Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 1

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[Intervention Review]

Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

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Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 1 August 2007.

Citation: Evans JR, Henshaw KS. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD000253. DOI: 10.1002/14651858.CD000253.pub2.

ABSTRACT

Background

Some observational studies have suggested that people who eat a diet rich in antioxidant vitamins (carotenoids, vitamins C and E) or minerals (selenium and zinc) may be less likely to develop age-related macular degeneration (AMD).

Objectives

The aim of this review was to examine the evidence as to whether or not taking vitamin or mineral supplements prevents the development of AMD.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in *The Cochrane Library* (2007, Issue 3), MEDLINE (1966 to August 2007), SIGLE (1980 to 2005/03), EMBASE (1980 to August 2007), National Research Register (NRR) (2007, Issue 3), AMED (1985 to January 2006) and PubMed (on 24 January 2006 covering last 60 days), reference lists of identified reports and the Science Citation Index. We contacted investigators and experts in the field for details of unpublished studies.

Selection criteria

We included all randomised trials comparing an antioxidant vitamin and/or mineral supplement (alone or in combination) to control. We included only studies where supplementation had been given for at least one year.

Data collection and analysis

Both review authors independently extracted data and assessed trial quality. Data were pooled using a fixed-effect model.

Main results

Three randomised controlled trials were included in this review (23,099 people randomised). These trials investigated alpha-tocopherol and beta-carotene supplements. There was no evidence that antioxidant vitamin supplementation prevented or delayed the onset of AMD. The pooled risk ratio for any age-related maculopathy (ARM) was 1.04 (95% CI 0.92 to 1.18), for AMD (late ARM) was 1.03 (95% CI 0.74 to 1.43). Similar results were seen when the analyses were restricted to beta-carotene and alpha-tocopherol.

Authors' conclusions

There is no evidence to date that the general population should take antioxidant vitamin and mineral supplements to prevent or delay the onset of AMD. There are several large ongoing trials. People with AMD should see the related Cochrane review "Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration" written by the same author.

PLAIN LANGUAGE SUMMARY

Antioxidant vitamins and mineral supplements to prevent the development of age-related macular degeneration

Age-related macular degeneration (AMD) is a condition affecting the central area of the retina (back of the eye). The retina can deteriorate with age and some people get lesions that can lead to loss of central vision. Some studies have suggested that people who eat a diet rich in antioxidant vitamins (carotenoids, vitamins C and E) or minerals (selenium and zinc) may be less likely to get AMD. The authors identified three large, high quality randomised controlled trials based in Australia, Finland and USA which had investigated the effects of vitamin E and beta-carotene supplementation. This review found no evidence that people in the general population should take antioxidant vitamin or mineral supplements in order to delay the onset of AMD. The results of ongoing trials are awaited.

BACKGROUND

Introduction

Age-related macular degeneration (AMD) is a disease affecting the central area of the retina (macula). In the early stages of the disease lipid material accumulates in deposits underneath the retinal pigment epithelium. These deposits are known as drusen, and can be seen as pale yellow spots on the retina. The pigment of the retinal pigment epithelium may become disturbed with areas of hyperpigmentation and hypopigmentation. In the later stages of the disease, the retinal pigment epithelium may atrophy completely. This loss can occur in small focal areas or can be widespread (geographic). In some cases, new blood vessels grow under the retinal pigment epithelium and occasionally into the subretinal space (exudative or neovascular). Haemorrhage can occur which often results in increased scarring of the retina.

Presentation and diagnosis

The early stages of the disease are in general asymptomatic. In the later stages there may be considerable distortion of vision and complete loss of visual function, particularly in the central area of vision.

Epidemiology

Population-based studies suggest that, in people 75 years and older, approximately 30% have early signs of the disease and 7% have late stage disease (Klein 1992). It is the most common cause of blindness and visual impairment in industrialised countries. In the UK for example, over 30,000 people are registered as blind or partially sighted annually, half of whom have lost their vision due to macular degeneration (Evans 1996).

Treatment options

Currently there is no treatment which can restore vision in AMD. Photoreceptors in the retina are subject to oxidative stress throughout life due to combined exposures to light and oxygen. It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals produced in the process of light absorption (Christen 1996).

There are a number of non-experimental studies that have examined the possible association between antioxidant micronutrients and AMD, although few studies have examined supplementation specifically (Chong 2007; Evans 2001). Data on vitamin intake in observational studies should be considered cautiously as people who have a diet rich in antioxidant vitamins and minerals or who choose to take supplements regularly, are different in many ways from those who do not; these differences may not be adequately controlled by statistical analysis. Inconsistent results have been found in these observational studies.

Rationale for a systematic review

Antioxidant vitamin and mineral supplements are increasingly being marketed for use in age-related eye disease, including AMD. The aim of this review was to examine the evidence as to whether or not taking vitamin or mineral supplements prevents the development of AMD. See also the related Cochrane review "Antioxidant vitamin and mineral supplements for slowing the progression of AMD" which considers whether supplementation for people with AMD slows down the progression of the disease (Evans 2006).

OBJECTIVES

The objective of this review was to determine whether antioxidant vitamin and/or mineral supplementation prevents the development of AMD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials comparing antioxidant vitamin and/or mineral supplementation (alone or in combination) to control.

Types of participants

Participants in the trials were people in the general population, with or without diseases other than AMD. We excluded trials in which the participants were exclusively people with AMD. These trials are considered in a separate Cochrane review examining the effect of supplementation on progression of the disease (Evans 2006).

Types of interventions

Antioxidants were defined as any vitamin or mineral which is known to have antioxidant properties in vivo or which is known to be an important component of an antioxidant enzyme present in the retina. We considered the following: vitamin C, vitamin E, carotenoids, selenium and zinc. We included studies where supplementation had been given for at least one year.

Types of outcome measures

The following outcomes were used:
(1) number of participants developing AMD;
(2) number of participants with visual loss due to AMD;
(3) quality of life measures;
(4) any adverse outcomes reported.
We used the following definitions:
AMD: this was taken as defined by trial investigators. It is commonly defined as: in the macular area 3,000 microns diameter from fovea: drusen with or without pigmentary abnormalities or geographic atrophy or characteristic choroidal neovascularisation with no other cause. Where possible, we have used the 'International Classification and Grading System for Age-related Maculopathy and Age-related Macular Degeneration' (ARM Study Group 1995). The group propose an overall term of age-related maculopathy (ARM) encompassing both early age-related macular changes (soft drusen >= 63 microns, hyper- and/or hypo-pigmentation) and late stage disease (neovascularisation and geographic atrophy), observed on grading of colour fundus photographs. The term AMD is restricted to describe late stage disease.
Visual loss: any well-defined outcome based on visual acuity was used depending on the way in which authors presented trial data.
Quality of life: any validated measurement scale which aims to measure the impact of visual function loss on quality of life of participants.

Search methods for identification of studies

Electronic searches

We searched for trials that tested antioxidant vitamin or mineral supplementation. Our initial search did not include terms for AMD or eye terminology as we planned to contact investigators of eligible trials to establish whether data on vision outcomes had been collected. We included eye terminology in subsequent searches, since no trials were identified in the first phase that had not included eye terminology. There were no language or date restrictions in the searches.
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in *The Cochrane Library,* MEDLINE, EMBASE, SIGLE, National Research Register (NRR), PubMed and Allied & Complementary Medicine (AMED). The searches in *The Cochrane Library*, MEDLINE, EMBASE and National Research Register were last updated on 2 August 2007.
See: Appendices for details of search strategies used for each database.

Searching other resources

We searched the Science Citation Index and the reference lists of reports of trials that were selected for inclusion. We contacted the investigators of included and excluded trials to ask if they knew of any other relevant published or unpublished trials.

Data collection and analysis

Selection of trials

Each review author assessed half of the titles and abstracts resulting from the searches and selected studies according to the definitions in the 'Criteria for considering studies for this review'. To check that we were consistent, we both assessed a subset of 100 records and compared results. We obtained full copies of all reports referring to controlled trials that definitely or potentially met the inclusion criteria. We assessed the full copies and selected studies according to the inclusion criteria. We wrote to authors of trials for which there were no published outcome data on AMD to ask whether they had collected any data on eye disease outcomes.
As none of the trials responded positively, i.e. gave us unpublished data on AMD, for further updates of this review we only considered trials with published data on AMD.

Assessment of methodological quality

Each author independently assessed the methodological quality of trials according to methods set out in the Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). Only trials that met the inclusion criteria and collected outcome data on eye diseases were assessed for quality. Five parameters were considered: allocation concealment, method of allocation to treatment, documentation of exclusions, masking of outcome assessment and completeness of follow-up. Each parameter of trial quality was graded: A - low risk of bias; B - moderate risk of bias; and C - high risk of bias. The review authors were not masked to any trial details. Trials scoring C on allocation concealment, that is, where allocation was inadequately concealed, were excluded.

Data collection

Both authors independently extracted data on included trials using a form developed by the Cochrane Eyes and Vision Group (available from the editorial base). The results were compared and discrepancies were resolved.

Data synthesis

We summarised data using the risk ratio, after testing for heterogeneity between trial results using a standard chi-squared test. We also planned to conduct sensitivity analyses to determine the impact of study quality on effect size.

RESULTS

Description of studies

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

Results of the search

The initial searches resulted in 3178 titles and abstracts. Of these, 208 were reports of potentially eligible trial reports. From these reports we identified seven primary prevention trials of antioxidant vitamin or mineral supplements (ATBC 1994; CARET; de Klerk 1998; LINXIAN; Nambour 1995; PHS I; WHS). Investigators from three trials have confirmed that they did not collect data on AMD (CARET; de Klerk 1998; Nambour 1995). These trials have been excluded from the review. We did not receive a response from one trial (LINXIAN) and this trial has been excluded. Two trials have published data on AMD outcomes (ATBC 1994; PHS I) and are included in this review. One ongoing trial is planning to publish information on AMD (WHS). Search of the National Eye Institute Clinical Research register identified one further ongoing trial which is collecting information on AMD - the Women's Antioxidant Cardiovascular Study (WACS). There are two trials that have recruited participants with and without AMD (AREDS; VECAT). VECAT is included in this review because 82% of participants did not have signs of ARM. AREDS is not included in this review because ARM outcomes for people without ARM at baseline were not reported; it is included in the Cochrane review examining the effect of supplementation on progression of the disease (Evans 2006).
The original search strategy involved identifying all trials of antioxidant interventions and asking trialists if they had collected data on AMD. We wrote to the authors of 60 trials of antioxidant interventions in people with diseases other than AMD. To date we have received 15 responses and none has collected any relevant data. All 60 trials are shown in the excluded studies section of this review. As this proved to be an inefficient way of identifying relevant trials, subsequent searches included terms for AMD. Three hundred and sixty seven reports of trials were found in May 2002, 343 in May 2005 and 64 reports in January 2006 but no further trials were identified that were relevant for inclusion in this review. The results of the PHS I study were published in 2007. The searches were repeated in August 2007 in which a total of 129 reports of studies were identified.

Included studies

Summary of trial characteristics

Below is a summary of the three trials included in this review. See the 'Characteristics of included studies' Table for more detailed information.

Types of participants

The studies took place in Australia, USA and Finland. Two studies recruited males only (ATBC 1994; PHS I) and one study recruited men and women (VECAT). People taking part in the trials were identified from the general population. Participants in PHS I were male physicians. In ATBC 1994, a random sample of 1035 men aged 65 years or above from the main study were invited to participate with a response rate of 91% (941 men). In VECAT 18% had ARM at baseline.

Types of intervention

In ATBC 1994, the groups received either alpha-tocopherol 50 mg per day alone, beta-carotene 20 mg per day alone, alpha-tocopherol and beta-carotene or placebo. All formulations were coloured with quinoline yellow. Treatment duration was five to eight years (median 6.1). In VECAT participants were randomised to vitamin E (500 IU a day) or placebo. Supplementation continued for four years. In PHS I the groups received aspirin 325 mg every other day, beta-carotene 50 mg every other day, aspirin and beta-carotene or placebo. Treatment duration averaged 12 years.

Types of outcome measures

In ATBC 1994, three photographs of each eye were taken with a Canon fundus camera at 40 and 60 degree angles on Kodak Ektachrome 100 ASA slide film. These photographs were graded by one observer masked to the participant's treatment group. The following grades of maculopathy were used: 0 = none; I = dry maculopathy with hard drusen and/or pigmentary changes; II = soft macular drusen; III = disciform degeneration; IV = geographic atrophy. These have been recategorised in this review according to the International Grading System (ARM Study Group 1995) as follows: early ARM = I and II; late ARM = III and IV; geographic atrophy = IV; and neovascular AMD = III.

In PHS I AMD was ascertained by self-report "Have you ever had macular degeneration diagnosed in your right or left eye?". If the participant answered yes to this question permission was gained to contact their ophthalmologist or optometrist and further details were obtained from the medical records.

In VECAT, photographs were taken with a Nidek 3-DX fundus camera on Kodachrome 64 ASA colour film. The photographs were graded at baseline independently by two trained graders according to the International Grading System (ARM Study Group 1995). The primary outcome was 'early AMD-3'. On photographic grading this was defined as soft drusen (distinct or indistinct) or pigmentary changes (hyperpigmentation or hypopigmentation). On clinical grading this was large/soft drusen or non-geographical RPE atrophy. VECAT used Bailey-Lovie Charts #4 and #5 (National Vision Research Institute, Australia).

Excluded studies

See Characteristics of excluded studies table.

Risk of bias in included studies

All three studies were of high quality and scored A - low risk of bias on all quality parameters. The allocation was concealed by means of coded tablets and randomly assigned; exclusions were documented and follow up was equal between the study groups; outcome assessment was masked to study group and analysis was intention-to-treat.

Effects of interventions

In ATBC 1994 there were 728 people randomised to any antioxidant and 213 to placebo. There was no association of treatment group with any sign of maculopathy. There were 216 cases of early ARM or AMD in the antioxidant groups and 53 in the placebo group (risk ratio (RR) 1.19 95% confidence interval (CI) 0.92 to 1.54). The majority of these cases were early ARM. There were only 14 cases of late AMD. Of these, four were geographic atrophy and 10 neovascular disease. There was one case of geographic atrophy and no cases of neovascular disease in the placebo group. The findings are similar when each of the antioxidant groups - alpha-tocopherol, beta-carotene, alpha-tocopherol and beta-carotene - are compared with placebo.

In VECAT there were 92/504 in the vitamin E group with ARM compared to 92/512 in the placebo group (RR 1.02, 95% CI 0.78 to 1.32). The majority of these cases were early ARM. There were nine cases of late AMD, five in the treatment group and four in the placebo group.

In PHS I there were 162 cases of ARM causing visual loss of 6/9 or worse in the beta carotene group vs 170 cases in the placebo group (RR adjusted for aspirin assignment 0.96, 95% CI 0.78 to 1.20). Secondary end points of ARM with or without vision loss (275 vs 274 cases, adjusted RR 1.01, 95% CI 0.86 to 1.20) and advanced ARM (63 vs 66 cases, adjusted RR 0.97, 95% CI 0.69 to 1.37) were reported.

Overall 23,099 participants were randomised in ATBC, VECAT and PHS I (see Data and analyses 1). There were 583 cases of ARM in the antioxidant groups and 419 cases of ARM in the placebo groups (Analysis 1.1). The results of the three studies were consistent (I^2 = 0%). There was little evidence of any effect of antioxidant supplementation (RR 1.04, 95% CI 0.92 to 1.18).

Similarly with AMD (late ARM) the trials were consistent and indicate little evidence of any effect of supplementation (RR 1.03, 95% CI 0.74 to 1.43) (Analysis 1.3). There were fewer late ARM events (81 antioxidant, 71 placebo).

There was less evidence available comparing alpha-tocopherol alone versus placebo (see Data and analyses 2). A total of 1466 people randomised in VECAT and ATBC resulted in 167 cases of ARM in the alpha-tocopherol group and 145 in the placebo group (Analysis 2.1). The trial results were reasonably consistent I^2 = 18.8%. There was little evidence of any effect of supplementation with alpha-tocopherol on the incidence of ARM RR 1.11 (95% CI 0.91 to 1.36). There were fewer cases of late ARM - 13 in the alpha-tocopherol groups and five in the placebo (Analysis 2.3). Again there was little evidence of any benefit from supplementation with a pooled RR in the direction of harm 2.51, 95% CI 0.89 to 7.10.

A total of 21,589 people have been randomised into ATBC and PHS I comparing beta-carotene with placebo Data and analyses 3). There were 343 cases of ARM in the beta-carotene groups and 327 in the control groups (Analysis 3.1). The results of the trials were consistent (I^2 = 0%) and did not indicate any benefit of supplementation (RR = 1.03, 95% CI 0.98 to 1.19). There were 65 cases of late ARM in the beta-carotene groups and 67 cases of late ARM in the control (Analysis 3.2). Again the results of the trials were consistent (I^2 = 0%) and indicated little effect of supplementation (RR = 0.97, 95% CI 0.69 to 1.18).

DISCUSSION

This review did not find evidence that supplementation with antioxidant vitamin supplements prevents the development of AMD. However, the trials included in this review have investigated vitamin E (alpha-tocopherol) and beta-carotene only. There is no evidence as to the possible benefits and harms of other antioxidant supplements with respect to the prevention of AMD.

This review includes three reasonably large high quality studies which have randomised over 23,000 members of the population to antioxidant supplementation or placebo. Duration of supplementation has ranged from four to 12 years.

In ATBC 1994 there was no association with the treatment group and development of early stages of the disease. If anything, there was a tendency for more cases to be present in the treatment rather than the placebo group. This was not statistically significant. One drawback of adding-on a maculopathy study to a trial of primary prevention is that we have no information on maculopathy status before supplementation. Therefore we have to assume that (1) maculopathy was equally distributed across study groups at the start of the study and (2) most observed events occurred during the study period. It is likely that this is true for a reasonable proportion of the events as the maculopathy study began eight years after recruitment for the main trial and randomisation should have ensured equal distribution of maculopathy between the two groups.

Supplementation in this study began at age 50 to 69 and lasted five to eight years. Currently we do not know at what age antioxidant protection may be important. It may be that this was too late or too short a period of supplementation to show an effect. This study was conducted in Finnish male smokers and we have to be cautious in extrapolating the findings to other geographical areas, to people in other age-groups, to women and to non-smokers. However, the incidence of AMD, particularly neovascular disease, is likely to be higher in smokers (Klein 1993) which means that they provide a good population to demonstrate any potential protective effects of antioxidant supplementation. There were no ophthalmological adverse effects recorded during the study although there was non-significant increased risk of maculopathy in the treatment groups. In the main trial it was observed that men who received beta-carotene had a higher incidence of lung cancer (ATBC 1994). This finding was also observed in CARET (Omenn 1996). It cannot be assumed that consumption of these supplements is without harm.

The results of VECAT similarly do not provide evidence of a benefit of supplementation in people with no or mild/borderline AMD, although again these studies have been underpowered to examine late-stage disease.

In the PHS I over 20,000 physicians received supplementation with beta-carotene over 12 years. There was little evidence of any benefit of beta-carotene supplementation. AMD was ascertained by medical record review and therefore may have been less accurate. However, there is no reason to suppose that the ascertainment will have been different in the treatment and control groups.

The Age-Related Eye Disease study is not included in this review. However, there were 2180 people recruited with no or mild/borderline AMD (AREDS 2001a). The study reported no benefit of the study treatment for these people however the number of events was small.

Although the number of people randomised in these studies is large there is still a degree of uncertainty in the pooled estimates. In the pooled analyses the risk ratios were largely around the null value or just above the null value. There were more cases of ARM. The lower 95% confidence interval for these analyses was around 0.90. This suggests that the most protective effect that these results are compatible with is of the order of a 10% risk reduction. There were fewer cases of AMD. In these analyses the lower 95% CI was around 0.75. This suggests that the maximum protective effect that these results are compatible with is a 25% risk reduction. The upper confidence intervals are in the region 1.20 to 1.50 indicating that vitamin supplementation could be associated with an increased risk of ARM or AMD.

Overall beta-carotene supplementation is unlikely to prevent the development of AMD in the general population. With the amount of information available, a protective effect would have been evident. For vitamin E there are less data available however the risk ratios are in the direction of harm. For that reason it is unlikely that vitamin E supplements prevent the development of AMD.

A recent systematic review of observational prospective studies also found little evidence of a protective effect of dietary antioxidants (Chong 2007). The only dietary antioxidant for which a reduction was seen was vitamin E, in contrast to the evidence from the trials included in this review. It is possible that natural vitamin E from dietary sources rather than artificial supplements has different effects, or alternatively high levels of dietary vitamin E might be a marker for other nutrients, for example, dietary fatty acids.

We are awaiting the results of several large ongoing studies in the USA and Australia. In the Women's Health Study 39,876 women were randomised using a 2x2 factorial design to low-dose aspirin and vitamin E (WHS). There is now a further Physicians Health Study (PHS II). In the Women's Antioxidant Cardiovascular Study 8171 female health professionals who are at high risk for cardiovascular disease morbidity and mortality are being randomised using a 2x2x2x2 factorial design to vitamin C, vitamin E, folate, vitamin B6 and vitamin B12 supplementation (WACS).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised trials that healthy people should take antioxidant vitamin and mineral supplements to prevent or delay the onset of AMD.

Implications for research

There are a number of unanswered questions in the prevention of AMD. The hypothesis that antioxidant micronutrients may protect against the disease is a reasonable one. We do not know at what stage the protective effect may be important, nor the potential interactions with genetic effects and other risk factors for the disease such as smoking. The research to date shows that we cannot extrapolate to taking vitamin supplements without good evidence of their effectiveness and safety. Further trials are warranted to address this question and the results of several large ongoing trials are awaited. The small number of incident events in healthy people mean that trials need to be very large. Four large primary and secondary prevention trials in the field of cancer and cardiovascular disease have added-on an examination of eye disease. This would seem to be a cost-effective way forward in research in this area.

ACKNOWLEDGEMENTS

We are grateful to:

- the Systematic Review Training Unit at Institute of Child Health, London for advice on the protocol for this review;
- all the trialists who responded to requests for information;
- peer reviewers Andrew Ness and Usha Chakravarthy for comments on an earlier version of this review.

The Cochrane Eyes and Vision Group editorial team prepared and executed the electronic searches for this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

ATBC

Methods	Method of allocation: random. Sponsor provided coded capsules. Masking: participant: yes; provider: yes; outcome: yes. Exclusions after randomisation: no. Losses to follow up: 31%. Random sample for maculopathy study: 9%. Unusual study design: 2x2 factorial design. Maculopathy add-on random sample in 2 regions
Participants	Country: Finland. Number of participants randomised: 29,133. Random sample of 1035 selected for maculopathy study. Age: 50 to 69 years in 1984. Maculopathy study 1992/3 in people aged 65 plus. Sex: Male. Inclusion criteria: 5 or more cigarettes daily. Exclusion criteria: history of cancer or serious disease limiting ability to participate; those taking supplements vitamine E, A or betacarotene in excess of predefined doses; those treated with anticoagulants
Interventions	Treatment: 3 regimens: alpha-tocopherol (50 mg), betacarotene (20 mg) or alpha-tocopherol and betacarotene. Control: placebo. Duration: 5 to 8 years (median 6.1).
Outcomes	ARM: Four grades: Grade I: Dry maculopathy with hard drusen and/or pigmentary changes. Grade II: Soft macular drusen. Grade III: Disciform degeneration. Grade IV: Geographic atrophy.
Notes	Compliance with treatment excellent; 4/5 active participants took more than 95% of sceduled capsules. Drop-out rate and compliance similar between all four groups

Risk of bias

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

PHS I

Methods	Method of allocation: Coded tablets. Masking: Participant: Yes Provider: Yes Outcome: Yes Exclusions after randomisation: Losses to follow-up: Unusual study design: Two by two factorial design.
Participants	Country: USA Number randomised: Originally 22,071 men were randomised: 11,036 to beta-carotene 11,035 to beta-carotene placebo. 21,142 participants were followed up for at least 7 years and provided information on diagnoses of ARM made during the first 7 years of the trial. 10,585 were in the beta carotene group and 10,557 were in the placebo group. Age: 40 to 84 years in 1982 Sex: Male Inclusion criteria: Physician aged 40 to 84 years in 1982 with no history of cancer, myocardial infarction, stroke or transient cerebral ischaemia. Exclusion criteria:
Interventions	Treatment: Four groups: 1.Aspirin 325mg every other day plus beta-carotene placebo. 2.Beta-carotene 50 mg every other day plus aspirin placebo. 3.Both active agents Control: 4.Both placebos Duration: Aspirin component terminated early January 1988 Beta carotene component terminated Dec 1995. Mean duration 12 years range (11.6 to 14.2 years)
Outcomes	Self-report of AMD followed by medical record review and questionnaire to relevant ophthalmologist. Primary endpoint: visually significant ARM, defined as a self-report confirmed by medical record evidence of an initial diagnosis after randomisation but before December 31st 1995 with a reduction in best-corrected visual acuity to 20/30 or worse attributable to ARM. Secondary endpoints: ARM with or without vision loss, composed of all incidence cases Advanced ARM, encompassed of cases of visually significant ARM with pathological signs of disciform scar, RPE detachment, geographic atrophy, or subretinal neovascular membrane
Notes	

Risk of bias

Item	Authors' judgement	Description

PHS I (*Continued*)

Allocation concealment?	Yes	A - Adequate

VECAT

Methods	Method of allocation: coded bottles. Masking: participant: yes; provider: yes; outcome: yes. Losses to follow up: not known.
Participants	Country: Australia. Number of participants randomised: 1204. Age: 55 to 80 years, mean 66. Sex: 56% female. Inclusion criteria: lens and retina of at least one eye available for documentation. Exclusion criteria: previous cataract surgery or advanced cataract in both eyes; steroid or anticoagulation use; serious disease; regular use or sensitivity to vitamin E
Interventions	Vitamin E 500 IU per day: natural vitamin E in soybean oil medium. Control: placebo identical in sight, taste and smell. Duration: 4 years.
Outcomes	2m logMAR visual acuity; clinical examination; colour stereoscopic fundus photographs graded using International Grading Scheme
Notes	Worse eye used as the study eye. Methodology published but results available from abstract only

Risk of bias

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

AMD: Age-related macular degeneration
ARM: Age-related maculopathy
ETDRS: Early Treatment Diabetic Retinopathy Study
IU: International units

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

Study	Reason for exclusion
ADSC	No published data on age-related macular degeneration. No response from author
Andrews 1969	No published data on age-related macular degeneration. Unable to contact author
AREDS	Age-related maculopathy outcomes for people without age-related maculopathy at baseline were not reported
Benner 1994	No published data on age-related macular degeneration. No response from author
Benton 1995	No data on age-related macular degeneration collected.
Blok 1997	No data on age-related macular degeneration collected.
Bogden 1990	No published data on age-related macular degeneration. No response from author
Brewer 1997	No published data on age-related macular degeneration. No response from author
Brown 1998	No published data on age-related macular degeneration. No response from author
Bussey 1982	No published data on age-related macular degeneration. No response from author
Caligiuri 1997	No published data on age-related macular degeneration. No response from author
CARET	No data on age-related macular degeneration collected.
CCSG	No published data on age-related macular degeneration. No response from author
Chandra 1992	No published data on age-related macular degeneration. No response from author
CHAOS	No data on age-related macular degeneration collected.
Clausen 1989	No published data on age-related macular degeneration. No response from author
Constans 1996	No published data on age-related macular degeneration. No response from author
Constantino 1988	No data on age-related macular degeneration collected.
Cucinotta 1994	No published data on age-related macular degeneration. No response from author
DATATOP	No published data on age-related macular degeneration. Unable to contact author
de Klerk 1998	No data on age-related macular degeneration collected.
DeCosse 1989	No published data on age-related macular degeneration. No response from author

(*Continued*)

Dobson 1984	No data on age-related macular degeneration collected.
ECP-IM	No published data on age-related macular degeneration. No response from author
EUROSCAN	No published data on age-related macular degeneration. No response from author
Fairley 1996	No published data on age-related macular degeneration. No response from author
Fontham 1995	No data on age-related macular degeneration collected.
Galan 1997	No published data on age-related macular degeneration. No response from author
Garawal 1995	No published data on age-related macular degeneration. No response from author
GISSI	No published data on age-related macular degeneration. No response from author
HOPE	No data on age-related macular degeneration collected.
Johnson 1997	No published data on age-related macular degeneration. No response from author
Jyothirmayi 1996	No published data on age-related macular degeneration. No response from author
Kuklinski 1994	No published data on age-related macular degeneration. No response from author
Leng 1997	No published data on age-related macular degeneration. Unable to contact author
Li 1992	No published data on age-related macular degeneration. No response from author
LINXIAN	No published data on age-related macular degeneration. No response from author
Mayne 1998	No data on age-related macular degeneration collected.
McKeown 1988	No data on age-related macular degeneration collected.
Meyskens 1994	No published data on age-related macular degeneration. No response from author
Munoz 1987	No published data on age-related macular degeneration. No response from author
Munoz 1996	No published data on age-related macular degeneration. No response from author
Nambour 1995	No follow-up data on age-related macular degeneration collected
NPCSG	No published data on age-related macular degeneration. No response from author
Pastorino 1991	No published data on age-related macular degeneration. No response from author

(*Continued*)

Peng 1993	No published data on age-related macular degeneration. No response from author
PPP	No published data on age-related macular degeneration. No response from author
PPSG	No data on age-related macular degeneration collected.
Prasad 1995	No published data on age-related macular degeneration. No response from author
Qidong 1997	No published data on age-related macular degeneration. No response from author
REACT	No published data on age-related macular degeneration. No response from author
Recchia 1995	No published data on age-related macular degeneration. No response from author
Ret Pig 1993	No published data on age-related macular degeneration. No response from author
SCPS 1989	No data on age-related macular degeneration collected.
SECURE	No published data on age-related macular degeneration. No response from author
Shandong 1998	No data on age-related macular degeneration collected.
Sharma 1989	No published data on age-related macular degeneration. No response from author
Steiner 1995	No published data on age-related macular degeneration. No response from author
SUVIMAX	No published data on age-related macular degeneration. No response from author
SWSCPSG	No data on age-related macular degeneration collected.
Takamatsu 1995	No published data on age-related macular degeneration. No response from author
Tomeo 1995	No published data on age-related macular degeneration. No response from author
Tsubono 1997	No data on age-related macular degeneration collected.
Wahlqvist 1994	No data on age-related macular degeneration collected.
Wright 1985	No published data on age-related macular degeneration. No response from author
YUNNAN	No published data on age-related macular degeneration. No response from author
Zaridze 1993	No published data on age-related macular degeneration. No response from author

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

PHS II

Trial name or title	Physician's Health Study II
Methods	
Participants	15,000 physicians aged 55 or older
Interventions	2x2x2x2 factorial design - alternate day betacarotene, alternate day vitamin E, daily vitamin C and a daily multivitamin
Outcomes	Age-related macular degeneration: reported diagnosis followed-up by contact with treating ophthalmologist/ optometrist
Starting date	
Contact information	
Notes	

WACS

Trial name or title	Women's Antioxidant Cardiovascular Study
Methods	
Participants	8171 female health professionals aged 40 plus with pre-existing cardiovascular disease (CVD) or high risk for developing CVD
Interventions	2x2x2x2 factorial design - vitamin E (600 IU on alternate days) - vitamin C (500 mg daily), - betacarotene (50 mg on alternate days) - combination of folate (800 mg daily), vitamin B6 (25 mg daily) and vitamin B12 (1 mg daily)
Outcomes	Self report and review of medical records
Starting date	1993
Contact information	
Notes	

WHS

Trial name or title	Women's Health Study
Methods	
Participants	39,876 women health professionals aged 45 plus
Interventions	Low dose aspirin (100 mg on alternate days) and vitamin E (600 IU on alternate days)
Outcomes	Self report and review of medical records
Starting date	1992
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. ANY ANTIOXIDANT VERSUS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any ARM	3	23099	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.18]
2 Early ARM	2	1957	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.29]
3 Late ARM	3	23099	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.43]

Comparison 2. ALPHA-TOCOPHEROL VERSUS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any ARM	2	1466	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.91, 1.36]
2 Early ARM	2	1466	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]
3 Late ARM	2	1466	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.89, 7.10]

Comparison 3. BETA-CAROTENE VERSUS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any ARM	2	21589	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]
2 Early ARM	1	447	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.85, 1.58]
3 Late ARM	2	21589	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.36]

Analysis 1.1. Comparison 1 ANY ANTIOXIDANT VERSUS PLACEBO, Outcome 1 Any ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 1 ANY ANTIOXIDANT VERSUS PLACEBO

Outcome: 1 Any ARM

Study or subgroup	Antioxidant n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	216/728	53/213		18.3 %	1.19 [0.92, 1.54]
PHS I	275/10585	274/10557		61.3 %	1.00 [0.85, 1.18]
VECAT	92/504	92/512		20.4 %	1.02 [0.78, 1.32]
Total (95% CI)	**11817**	**11282**		**100.0 %**	**1.04 [0.92, 1.18]**

Total events: 583 (Antioxidant), 419 (Placebo)

Heterogeneity: Chi^2 = 1.31, df = 2 (P = 0.52); I^2 =0.0%

Test for overall effect: Z = 0.61 (P = 0.54)

Analysis 1.2. Comparison 1 ANY ANTIOXIDANT VERSUS PLACEBO, Outcome 2 Early ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 1 ANY ANTIOXIDANT VERSUS PLACEBO

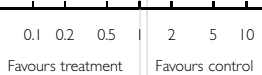
Outcome: 2 Early ARM

Study or subgroup	Antioxidant n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	203/728	52/213		48.0 %	1.14 [0.88, 1.49]
VECAT	87/504	88/512		52.0 %	1.00 [0.77, 1.32]
Total (95% CI)	**1232**	**725**		**100.0 %**	**1.07 [0.89, 1.29]**

Total events: 290 (Antioxidant), 140 (Placebo)

Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 0.71 (P = 0.48)



Analysis 1.3. Comparison 1 ANY ANTIOXIDANT VERSUS PLACEBO, Outcome 3 Late ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 1 ANY ANTIOXIDANT VERSUS PLACEBO

Outcome: 3 Late ARM

Study or subgroup	Antioxidant n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	13/728	1/213		2.2 %	3.80 [0.50, 28.91]
PHS I	63/10585	66/10557		92.3 %	0.95 [0.67, 1.34]
VECAT	5/504	4/512		5.5 %	1.27 [0.34, 4.70]
Total (95% CI)	**11817**	**11282**		**100.0 %**	**1.03 [0.74, 1.43]**

Total events: 81 (Antioxidant), 71 (Placebo)

Heterogeneity: Chi^2 = 1.90, df = 2 (P = 0.39); I^2 =0.0%

Test for overall effect: Z = 0.18 (P = 0.85)

Analysis 2.1. Comparison 2 ALPHA-TOCOPHEROL VERSUS PLACEBO, Outcome 1 Any ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 2 ALPHA-TOCOPHEROL VERSUS PLACEBO

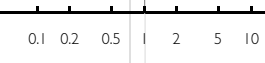
Outcome: 1 Any ARM

Study or subgroup	Alpha-tocopherol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	75/237	53/213		38.0 %	1.27 [0.94, 1.72]
VECAT	92/504	92/512		62.0 %	1.02 [0.78, 1.32]
Total (95% CI)	**741**	**725**		**100.0 %**	**1.11 [0.91, 1.36]**

Total events: 167 (Alpha-tocopherol), 145 (Placebo)

Heterogeneity: Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =19%

Test for overall effect: Z = 1.07 (P = 0.29)

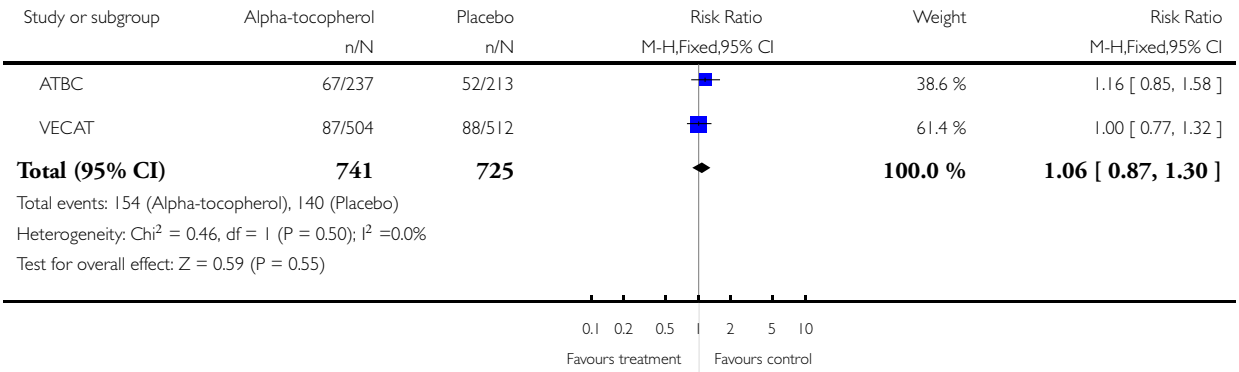


Analysis 2.2. Comparison 2 ALPHA-TOCOPHEROL VERSUS PLACEBO, Outcome 2 Early ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 2 ALPHA-TOCOPHEROL VERSUS PLACEBO

Outcome: 2 Early ARM

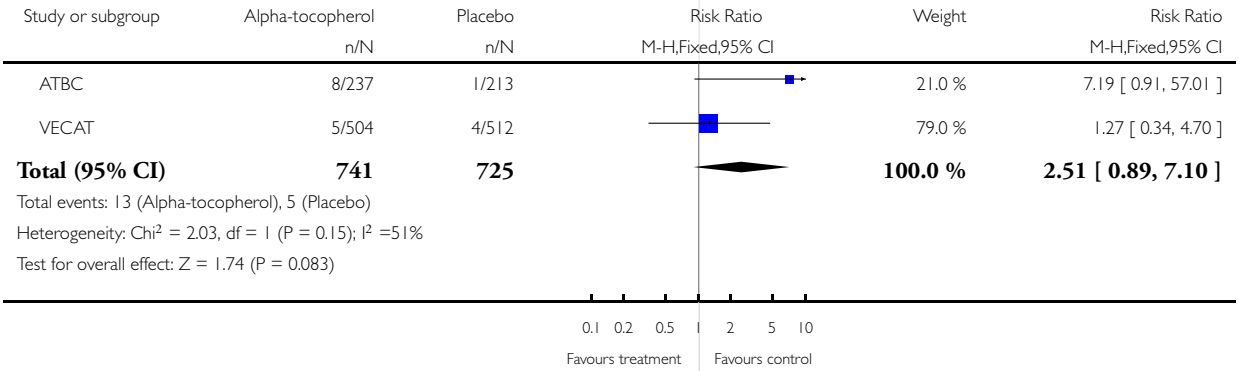


Analysis 2.3. Comparison 2 ALPHA-TOCOPHEROL VERSUS PLACEBO, Outcome 3 Late ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 2 ALPHA-TOCOPHEROL VERSUS PLACEBO

Outcome: 3 Late ARM



Analysis 3.1. Comparison 3 BETA-CAROTENE VERSUS PLACEBO, Outcome 1 Any ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 3 BETA-CAROTENE VERSUS PLACEBO

Outcome: 1 Any ARM

Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	68/234	53/213		16.8 %	1.17 [0.86, 1.59]
PHS I	275/10585	274/10557		83.2 %	1.00 [0.85, 1.18]
Total (95% CI)	**10819**	**10770**		**100.0 %**	**1.03 [0.89, 1.19]**
Total events: 343 (Beta-carotene), 327 (Placebo)					
Heterogeneity: Chi^2 = 0.76, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.70)					

Analysis 3.2. Comparison 3 BETA-CAROTENE VERSUS PLACEBO, Outcome 2 Early ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 3 BETA-CAROTENE VERSUS PLACEBO

Outcome: 2 Early ARM

Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	66/234	52/213		100.0 %	1.16 [0.85, 1.58]
Total (95% CI)	**234**	**213**		**100.0 %**	**1.16 [0.85, 1.58]**
Total events: 66 (Beta-carotene), 52 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.37)					

Analysis 3.3. Comparison 3 BETA-CAROTENE VERSUS PLACEBO, Outcome 3 Late ARM.

Review: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration

Comparison: 3 BETA-CAROTENE VERSUS PLACEBO

Outcome: 3 Late ARM

Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	2/234	1/213		1.6 %	1.82 [0.17, 19.93]
PHS I	63/10585	66/10557		98.4 %	0.95 [0.67, 1.34]
Total (95% CI)	**10819**	**10770**		**100.0 %**	**0.97 [0.69, 1.36]**

Total events: 65 (Beta-carotene), 67 (Placebo)

Heterogeneity: $Chi^2 = 0.28$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

APPENDICES

Appendix 1. CENTRAL and NRR search strategies used for Issue 3, 2007

#1 MeSH descriptor Macular Degeneration
#2 MeSH descriptor Retinal Degeneration
#3 MeSH descriptor Retinal Neovascularization
#4 MeSH descriptor Choroidal Neovascularization
#5 MeSH descriptor Macula Lutea
#6 macula* near lutea*
#7 ((macul* OR retina* OR choroid*:TI) AND (degener* OR neovasc*:TI))
#8 ((macul* OR retina* OR choroid*:AB) AND (degener* OR neovasc*:AB))
#9 maculopath*
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Vitamins
#12 vitamin*
#13 MeSH descriptor Vitamin A
#14 retinol*
#15 MeSH descriptor beta Carotene
#16 caroten*
#17 MeSH descriptor Ascorbic Acid
#18 ascorbic next acid
#19 MeSH descriptor Vitamin E
#20 MeSH descriptor alpha-Tocopherol
#21 alpha tocopherol*

#22 MeSH descriptor Vitamin B 12
#23 cobalamin*
#24 MeSH descriptor Antioxidants
#25 antioxidant* or anti oxidant*
#26 MeSH descriptor Carotenoids
#27 carotenoid*
#28 MeSH descriptor Zinc
#29 zinc*
#30 MeSH descriptor Riboflavin
#31 riboflavin*
#32 MeSH descriptor Selenium
#33 selenium*
#34 MeSH descriptor Lutein
#35 lutein*
#36 MeSH descriptor Xanthophylls
#37 xanthophyll*
#38 zeaxanthin*
#39 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#40 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#41 (#39 OR #40)
#42 (#10 AND #41)

Appendix 2. MEDLINE search strategy used on OVID up to August 2007

1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp macular degeneration/
14. exp retinal degeneration/
15. exp retinal neovascularization/
16. exp choroidal neovascularization/
17. exp macula lutea/
18. maculopath$.tw.
19. ((macul$ or retina$ or choroid$) adj3 degener$).tw.
20. ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
21. (macula$ adj2 lutea).tw.
22. or/13-21
23. exp vitamins/
24. exp vitamin A/
25. vitamin A.tw.
26. retinol$.tw.
27. exp beta carotene/
28. caroten$.tw.

29. exp ascorbic acid/
30. ascorbic acid$.tw.
31. vitamin C.tw.
32. exp Vitamin E/
33. exp alpha tocopherol/
34. alpha?tocopherol$.tw.
35. alpha tocopherol$.tw.
36. vitamin E.tw.
37. exp Vitamin B12/
38. vitamin B12.tw.
39. cobalamin$.tw.
40. exp antioxidants/
41. ((antioxidant$ or anti) adj1 oxidant$).tw.
42. exp carotenoids/
43. carotenoid$.tw.
44. exp zinc/
45. zinc$.tw.
46. exp riboflavin/
47. riboflavin$.tw.
48. exp selenium/
49. selenium$.tw.
50. exp lutein/
51. lutein$.tw.
52. exp xanthophylls/
53. xanthophyll.tw.
54. zeaxanthin$.tw.
55. or/23-54
56. 22 and 55
57. 12 and 56

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE search strategy used on OVID up to August 2007

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/

20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula degeneration/
34. exp retina degeneration/
35. exp retina neovascularization/
36. exp subretinal neovascularization/
37. maculopath$.tw.
38. ((macul$ or retina$ or choroid$) adj3 degener$).tw.
39. ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
40. exp retina macula lutea/
41. (macula$ adj2 lutea$).tw.
42. or/33-41
43. exp vitamins/
44. exp Retinol/
45. vitamin A.tw.
46. retinol$.tw.
47. exp beta carotene/
48. caroten$.tw.
49. exp ascorbic acid/
50. ascorbic acid$.tw.
51. vitamin C.tw.
52. exp alpha tocopherol/
53. alpha?tocopherol$.tw.
54. alpha tocopherol$.tw.
55. vitamin E.tw.
56. vitamin B12.tw.
57. exp cyanocobalamin/
58. cobalamin$.tw.
59. exp antioxidants/
60. ((antioxidant$ or anti) adj1 oxidant$).tw.
61. exp carotenoid/
62. exp zinc/
63. zinc$.tw.
64. exp riboflavin/
65. riboflavin$.tw.
66. exp selenium/
67. selenium$.tw.
68. exp zeaxanthin/
69. zeaxanthin$.tw.
70. lutein$.tw.
71. xanthophyll.tw.
72. or/43-71

73. 42 and 72
74. 32 and 73

Appendix 4. SIGLE search strategy used up to 2005/03

#1 anti-oxidant* or antioxidant* or vitamin* or caroten*
#2 (beta next epsilon next caroten*) or beta-epsilon-caroten* or (alpha next tocopherol) or alpha-tocopherol or selenium or lutein* or zeaxanthin*
#3 (ascorbic next acid) or caroten* or beta-caroten* or betacaroten*
#4 #1 or #2 or #3
#5 macula* next lutea*
#6 (macul* or retina* or choroid*) and (degener* or neovasc*)
#7 AMD or maculopath*
#8 #5 or #6 or #7
#9 #4 and #8

Appendix 5. PubMed search strategy used to 24 January 2006 (last 60 days)

#1 anti-oxidant* or antioxidant* or vitamin* or caroten*
#2 (beta next epsilon next caroten*) or beta-epsilon-caroten* or (alpha next tocopherol) or alpha-tocopherol or selenium or lutein* or zeaxanthin*
#3 (ascorbic next acid) or caroten* or beta-caroten* or betacaroten*
#4 #1 or #2 or #3
#5 macula* next lutea*
#6 (macul* or retina* or choroid*) and (degener* or neovasc*)
#7 AMD or maculopath*
#8 #5 or #6 or #7
#9 #4 and #8

Appendix 6. Allied & Complementary Medicine search strategy used up to January 2006

#1 anti-oxidant* or antioxidant* or vitamin* or caroten*
#2 (beta next epsilon next caroten*) or beta-epsilon-caroten* or (alpha next tocopherol) or alpha-tocopherol or selenium or lutein* or zeaxanthin*
#3 (ascorbic next acid) or caroten* or beta-caroten* or betacaroten*
#4 #1 or #2 or #3
#5 macula* next lutea*
#6 (macul* or retina* or choroid*) and (degener* or neovasc*)
#7 AMD or maculopath*
#8 #5 or #6 or #7
#9 #4 and #8

WHAT'S NEW

Last assessed as up-to-date: 1 August 2007.

Date	Event	Description
28 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 4, 1999

Date	Event	Description
8 November 2007	New citation required and conclusions have changed	Substantive amendment. Issue 1 2008: The results for PHS I are included. AREDS was previously included in this review but as no numerical data were available from the study as regards prevention of AMD, it was excluded from the review. The results of AREDS are presented in the review "Antioxidants for slowing down the progression of AMD"

CONTRIBUTIONS OF AUTHORS

JE assessed studies for inclusion/exclusion, assessed quality, extracted data, entered data, and wrote the text of the review.

KH assessed studies for inclusion/exclusion, assessed quality, extracted data, contacted trialists and commented on the text of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Antioxidants [*administration & dosage]; Macular Degeneration [*prevention & control]; Minerals [*administration & dosage]; Randomized Controlled Trials as Topic; Vitamins [*administration & dosage]; alpha-Tocopherol [administration & dosage]; beta Carotene [administration & dosage]

MeSH check words

Humans