatment groups and the placebo group were found. However, once the authors made adjustments for multiple comparisons no significant differences between groups were found.

Lloret 2009 divided participants treated with vitamin E into two groups depending on changes in oxidative stress markers with treatment. Those who showed a decrease in GSSG values of more than 10 nmol per mL of blood after six months of vitamin E treatment were termed 'responders' and those who did not were termed 'non-responders'. These groups had not been defined in advance of data collection. They reported 'completers' results only (33/57 randomised patients). The percentage change in performance from baseline to six months on the BDS, Clock drawing test and MMSE were then compared across responders (N = 9), non-responders (N = 10) and placebo-treated groups (N = 14). There was no significant difference reported between groups on the Clock drawing test or BDS. The MMSE score increased in the responder group but decreased in the placebo group and more so in the non-responders. A significant difference was reported between the two vitamin E-treated groups ($P < 0.05$). The responders did not differ significantly from the placebo-treated group. The decline in MMSE in the non-responders was significantly greater than in the placebo group ($P < 0.05$).

Lloret 2009 reported a negative correlation between change in MMSE score and change in blood levels of GSSG from baseline to six months; that is, there was a greater decline in cognitive performance in AD patients whose blood GSSG levels stayed higher (reflecting higher oxidative stress).

No data were presented with regards to the effects of vitamin E on cognitive measures in the treated group as a whole compared to the placebo group. Subgroups could not be combined as data were reported as statistical changes only and the data set was not made available.

MCI and the prevention of progression of cognitive impairment

The prevention study (Petersen 2005) had three treatment groups of people with MCI, but only data from the vitamin E and placebo groups were evaluated. The donepezil group was excluded.

The primary outcome was the time to the development of possible or probable AD. Petersen 2005 reported that over the three years of the trial, there was no significant difference in the probability of progression from MCI to AD on the basis of Cox analysis between the vitamin E group and placebo group (HR 1.02; 95% CI 0.74 to 1.41; P = 0.91). The 36-month analysis was followed by a pre-specified assessment of the treatment effects at each six-month evaluation point. This analysis showed that there was no significant difference between vitamin E and placebo groups on the primary outcome at any time point measured during the trial. A total of 38 subjects (out of 259) in the placebo group and 33 subjects (out of 257) in the vitamin E group had progression to AD in the first 12 months. By 36 months, the numbers of subjects with progression to AD did not differ, with 73 in the placebo group and 76 in the vitamin E group. Although subjects were assessed at 6, 12, 18, 24, 30 and 36 months, numbers were only reported for 12 and 36 months; for the remainder only changes from baseline were reported.

A total of 138 subjects discontinued treatment in the placebo group (N = 72) and the vitamin E group (N = 66). The leading

reasons for dropout were death, adverse events and withdrawal of consent. However, there was no information on the distribution of reasons for dropout across groups. The authors carried out sensitivity analysis and z-testing to assess the effect of missing data as a result of dropouts and concluded that the results of these analyses were non-significant.

Changes in cognitive function scores from baseline to each of the six-monthly time points were reported in both vitamin E and placebo groups. No significant increases in any cognitive domain scores were reported compared to baseline in the placebo group. There were a few differences compared to baseline in the vitamin E group and those that were seen (in the executive, language and overall cognitive scores) were confined to the first 18 months of the study. Specifically, executive function was significantly greater at six months compared to baseline in the vitamin E group ($P < 0.05$). Language scores were significantly greater compared to baseline in the vitamin E group at six months ($P < 0.05$), 12 months ($P < 0.05$) and 18 months ($P < 0.05$). Overall cognitive scores in the vitamin E group were significantly greater at six months compared to baseline ($P < 0.01$). No between-group comparisons were reported for the secondary outcomes.

DISCUSSION

Three studies met the inclusion criteria and were selected for this review. To our knowledge there are currently no relevant ongoing trials. Two studies (Lloret 2009; Sano 1996) assessed the efficacy of vitamin E in AD patients while one study (Petersen 2005) assessed vitamin E in MCI patients. A significant limitation of this review is that synthesis of data from the AD studies was not possible owing to different outcome measures. The primary outcome measures from the Lloret 2009 study were performance-based cognitive tasks. Conversely the primary outcome measure in the Sano 1996 study was reaching a series of clinical end points. It would not have been appropriate to pool data from the MCI study with those from the AD studies as the MCI study evaluated a distinct diagnostic entity.

There was no strong evidence that vitamin E when compared to placebo was efficacious in improving outcomes of AD. In the Sano 1996 study there was no significant difference between vitamin E and placebo group when using unadjusted data, although adjusted data presented showed a significant delay to the primary end point.

Lloret 2009 implemented very different outcome measures compared to Sano 1996, measuring changes in cognitive performance as opposed to an end point index. Performance change was compared between responders and non-responders (as determined by the degree of change in markers of oxidative stress, defined post hoc) and a placebo group. The Lloret 2009 study has opened a new research avenue for studying the response to vitamin E among different patient subgroups. We agree with Brewer 2010 and Lloret 2009 that future research should also include concomitant measurement of antioxidants and oxidative stress markers. However, the Lloret 2009 study itself needs to be considered exploratory in nature. The mechanisms that may explain why only a proportion of patients respond 'oxidatively' to the antioxidant vitamin E remains unknown. Another significant limitation is the small number of participants, which made the subsequent subgroup analysis less informative. A further limitation is the high drop-out rate reported. Notwithstanding the limitations of this study, in those patients where vitamin E did not reduce oxidative stress there was a paradoxical accelerated decline in cognitive abilities compared to placebo. Hence, additional caution is needed in the design of future clinical trials utilising vitamin E treatment.

Petersen 2005 found no difference in the probability of progression from MCI to AD between the vitamin E group and placebo group during the three years of the study. Therefore the investigators carried out a pre-specified assessment of the treatment effect at each six-month evaluation point. The analysis confirmed that there was no significant difference between the vitamin E and placebo groups at any time during the trial. Vitamin E was also shown to have very limited efficacy of improving cognitive outcomes in a few cognitive domains. All cognitive improvements dissipated after 18 months of treatment. Conclusions are necessarily limited because no between-group analysis was conducted.

Old age is associated with vitamin E deficiency (Dror 2011). However, there is a difference between addressing deficiency with adequate daily recommended levels and the use of high or very high doses of vitamin E. The latter is much more likely to produce significant side effects. High doses of alpha-tocopherol also have potential to induce enzymes involved in drug metabolism with an associated risk of serious interactions with some concomitant medication (Brigelius-Flohé 2007).

Vitamin E assessed in epidemiological studies in relation to cognition has consisted of the various naturally occurring forms (Engelhart 2002; Morris 2002; Morris 2005). These studies have generally reported a positive association between intake of vitamin E and cognition. Morris 2005 suggested that the combined intake of tocopherols is likely to be more important than alpha-tocopherol alone. This is further supported by Mangialasche 2010 who studied the relationship between cognitive impairment and the eight individual forms of vitamin E and concluded that any potential neuroprotective effect for vitamin E may result from interaction of various forms. In addition to the forms of vitamin E used, the potential biological benefits of vitamin E did not translate to an effective treatment of AD and MCI possibly owing to the relatively short intervention period.

AUTHORS' CONCLUSIONS

Implications for practice

This review found no evidence for efficacy of vitamin E in the treatment of AD. Taken together with other evidence that vitamin E, especially in the large doses used in the included studies, may be associated with potentially significant side effects and even an increased rate of all-cause mortality (Miller 2005), we conclude that vitamin E should not be used in the treatment of AD. We consider it important to educate patients, carers and professionals alike about the lack of confirmed efficacy and the potential hazards of using vitamin E in AD. It is important to note that the efficacy conclusions are based only on the alpha-tocopherol formulation of vitamin E, and hence no comment can be made on the efficacy of other preparations.

Implications for research

Vitamin E is a powerful antioxidant and plays an important role in protecting cells against the harmful effects of free radicals. There is sufficient evidence from laboratory and animal studies to justify human investigation of this medicinal product for AD patients. However, there continues to be a paucity of RCTs investigating the efficacy of vitamin E in AD. The study of Lloret, which met the inclusion criteria for this study, is of interest as it showed a harmful effect on the cognition in those patients whose oxidative stress markers did not respond to vitamin E intake (Lloret 2009). However, the high number of drop-outs in this study limits the conclusions that can be made. Findings are in need of replication from sufficiently powered clinical trials incorporating the assessment of oxidative stress markers in order to understand further the oxidant-antioxidant balance in relation to vitamin E effects on AD. In addition, the exclusive use of the alpha-tocopherol form of vitamin E in clinical trials has been questioned. Therefore, future studies must not restrict treatment to alpha-tocopherol, and should investigate other tocopherol and tocotrienol forms. Future updates of this review will specify sub-groups by vitamin E formulation and oxidative stress response.

ACKNOWLEDGEMENTS

The review authors are grateful to Sue Marcus, Managing Editor, Cochrane Dementia and Cognitive Improvement Group, for her support throughout the review.

The review authors would also like to thank Dr Jenny McCleery, Assistant Co-ordinating Editor, Cochrane Dementia and Cognitive Improvement Group, for her comments and contributions in the amendment process of the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Lloret 2009

Methods	Randomised, placebo-controlled, double-blind study
Participants	Country: Spain Single centre Diagnosis: probable AD according to NINCDS-ADRDA Number of participants: 57 patients, 18 healthy controls Age: not stated Inclusion criteria: not stated Exclusion criteria: patients taking antioxidant supplements, patients taking any medication other than cholinesterase inhibitors Severity of patients based on the Geriatric Dementia Scale - mild (N = 25), moderate (N = 26) and severe (N = 6)
Interventions	6-month intervention 1. Vitamin E (800 IU/day) 2. Placebo daily
Outcomes	1. Clock drawing 2. BDS 3. MMSE 4. Oxidative stress levels
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to groups using a randomised list of numbers
Allocation concealment (selection bias)	Unclear risk	No reference was made to allocation concealment was ensured
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Though it is a double-blinded study, and random assignment occurred before the trial, there is no mention of how/if participants and personnel were blinded throughout
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although it states it is a double-blinded study, there is no indication to whether the assessors were blinded

Lloret 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 24/57 AD participants did not complete the research. "Of the patients who finished the study, 14 had been treated with placebo and 19 with vitamin E." The reason for participant drop-out was not described
Selective reporting (reporting bias)	Unclear risk	All outcomes reported sufficiently
Other bias	Low risk	No evidence of additional bias

Petersen 2005

Methods	Randomised, placebo-controlled, double-blind study
Participants	Country: US and Canada Multicentre Diagnosis: amnestic type of MCI Subjects: 769 (46% females) Age: 55 to 90 years, mean 73 years Inclusion criteria: amnestic MCI of a degenerative nature, impaired memory, a Logical Memory delayed-recall score approximately 1.5 to 2 SD below an education adjusted-norm, a CDR of 0.5, a score of 24 to 30 on the MMSE, and an age of 55 to 90 years. Adequate vision and hearing for neuropsychological testing, normal vitamin B12 and thyroid function studies and non-reactive RPR. ECG normal or no clinical significant abnormalities. Study informant available Exclusion criteria: significant cerebral vascular disease, modified Hachinski > 4; Hamilton Depression Rating Scale > 12; central nervous system infarct, infection or focal lesions of clinical significance on CT or MRI scan. Medical diseases or psychiatric disorders that could interfere with study participation. Pregnant, lactating or of child bearing potential; taking vitamin supplements, other supplements or multi-vitamin. Restriction on concomitant medication usage, including those with significant cholinergic or anticholinergic effects or potential adverse effects on cognition
Interventions	Both vitamin E and donepezil were tested using a parallel group design, with 3 groups, vitamin E group (vitamin E 2000 IU, placebo donepezil and a multivitamin daily), donepezil group (donepezil 10 mg, placebo vitamin E and a multivitamin daily), and placebo group (placebo vitamin E, placebo donepezil and a multivitamin daily). The multivitamin contained vitamin E 15 IU N.B. the initial dose of vitamin E was 1000 IU/day, and the dose was increased to 2000 IU (1000 IU twice daily) after 6 weeks
Outcomes	1. The time to possible or probable development of AD 2. MMSE 3. ADAS-Cog 4. Global CDR 5. ADCS Mild Cognitive Impairment Activities of Daily Living Scale 6. GDS

	7. Neuropsychological battery including; New York University paragraph-recall test, the Symbol Digit Modalities Test, the category-fluency test, a number-cancellation test, the Boston Naming Test, the digits-backward test, the Clock drawing test, and a maze-tracing task 8. Adverse events
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random assignment of participants using an adaptive allocation scheme with MMSE score, age and APoE A4 status as a balancing covariates
Allocation concealment (selection bias)	Unclear risk	No reference was made to the method in which allocation concealment was ensured
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were blinded, though no evidence was presented to suggest if this was maintained throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no information presented about how the study controlled for detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	This was an intention-to-treat analysis with 230 subjects withdrawing during the double-blind phase and 539 subjects completing the double-blind or the open-label phase, or both phases. A sensitivity analysis was carried out that showed no significant difference in the results regarding vitamin E and placebo groups
Selective reporting (reporting bias)	Low risk	All outcomes reported sufficiently
Other bias	Low risk	No evidence of other bias

Sano 1996

Methods	Randomised, placebo-controlled, double-blind study Duration: 2 years
Participants	Country: US Multicentre: 23 sites Diagnosis: probable AD according to NINCDS-ADRDA Number of subjects: 341 (65% females) Age: mean 73 years Inclusion criteria: CDR score: 2, Hachinski score > 4, dementia of moderate severity, living at home with responsible carer, good general health Exclusion criteria: neurological diagnoses other than AD, psychiatric DSM-III-R diagnoses other than primary progressive dementia of Alzheimer's type, recent history of psychoactive medication use, no antipsychotic/neuroleptic medications, no antidepressants
Interventions	1. Placebo 2. Vitamin E (2000 IU total daily dose divided into 2 doses) 3. Selegiline (10 mg total daily dose divided into 2 doses) 4. Vitamin E (2000 IU total daily dose divided into 2 doses) plus selegiline (10 mg total daily dose divided into 2 doses)
Outcomes	1. Delay in any of 4 end points: death; institutionalisation; severity of dementia; loss of activities of daily living 2. ADAS-Cog (Rosen 1984) evaluates cognition across 11 tests: spoken language ability, comprehension of spoken language, recall of test instructions, word finding difficulty, following commands, naming objects construction drawing, ideational praxis, orientation, word recall, and word recognition 3. MMSE (Folstein 1975) evaluates cognition in five areas; orientation, immediate recall, attention and calculation, delayed recall and language 4. BDS (Blessed 1968) is composed of a series of scales split into 6 sections: the first 3 measure changes in performance of everyday activities, habits, personality, interests and drive. The second 3 sections form the cognitive test 5. DS (Stern 1994), a 7-point scale that rates the need for care and supervision 6. BRSD (Tariot 1995). The BRSD measures psychopathological signs and symptoms frequently seen in mild to moderate dementia. The covers the domains of depressive features, psychotic features, defective self-regulation, irritability and agitation, vegetative features, apathy, aggression and affective lability 7. Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random assignment of patients followed stratification according to centre using a permuted-block procedure. This is one of the most widely used sequential allocation procedure and is designed to achieve stra-

Sano 1996 (*Continued*)

		tum balance. This method ensures an equal distribution of all variables in the different groups
Allocation concealment (selection bias)	Unclear risk	The method in which allocation concealment was ensured was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were blinded prior to the beginning of trial. No reference is made to whether they remained blinded throughout
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no reference of how the outcome assessors were blinded to the allocated condition
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up was defined as those who did not reach an end point and did not complete the study: 6/84 for the placebo group and 8/85 for the vitamin E group, 4/87 for selegiline and 5/85 for vitamin E plus selegiline. The reasons for withdrawal were not described in each treatment group
Selective reporting (reporting bias)	Low risk	All outcome measures were reported
Other bias	Low risk	No evidence of other bias

AD: Alzheimer's dementia; ADAS-Cog: Alzheimer's Disease Assessment Scale - Cognitive section; ADCS: Alzheimer's Disease Cooperative Study; APoE: apolipoprotein E; BDS: Blessed Dementia Scale; BRSD: Behavior Rating Scale for Dementia; CDR: Clinical Dementia Rating; CT: computer tomography; DS: Dependence Scale; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition; ECG: electrocardiography; GDS: Global Deterioration Scale; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; RPR: rapid plasmin reagin; SD: standard deviation.

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

Study	Reason for exclusion
Alzoubi 2012	Sample population did not have a diagnosis of MCI or AD
Anand 2011	Sample population did not have a diagnosis of MCI or AD
Biesalski 2010	Review

(*Continued*)

Bittner 2009	Retrospective design
Brewer 2010	Review
Carlsson 2002	Sample population did not have a diagnosis of MCI or AD
Chan 2008-2009	Used a nutriceutical formulation and there was no placebo
Chan 2010	Used a nutriceutical formulation. Placebo was just inert ingredients
Clarke 2003	Vitamin E was used in conjunction with vitamin C It examined the association of cognitive impairment with platelet activation and reactive oxygen species and total homocysteine levels
Cornelli 2010	Used a nutriceutical formulation, not vitamin E separately
Dysken 2009	No vitamin E intervention, just a questionnaire
Geldmacher 2011	Pioglitazone was the primary intervention. Placebo was administered alongside vitamin E
Guan 2012	The study did not have relevant outcome measures
Gutierrez 2009	Sample population did not have a diagnosis of MCI or AD
Jacoby 2002	Pilot study, compared aspirin to vitamin E (600 mg) in conjunction with vitamin C and placebo
Jae 2006	Vitamin E intervention given to healthy elderly women
Joshi 2012	Review
Kamat 2008	Literature review about antioxidants
Kesse-Guyot 2011	Sample population did not have a diagnosis of MCI or AD
Kesse-Guyot 2011a	Sample population did not have a diagnosis of MCI or AD
Lee 2010	Literature review about antioxidants
Lott 2011	Sample population had a diagnosis of Down's syndrome and dementia
Lu 2009	Focus of intervention was towards depressed vs. non-depressed MCI population
MacPherson 2012	Sample population did not have a diagnosis of MCI or AD
Mecocci 2012	Review
Onofrj 2002	Vitamin E compared to donepezil not placebo

(*Continued*)

Pavlik 2009	Retrospective in nature. No controls or placebo group
Pribis 2012	Did not use vitamin E as an intervention
Péneau 2011	Not a randomised double-blinded study; investigated the intake of fruits and vegetables
Remington 2009	Used a nutriceutical formulation and the placebo was inert
Schmitt 2009	Used a healthy population
Schneider 2009	Same data as Petersen 2005
Takahashi 2009	Case study, no placebo and no controls
Usoro 2010	Review
Vinyoles-Bargallo 2010	Not an original paper, just a personal comment
Whitehair 2010	Same data as Petersen 2005

AD: Alzhimer's dementia; MCI: mild cognitive impairment.

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

NCT01320527

Trial name or title	A Phase II Clinical Trial of a Vitamin/Nutriceutical Formulation for Alzheimer's Disease
Methods	
Participants	Alzheimer's dementia and mild cognitive impairment. Must be able to swallow pills. Must not have a known or suspected bipolar disorder
Interventions	Nutriceutical formulation
Outcomes	1. Cognitive performance 2. Behavioural/psychotic symptoms
Starting date	August 2008
Contact information	Contact: Ruth Remington, Ph.D. 978-934-4423 Ruth_remington@uml.edu Contact: Thomas B Shea, Ph.D. 978 934-2881 thomas_shea@uml.edu

NCT01320527 (*Continued*)

Notes	Not likely to be relevant to future reviews as it uses a Nutriceutical formulation

Markesbery 2002

Trial name or title	Prevention of Alzheimer's Disease by Vitamin E and Selenium
Methods	
Participants	Healthy volunteers, 60 to 90 years of age excluding Alzheimer's dementia, or any other form of dementia, Huntington's disease, epilepsy, Parkinson's disease, brain tumour, multiple sclerosis, manic-depressive disorder or schizophrenia; head injury with over 30 minutes' loss of consciousness within last 5 years; current alcohol or substance abuse; depression or anxiety disorder in the past 4 months or under treatment for depression or anxiety; using Aricept (donepezil), Cognex (tacrine), Exelon (rivastigmine), Reminyl (galantamine) or Hydergine (dihydroergotoxine); disabilities that may prevent completion of memory screen
Interventions	Vitamin E and selenium
Outcomes	Developing Alzheimer's disease, memory impairment
Starting date	May 2002 to 2003
Contact information	Cecil R. Runyons: 001 859 257 1412 Ext. 235; email: preadvise@1sv.uky.edu William Markesbery, Principle Investigator, Alzheimer's Disease Research Center, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA. wmark0@email.uky.edu
Notes	Expected total enrolment 10,400. Same participants of the SELECT (Selenium and Vitamin E Cancer Prevention Trial) study looking at use of vitamin E and selenium for prevention of prostate cancer. Estimated completion August 2012. This trial is likely to be ineligible as participants are healthy controls

NCT00056329 2000

Trial name or title	Multicenter Vitamin E Trial in Aging Persons With Down Syndrome
Methods	Interventional
Participants	Clinically determined Down's syndrome (karyotypes optional), aged 50 years or older at the start of the protocol
Interventions	1000 UI alpha-tocopherol tice daily
Outcomes	Primary outcome measures: • Brief Praxis test Secondary outcome measures: • Fuld Object Memory test • New Dot test • Orientation test • Vocabulary test

NCT00056329 2000 (*Continued*)

	• Behaviour and Function • Clinical Global Impression • Incident Dement
Starting date	September 2000
Contact information	Arthur Dalton Deputy Director New York State Institute for Basic Research daltonaj@aol.com
Notes	Not relevant for future reviews as it uses a Down's syndrome population

Gopal 2005

Trial name or title	Effects of Vitamin E on Cognition and Measures of Activities of Daily Living in Patients with Moderately Severe Alzheimer's Disease
Methods	
Participants	Patients with moderately severe Alzheimer's disease
Interventions	Vitamin E 500 mg twice daily with cholinesterase inhibitors
Outcomes	Changes in cognition and activities of daily living
Starting date	1 November 2002
Contact information	Dr Vishnu Gopal Argyll House 9 Williamson Road, Nether Edge Sheffield S11 9AR telephone 0114 2718656 Fax: 01142716643 vgopal@doctors.org.uk
Notes	Study topic and author searched online, no evidence of trial or published data. Author no longer at contact address, emailed for an update but no response

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Source, search strategy and hits retrieved: June 2012 search

Source	Search strategy	Hits received
1. ALOIS (www.medicine.ox.ac.uk/alois)	Advanced search: [Study design: RCT OR CCT] AND [Health condition: Alzheimer OR MCI] AND [Intervention: "vitamin E"] (all dates)	June 2012: 39 (all dates)
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950 to present (Ovid SP)	1. *Vitamin E/ 2. "vitamin E".ti,ab. 3. "alpha-tocopherol".ti,ab. 4. or/1-3 5. Alzheimer*.ti,ab. 6. Alzheimer Disease/ 7. AD.ti,ab. 8. "cognit* impair*".ti,ab. 9. MCI.ti,ab. 10. (AACI or memory or CIND or ARCD or ACMI).ti,ab. 11. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 12. (nMCI or aMCI or mMCI).ti,ab. 13. (CDR adj2 "0.5").ab. 14. or/5-13 15. 4 and 14 16. randomized controlled trial.pt. 17. controlled clinical trial.pt. 18. randomi?ed.ab. 19. placebo.ab. 20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab. 24. or/16-23 25. (animals not (humans and animals)).sh. 26. 24 not 25 27. 15 and 26	June 2012: 16

(*Continued*)

3. EMBASE 1980 to 2011 week 27 (Ovid SP)	1. *Vitamin E/ 2. "vitamin E".ti,ab. 3. "alpha-tocopherol".ti,ab. 4. or/1-3 5. Alzheimer*.ti,ab. 6. Alzheimer Disease/ 7. AD.ti,ab. 8. "cognit* impair*".ti,ab. 9. MCI.ti,ab. 10. (AACI or memory or CIND or ARCD or ACMI).ti,ab. 11. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 12. (nMCI or aMCI or mMCI).ti,ab. 13. (CDR adj2 "0.5").ab. 14. or/5-13 15. 4 and 14 16. randomi?ed.ab. 17. placebo.ab. 19. trial.ab. 20. groups.ab. 21. randomized controlled trial/ 22. controlled clinical trial/ 23. ("double-blind*" or "single-blind*").ti,ab. 24. or/16-23 25. 15 to 24	June 2012: 28
4. PsycINFO 1806 to July week 2 2011 (Ovid SP)	1. "vitamin E".ti,ab. 2. "alpha-tocopherol".ti,ab. 3. Alzheimer*.ti,ab. 4. Alzheimer Disease/ 5. AD.ti,ab. 6. "cognit* impair*".ti,ab. 7. MCI.ti,ab. 8. (AACI or memory or CIND or ARCD or ACMI).ti,ab. 9. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 10. (nMCI or aMCI or mMCI).ti,ab. 11. (CDR adj2 "0.5").ab. 12. randomi?ed.ab. 13. placebo.ab. 14. randomly.ab. 15. trial.ab. 16. groups.ab. 17. ("double-blind*" or "single-blind*").ti,ab. 18. Clinical Trials/	June 2012: 6

(*Continued*)

	19. 1 or 2 20. or/3-11 21. or/12-18 22. 19 and 20 and 21	
5. CINAHL (EBSCOhost)	S1 (MM "Vitamin E") S2 TX "vitamin E" S3 TX "alpha-tocopherol" S4 S1 or S2 or S3 S5 (MH "Alzheimer's Disease") S6 TX AD OR alzheimer* S7 "mild cognitive impairment" S8 TX "cognit* impair*" S9 TX AACI OR memory OR CIND OR ARCD OR ACMI S10 TX MCI S11 TX nMCI OR aMCI OR mMCI S12 S5 or S6 or S7 or S8 or S9 or S10 or S11 S13 S4 and S12 S14 TX random* S15 TX placebo* S16 TX trial S17 TX groups S18 TX RCT OR CCT S19 (MH "Randomized Controlled Trials") S20 S14 or S15 or S16 or S17 or S18 or S19 S21 S13 and S20 S22 EM 2009 S23 EM 2010 S24 EM 2011 S25 S22 or S23 or S24 S26 S21 and S25	June 2012: 6
6. ISI Web of Knowledge - all databases [includes: Web of Science (1945 to present); BIOSIS Previews (1926 to present); MEDLINE (1950 to present); Journal Citation Reports]	#1 Topic=(alzheimer* OR AD OR MCI OR memory OR cognitive OR "cognit* impair*") AND Topic=("vitamin e" OR "alpha-tocopherol") AND Year Published=(2009-2011) Timespan=All Years #2 Topic=(random* OR placebo* OR "double-blind*" OR "single-blind*") Timespan=All Years #3 #2 AND #1 Timespan=All Years	June 2012: 174
7. LILACS (BIREME)	vitamin-e OR alpha-tocopherol	June 2012: 0

(*Continued*)

8. CENTRAL (*The Cochrane Library*) (Issue 4 of 4, Oct 2010)	#1 "vitamin e" #2 "alpha-tocopherol" #3 (#1 OR #2) #4 MeSH descriptor Vitamin E, this term only #5 (#3 OR #4) #6 alzheimer* OR AD OR "cognit* impair*" OR MCI #7 (#5 AND #6), from 2011 to 2012	June 2012: 9
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Interventional Studies | alzheimer OR alzheimer's OR alzheimers OR MCI OR cognitive OR cognition OR memory | vitamin E OR alpha-tocopherol | received from 01/01/2011 to 07/15/2012	June 2012: 2
10. ICTRP Search Portal (apps.who.int/trialsearch) (includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register)	Interventional Studies | alzheimer OR alzheimer's OR alzheimers OR MCI OR cognitive OR cognition OR memory | vitamin E OR alpha-tocopherol | received from 01/07/2011 to 15/07/2012	June 2012: 2
TOTAL before de-duplication		282
TOTAL after de-duplication and first assessment		14

WHAT'S NEW

Last assessed as up-to-date: 25 June 2012.

Date	Event	Description
25 June 2012	New citation required and conclusions have changed	An update search was performed for this review on 15 July 2011 and 25 June 2012. One additional study was included (Lloret 2009); the results and conclusions have changed. The authors of the review have changed

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 4, 2000

Date	Event	Description
15 July 2011	New search has been performed	An update search was performed for this review on 15 July 2011
18 March 2009	New search has been performed	Update search of 5 March 2009 retrieved new studies for consideration for inclusion
25 April 2008	New citation required but conclusions have not changed	In 2007, the scope of this review was broadened to include both Alzheimer's disease patients and patients with mild cognitive impairment
16 January 2007	New search has been performed	Update 2007: one new study was included (Petersen 2005). The included study did not affect the results as it also showed that vitamin E has no more significant effect than placebo for mild cognitive impairment. The overall conclusion of the review has not changed as there is not enough evidence to support the use of vitamin E in the treatment of Alzheimer's disease or mild cognitive impairment
2 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Original: NT drew up the protocol. MI planned the review and protocol, selected studies, critiqued the trials, advised on analyses, revised drafts of protocol and review and supervised the review process. AS assisted in devising the protocol, searched the literature, co-reviewed studies and revised drafts of the paper.

Update 2006: MI and RQ reviewed and selected the included studies. MI extracted the data, performed the analysis and wrote the draft. NT contributed to the text and supervised. The search was carried out by Dymphna Hermans.

Update 2011: NF and MI reviewed and selected the included studies. NF extracted the data and wrote the draft. AC, JR and NT contributed to the text. JR and NT supervised. The search was carried out by Anna-Noel Storr.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- School of Psychology, University of Sussex, UK.

External sources

- NHS R&D, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods of the review were adapted to include the subgroup analysis of those that did ('responders') and did not ('non-responders') report a decline in oxidative stress as a result of a vitamin E intervention. This adaptation was decided on the basis that the primary mechanism for vitamin E is to act as an antioxidant and hence it is important to determine whether the intervention is achieving its desired results.

The methods of the review were updated to comply with the most recent version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1; Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy]; Antioxidants [*therapeutic use]; Cognitive Dysfunction [*drug therapy]; Disease Progression; Outcome Assessment (Health Care); Randomized Controlled Trials as Topic; Vitamin E [*therapeutic use]

MeSH check words

Humans