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

Evans JR, Lawrenson JG

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[Intervention Review]

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

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ABSTRACT

Background

There is inconclusive evidence from observational studies to suggest 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

To examine the evidence as to whether or not taking antioxidant vitamin or mineral supplements prevents the development of AMD.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2011, Issue 12), MEDLINE (January 1950 to January 2012), EMBASE (January 1980 to January 2012), Open Grey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 26 January 2012.

Selection criteria

We included all randomised controlled trials (RCTs) comparing an antioxidant vitamin and/or mineral supplement (alone or in combination) to control.

Data collection and analysis

Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5 and the other author checked the data entry. We pooled data using a fixed-effect model.

Main results

We included four RCTs in this review; 62,520 people were included in the analyses. The trials were conducted in Australia, Finland and the USA and investigated vitamin E and beta-carotene supplements. Overall the quality of the evidence was high. People who took these supplements were not at decreased (or increased) risk of developing AMD. The pooled risk ratio for any antioxidant supplement in the prevention of any AMD was 0.98 (95% confidence interval 0.89 to 1.08) and for advanced AMD was 1.05 (95% CI 0.80 to 1.39). Similar results were seen when the analyses were restricted to beta-carotene and alpha-tocopherol alone.

Authors' conclusions

There is accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. There is no evidence with respect to other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations. Although generally regarded as safe, vitamin supplements may have harmful effects and clear evidence of benefit is needed before they can be recommended. 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 review team.

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 four large, high-quality randomised controlled trials which included 62,520 people. The trials were conducted in Australia, Finland and the USA and investigated the effects of vitamin E and beta-carotene supplementation. These trials provide evidence that taking vitamin E and beta-carotene supplements is unlikely to prevent the onset of AMD. There was no evidence for other antioxidant supplements and commonly marketed combinations. Although generally regarded as safe, vitamin supplements may have harmful effects and clear evidence of benefit is needed before they can be recommended.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antioxidant supplement compared with placebo for prevention of AMD

Patient or population: general population
Settings: community
Intervention: vitamin E
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antioxidant supplementation				
Any AMD	180 per 1000	181 per 1000 (159 to 204)	RR 0.97 (0.85 to 1.09)	40,887 (4)	⊕⊕⊕⊕ high	
Advanced AMD	6 per 1000	8 per 1000 (5 to 13)	RR 1.34 (0.84 to 2.14)	40,887 (4)	⊕⊕⊕⊕ high	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMD: age-related macular degeneration; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

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.

The early stages of the disease are in general asymptomatic. In the later stages there may be considerable distortion within the central visual field leading to a complete loss of central visual function.

Population-based studies suggest that, in people 65 years and older, approximately 5% have advanced AMD (Owen 2012). 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 (Bunce 2006).

Description of the intervention

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. The results of these observational studies have been inconclusive.

How the intervention might work

The underlying theory is that antioxidant vitamin and mineral supplements will protect the retina against oxidative stress and that this protection will delay the onset of AMD.

Why it is important to do this 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

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 controlled trials (RCTs) 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 (including the macula pigment carotenoids lutein and zeaxanthin), selenium and zinc.

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 3000 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 Age-Related Eye Disease Study System for classifying age-related macular degeneration (AREDS 2001b). In particular, the term 'advanced AMD' refers to geographic atrophy or neovascular AMD.

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 the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 12, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 26 January 2012), MEDLINE (January 1950 to January 2012), EMBASE (January 1980 to January 2012), Open Grey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 26 January 2012.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), Open Grey (Appendix 5), *m*RCT (Appendix 6), ClinicalTrials.gov (Appendix 7) and the ICTRP (Appendix 8).

For the update in 2012 we specifically looked for adverse effects using a simple search aimed to identify systematic reviews of adverse effects of vitamin supplements, see Appendix (Appendix 9) for search strategy.

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 studies

Our initial searches identified all trials of antioxidant supplements and therefore generated many citations. 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.

In updates to this review, both authors went through the titles and abstracts resulting from the searches independently and resolved disagreements by discussion.

Data extraction and management

We extracted data using methods forms developed by the Cochrane Eyes and Vision Group (http://eyes.cochrane.org/resources-review-authors). We extracted data independently and resolved disagreements by discussion. One author cut and pasted the data into RevMan 5 (Review Manager 2011) and the other author checked that this had been done correctly.

Assessment of risk of bias in included studies

Two authors independently assessed risk of bias using the Cochrane Collaboration's tool for assessing risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion. We contacted trial authors for clarification on any parameter graded as 'unclear'. The review authors were not masked to any trial details.

Measures of treatment effect

Our measure of treatment effect was the risk ratio for dichotomous outcomes and the mean difference for continuous outcomes. Currently the review only includes analysis of dichotomous outcomes.

Unit of analysis issues

The interventions, by definition, are applied to the person but as most people have two eyes trials can analyse data from one or both eyes. The trials included in this review reported the development of AMD in either eye of the person therefore the unit of analysis was the same as the unit of randomisation.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plot, the χ^2 test for heterogeneity and the I^2 statistic.

Data synthesis

We summarised data using the risk ratio, after testing for heterogeneity between trial results using a standard Chi^2 test.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were planned. Only four trials are included at present which means that it is not possible to investigate heterogeneity formally.

Sensitivity analysis

We planned to conduct sensitivity analyses to determine the impact of study quality on effect size. Currently there are four high-quality trials included in the review and therefore this is not relevant at present.

RESULTS

Description of 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. Three trials have published data on AMD outcomes (ATBC 1994; PHS I; WHS) and are included in this review. 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 AMD. AREDS is not included in this review because AMD outcomes for people without AMD 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. We received 15 responses and none had 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. The Trials Search Co-ordinator (TSC) scanned the search results and removed 84 references which were not relevant to the scope of the review. We screened the title and abstracts of the remaining 45 references and obtained full-text copies of four reports to assess for potential inclusion in the review. We identified one new report from the PHS I study to be included in the review and the three remaining studies were excluded. For reasons of exclusion, see 'Characteristics of excluded studies' table.

An update search was done in January 2012 which yielded 477 titles and abstracts. The TSC scanned the search results and removed 206 references which were not relevant to the scope of the review. We screened the title and abstracts of the remaining 271 references. We rejected 267 abstracts as not eligible for inclusion in the review. We obtained full-text copies of four reports for further examination. One new report from the WHS study has been included in the review and three other studies were excluded. For reasons of exclusion, see 'Characteristics of excluded studies' table.

Included studies

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 men only (ATBC 1994; PHS I), one study recruited women only (WHS) 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 and in WHS were female health professionals. 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 AMD 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 years). 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. In WHS, participants received vitamin E (600 IU on alternate days) or placebo and were followed up for 10 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.

In PHS I and WHS, 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. Early AMD (the primary outcome) was defined as soft drusen (distinct or indistinct) or pigmentary changes (hyperpigmentation or hypopigmentation) on photographic grading. On clinical grading this was large/soft drusen or non-geographical retinal pigment epithelium atrophy. VECAT used Bailey-Lovie visual acuity charts #4 and #5 (National Vision Research Institute, Australia).

Excluded studies

See the 'Characteristics of excluded studies' table for further information.

Risk of bias in included studies

We considered all four trials to be at low risk of bias (Figure 1; Figure 2). See 'Risk of bias' tables for each included study for details of the assessment.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

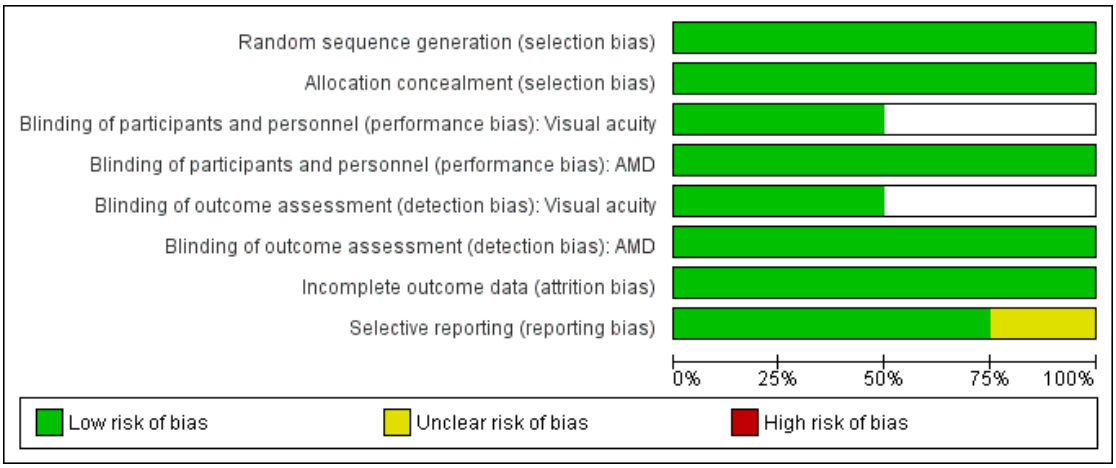
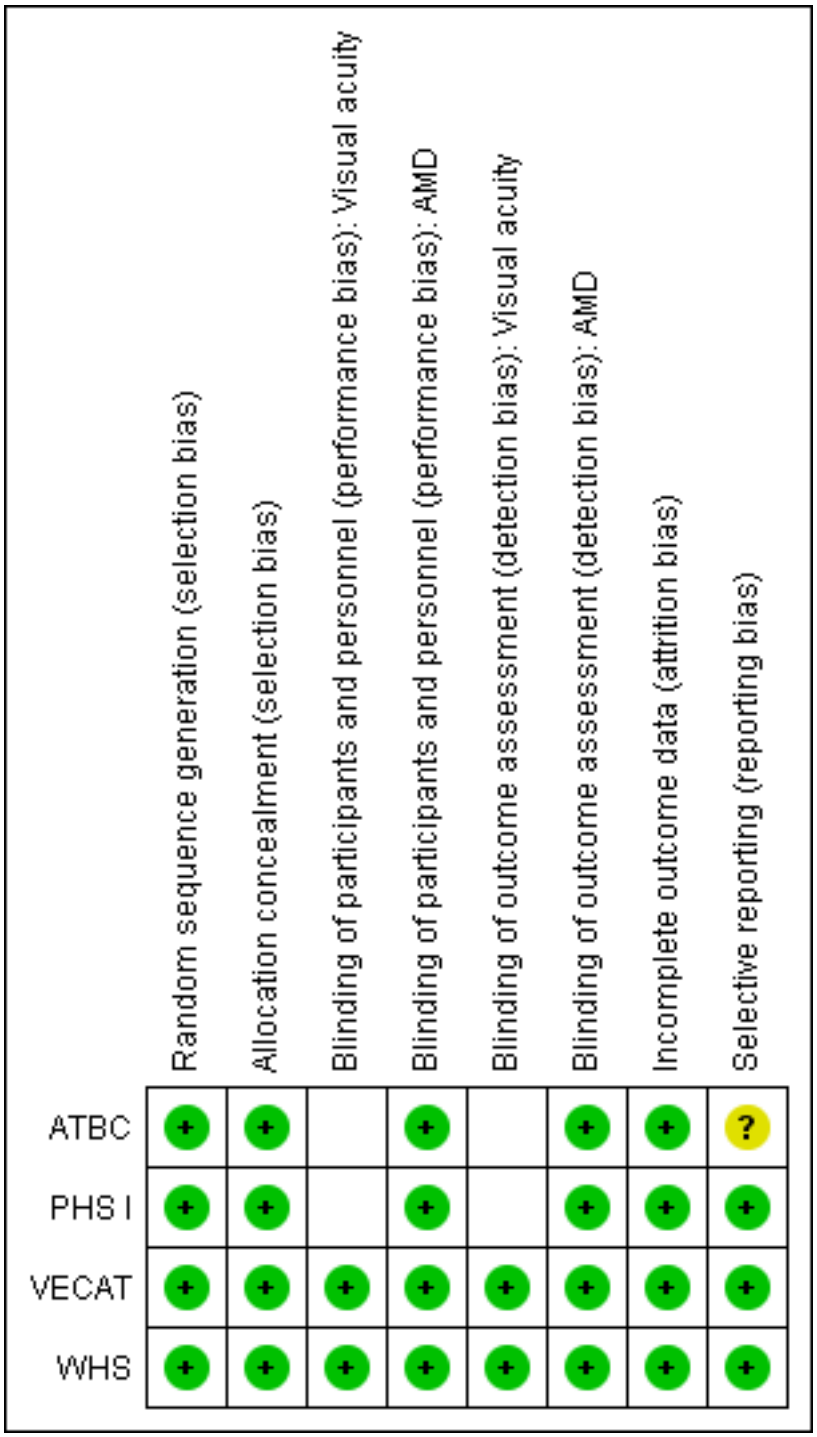


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: vitamin E; **Summary of findings 2** Summary of findings: beta-carotene

Overall 62,520 participants were included in the analyses of the four included trials. There were 863 cases of AMD in the antioxidant groups and 732 cases of AMD in the placebo groups (Analysis 1.1). The results of the four studies were reasonably consistent (I^2 = 16%). There was little evidence of any effect of antioxidant supplementation (RR 0.98, 95% CI 0.89 to 1.08).

Similarly with advanced AMD the trials were consistent (I^2 = 0%) and indicate little evidence of any effect of supplementation (RR 1.05, 95% CI 0.80 to 1.39) (Analysis 1.2). There were fewer advanced AMD events (110 cases in the antioxidant groups and 97 in the placebo groups).

Similar results were seen for analyses of alpha-tocopherol alone versus placebo (Analysis 2.1; Analysis 2.2). A total of 40,887 people randomised in ATBC, VECAT and WHS resulted in 447 cases of AMD in the alpha-tocopherol group and 458 in the placebo group (Analysis 2.1). The trial results were less consistent (I^2 = 53%). There was little evidence of any effect of supplementation with alpha-tocopherol on the incidence of AMD (RR 0.97, 95% CI 0.85 to 1.09). There were fewer cases of advanced AMD: 42 in the alpha-tocopherol groups and 31 in the placebo (Analysis 2.2). Again there was little evidence of any benefit from supplementation with a pooled RR in the direction of harm 1.34 (95% CI 0.84 to 2.14).

A total of 21,589 people were randomised into ATBC and PHS I comparing beta-carotene with placebo (Analysis 3.1; Analysis 3.2). There were 343 cases of AMD 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 0.89 to 1.19). There were 65 cases of advanced AMD in the beta-carotene groups and 67 cases of advanced AMD 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 1.36).

Adverse effects

None of the trials included in this review reported eye-related adverse effects. The main ATBC trial found an increased risk of lung cancer associated with beta-carotene supplementation (ATBC 1994), a finding that was repeated in the large CARET trial (Omenn 1996). Beta-carotene supplementation is contraindicated in people who smoke or have been exposed to asbestos. The AREDS study found an increased risk of hospitalisation for genitourinary conditions in men taking high-dose zinc supplementation (Johnson 2007) and increased yellowing of the skin (AREDS 2001a).

Huang 2006 did not identify any consistent adverse effects of mineral and vitamin supplements but only included nine RCTs in their review. A subsequent Cochrane review including 78 trials with 296,707 participants concluded "*We found no evidence to support antioxidant supplements for primary or secondary prevention. Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A*" (Bjelakovic 2012).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Antioxidant supplement compared with placebo for prevention of AMD

Patient or population: general population
Settings: community
Intervention: beta-carotene
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antioxidant supplementation				
Any AMD	180 per 1000	193 per 1000 (166 to 223)	RR 1.03 (0.89 to 1.19)	21,589 (3)	⊕⊕⊕⊕ high	
Advanced AMD	6 per 1000	6 per 1000 (4 to 8)	RR 0.97 (0.69 to 1.36)	21,589 (3)	⊕⊕⊕⊕ high	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AMD: age-related macular degeneration; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

DISCUSSION

Summary of main results

This review provides evidence that people who take vitamin E or beta-carotene supplements do not reduce their risk of developing AMD (Summary of findings for the main comparison; Summary of findings 2).

Overall completeness and applicability of evidence

This review includes four large, high-quality studies which have randomised over 64,000 members of the population to antioxidant supplementation or placebo. Duration of supplementation has ranged from four to 12 years.

This review does not provide evidence as to the effects of other antioxidant vitamin and mineral supplements on the development of AMD, in particular it does not provide evidence as to the effects of commonly marketed vitamin combinations.

There are additional ongoing studies, including 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 2 x 2 x 2 x 2 factorial design to vitamin C, vitamin E, folate, vitamin B6 and vitamin B12 supplementation (WACS).

Although generally regarded as safe, antioxidant supplements may have harmful effects. Beta-carotene increases the risk of lung cancer and overall there is some evidence of a small increased risk of mortality in people who take beta-carotene or vitamin E.

Quality of the evidence

Overall the quality of the evidence was considered to be high (Summary of findings for the main comparison; Summary of findings 2).

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.

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.

Agreements and disagreements with other studies or reviews

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.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised controlled 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 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.

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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: 2 x 2 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 vitamin E, A or beta-carotene in excess of predefined doses; those treated with anticoagulants
Interventions	Treatment: 3 regimens: alpha-tocopherol (50 mg), beta-carotene (20 mg) or alpha-tocopherol and beta-carotene Control: placebo Duration: 5 to 8 years (median 6.1)
Outcomes	AMD: 4 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 scheduled capsules. Drop-out rate and compliance similar between all 4 groups

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*The participants were randomly assigned to one of four treatment groups: AT alone, AT and BC, BC alone, or placebo in a complete 2 x 2 factorial design*" and "*Randomization was performed in blocks of eight within each of the study areas.*" The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant

ATBC (*Continued*)

		characteristics, and compliance. *Annals of Epidemiology* 1994;4: page 1
Allocation concealment (selection bias)	Low risk	"*A coded reserve supply of capsule packs...*" *page 3* Not clearly stated that allocation concealed but the study was described as being "double-blind"
Blinding of participants and personnel (performance bias) AMD	Low risk	"*The retinal specialist [...] examined six photographs (three per eye) of each participant without knowledge of the subject's treatment group*" Teikari et al page 226
Blinding of outcome assessment (detection bias) AMD	Low risk	"*The retinal specialist [...] examined six photographs (three per eye) of each participant without knowledge of the subject's treatment group*" Teikari et al page 226
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*A total of 941 persons participated (91%) and non-participation rates were similar across the intervention groups*." Teikari et al page 226
Selective reporting (reporting bias)	Unclear risk	Visual acuity measured but not reported but as the main results for AMD showed no difference between groups it is not clear whether this is an example of selective reporting or whether in fact the investigators considered that visual acuity in this age group might be attributed to a variety of causes and therefore was not a relevant outcome

PHS I

Methods	Method of allocation: coded tablets Masking: participant: yes; provider: yes; outcome: yes 99% follow-up Unusual study design: 2 x 2 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 AMD 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

PHS I (*Continued*)

	Inclusion criteria: Physician aged 40 to 84 years in 1982 with no history of cancer, myocardial infarction, stroke or transient cerebral ischaemia Exclusion criteria:personal history of cardiovascular disease or cancer; contraindications or current use of study medication;
Interventions	Treatment: 4 groups: 1. Aspirin 325 mg 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 December 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 AMD, defined as a self report confirmed by medical record evidence of an initial diagnosis after randomisation but before 31 December 1995 with a reduction in best-corrected visual acuity to 20/30 or worse attributable to AMD Secondary endpoints: AMD with or without vision loss, composed of all incidence cases Advanced AMD, encompassed of cases of visually significant AMD with pathological signs of disciform scar, RPE detachment, geographic atrophy or subretinal neovascular membrane
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The PHS I was a randomized, double-masked, placebo controlled trial...*" Page 334 Christen et al 2007 *"A total of 22,071 physicians were then randomized according to a two-by-two factorial design, with use of a computer-generated list of random numbers..."* Page 262 *New England Journal of Medicine* 1982
Allocation concealment (selection bias)	Low risk	"*The PHS I was a randomized, double-masked, placebo controlled trial...*" Page 334 Christen et al 2007

PHS I (*Continued*)

Blinding of participants and personnel (performance bias) AMD	Low risk	"*The PHS I was a randomized, double-masked, placebo controlled trial...*" Page 334 Christen et al 2007 Although this aspect of the trial was not well described the placebo control was described (placebo and supplement identical appearance and packaging) and the study was described as double-blind
Blinding of outcome assessment (detection bias) AMD	Low risk	"*The PHS I was a randomized, double-masked, placebo controlled trial...*" Page 334 Christen et al 2007 Although this aspect of the trial was not well described the placebo control was described and the study was described as double-blind. Diagnosis of AMD by self report based on health questionnaire (confirmed by ophthalmologist and optometrist). Patients and researchers unaware of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*At the end of 11 years of follow-up (the last year completed for all participants), 99.2% were still providing information on morbidity, and the follow-up for mortality was 99. 9% complete. Eighty percent of participants in the beta carotene group and in the placebo group* *were still taking the study pills, with a mean compliance among pill takers of more than 97%. Therefore, even after 11 years, 78% of the study pills assigned in the beta carotene group were reported as still being taken. In the placebo group, 6% of participants reported taking supplemental beta carotene or vitamin A."* Christen et al 2007 page 334
Selective reporting (reporting bias)	Low risk	Reported AMD outcomes as expected

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

VECAT (*Continued*)

	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	2 m 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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*This random allocation was performed by using a "permuted blocks" allocation scheme*" Page 2
Allocation concealment (selection bias)	Low risk	"*Study numbers were allocated sequentially by the study coordinator as participants were enrolled in the study. Participants were then randomly allocated to treatment group. The allocation list was stored at a remote site*." Page 2
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*Participants randomly received either 500 IU natural vitamin E (335 mg dá tocopherol) in a soybean oil suspension encapsulated in gelatin or a matched placebo capsule containing only the soybean oil." [...] "Bulk medications were dispensed into labelled jars by a person not involved in the study. Vitamin E and placebo were dispensed on different days to avoid confusion. Identical containers were used. The jars were packed in numerical order and then dispensed by study personnel. Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo.*" Page 2

Blinding of participants and personnel (performance bias) AMD	Low risk	"*Participants randomly received either 500 IU natural vitamin E (335 mg dá tocopherol) in a soybean oil suspension encapsulated in gelatin or a matched placebo capsule containing only the soybean oil." [...] "Bulk medications were dispensed into labelled jars by a person not involved in the study. Vitamin E and placebo were dispensed on different days to avoid confusion. Identical containers were used. The jars were packed in numerical order and then dispensed by study personnel. Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo.*" Page 2
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo.*" Page 2
Blinding of outcome assessment (detection bias) AMD	Low risk	"*Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo.*" Page 2 *"At the end of the study we reassessed the initial and final photographs for any change with a "side by side" comparison in a masked and randomised fashion".* Page 2
Incomplete outcome data (attrition bias) All outcomes	Low risk	*"From the 1906 people who were screened by telephone, 1289 (69%) were examined and 1204 (93%) of these were enrolled and randomised. We excluded 11 participants after randomisation as they were outside the required age range at enrolment."* Page 1 *"In the vitamin E group eight people were excluded from final data analysis: six developed diabetic retinopathy, one had myopic degeneration, and one had missing data. Six people were excluded from the placebo group: two developed adult vitelliform macular degeneration and four had*

VECAT (*Continued*)

		missing data" Page 3 Figure 3 Page 4 1204 randomised, 11 excluded after randomisation, 14 excluded from analysis 8/595 vitamin E group and 6/598 placebo group
Selective reporting (reporting bias)	Low risk	AMD incidence and progression reported but no difference between groups; visual acuity not reported but "*Analysis of best corrected visual acuity and visual function data showed no differences between the groups (data not shown).*" Page 4. Therefore no evidence that outcomes with "better" results selectively reported

WHS

Methods	Method of allocation: Masking: participant: yes; provider: yes; outcome: yes Losses to follow-up: not known
Participants	Country: USA Number of participants randomised: 39,876 women health professionals Age: 45+ Sex: 100% female Inclusion/exclusion criteria: a) Female; (b) aged 45 years or older; (c) postmenopausal or with no intention of becoming pregnant; (d) no reported personal history of cardiovascular disease, cancer (other than non-melanoma skin cancer), gout, peptic ulcer, chronic renal or liver disease, or other serious illness precluding participation; (e) no reported history of serious side effects to the study treatments; (f) not currently taking aspirin, aspirin containing medication, or nonsteroidal anti-inflammatory drugs (NSAIDs) more than 1 day per week or, if so doing, willing to forego use of these medications; (g) not currently taking individual supplements of vitamin E or beta-carotene more than 1 day per week; (h) not currently taking anticoagulants or corticosteroids
Interventions	Vitamin E (600 IU on alternate days) or placebo
Outcomes	Self report and review of medical records
Notes	NCT00000161

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

WHS (*Continued*)

Random sequence generation (selection bias)	Low risk	"*The WHS was a randomized, double-blind, placebo-controlled, 2x2 factorial trial. ..*" Page 1163
Allocation concealment (selection bias)	Low risk	"*The WHS was a randomized, double-blind, placebo-controlled, 2x2 factorial trial. ..*" Page 1163
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*Study medications and end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial (March 31, 2004).*" Ridker et al 2005 page 1294 *"Pill taking and end point ascertainment were continued in blinded fashion through the scheduled end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97. 2% and 99.4% complete, respectively.*" Page 1164
Blinding of participants and personnel (performance bias) AMD	Low risk	"*Study medications and end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial (March 31, 2004).*" Ridker et al 2005 page 1294 *"Pill taking and end point ascertainment were continued in blinded fashion through the scheduled end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97. 2% and 99.4% complete, respectively.*" Page 1164
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Study medications and end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial (March 31, 2004).*" Ridker et al 2005 page 1294 *"Pill taking and end point ascertainment were continued in blinded fashion through the scheduled end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97. 2% and 99.4% complete, respectively.*" Page 1164
Blinding of outcome assessment (detection bias) AMD	Low risk	"*Study medications and end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial (March 31, 2004).*" Ridker et al 2005 page 1294 *"Pill taking and end point ascertainment were continued in blinded fashion through the scheduled end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97.*

WHS (*Continued*)

		2% and 99.4% complete, respectively." Page 1164
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Compliance (defined as taking at least two thirds of the study capsules) was 78.9% at 5 years and 71.6% at 10 years, and averaged 75.8% throughout the trial.*" Page 1164 "*Pill taking and end point ascertainment were continued in blinded fashion through the scheduled end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97. 2% and 99.4% complete, respectively.*" Page 1164 Follow-up balanced across treatment groups. See figure 1 page 1164
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. The outcome was limited to the study design - medical record review. Primary and secondary outcomes were apparently defined a priori and were reported

AMD: age-related macular degeneration
ETDRS: Early Treatment Diabetic Retinopathy Study
IU: international units
RPE: retinal pigment epithelium

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

(*Continued*)

Bogden 1990	No published data on age-related macular degeneration. No response from author
Bone 2010	Biological availability study only
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
CARMIS	Study on people with AMD (non-advanced AMD) therefore not on prevention in healthy people
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
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
Falsani 2010	Participants had early AMD

(*Continued*)

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
Kvansakul 2006	No AMD outcomes
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
NCT00718653	Study of macular pigment only
NCT01208948	No AMD outcomes
Newsome, 2008	Study on people with AMD
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
Pemp 2010	Study of ocular blood flow and endothelial function only in model of oxidative stress in health volunteers

(*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
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
Rein 2007	Study not a randomised controlled trial
Ret Pig 1993	No published data on age-related macular degeneration. No response from author
Rodriguez-Carmona 2006	No AMD outcomes
SAINTS	Study on people with AMD
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
WAFACS	Reported on folic acid, pyridoxine and cyanocobalamin combination treatment
Wahlqvist 1994	No data on age-related macular degeneration collected
Wong 2010	Participants had geographic atrophy

(*Continued*)

Wright 1985	No published data on age-related macular degeneration. No response from author
Yu 1991	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

AMD: age-related macular degeneration

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

AREDS2

Trial name or title	Age-Related Eye Disease Study 2 (AREDS2): a multi-center, randomized trial of lutein, zeaxanthin and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) in age-related macular degeneration
Methods	AREDS2 is a multi-centre randomised trial of approximately 4200 participants, designed to assess the effects of oral supplementation of high doses of macular xanthophylls (lutein and zeaxanthin) and omega-3 LCPUFAs (DHA and EPA) for the treatment of AMD and cataract. AREDS2 was designed to evaluate the effects of high supplemental doses of lutein and zeaxanthin and omega-3 LCPUFAs on the development of advanced AMD. The study enrolled participants aged 50 to 85 years, with sufficiently clear ocular media to allow accurate assessment of AMD from fundus photographs. All participants are offered additional treatment with the original AREDS formulation (now considered standard of care) and 3 variations of this formula. These are: (1) no beta-carotene; (2) lower amounts of zinc; and (3) no beta-carotene and lower amounts of zinc. Eligible participants are followed for a minimum of 5 years
Participants	Participants were enrolled on the basis of the AREDS Simplified Severity Scale for defining risk categories for development of advanced age-related macular degeneration
Interventions	10 mg lutein and 2 mg zeaxanthin (1 tablet) 350 mg DHA and 650 mg EPA (2 soft-gel capsules) Factorial design, 3 arms (no arm with placebo for both)
Outcomes	Primary outcome measures: Progression to advanced AMD in people at moderate to high risk for progression Secondary outcome measures: Progression to moderate vision loss Adverse events Progression of lens opacity or incidence of cataract surgery Effect of study supplements on cognitive function Effect of DHA/EPA on cardiovascular morbidity and mortality
Starting date	2006

AREDS2 (*Continued*)

Contact information	See: http://clinicaltrials.gov/show/NCT00345176
Notes	-

LIMPIA

Trial name or title	Lutein influence on macula of persons issued from AMD parents
Methods	Multicentre, double-masked, randomised clinical trial of supplementation with 'Nutrof Total' (lutein and zeaxanthin) versus placebo
Participants	People at high genetic risk for AMD because their parents had AMD. Age 40 to 70 years
Interventions	Nutrof Total or placebo
Outcomes	Primary outcome measure: Macular pigment density at 6 months after supplementation Secondary outcome measures: Best corrected visual acuity 12 months Cognitive ability 12 months Plasma fatty acids 12 months Macular pigment density during supplementation and after stopping supplementation
Starting date	-
Contact information	Jean-Francois Korobelnik jean-francois.korobelnik@chu-bordeaux.fr
Notes	http://clinicaltrials.gov/show/NCT01269697

PHS II

Trial name or title	Physician's Health Study II
Methods	Randomised controlled trial
Participants	15,000 physicians aged 55 or older
Interventions	2 x 2 x 2 x 2 factorial design Alternate day beta-carotene, 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	-

PHS II (*Continued*)

Notes	-

SELECT

Trial name or title	Selenium and Vitamin E Cancer Prevention Trial (SELECT) for prostate cancer
Methods	This is a randomised, double-masked, multi-centre study. Participants are randomised to one of 4 prevention arms: Arm I: participants receive 2 different oral placebos once daily Arm II: participants receive oral selenium and oral placebo once daily Arm III: participants receive oral vitamin E and oral placebo once daily Arm IV: participants receive oral selenium and oral vitamin E once daily Treatment continues for 7 to 12 years in the absence of unacceptable toxicity or diagnosis of prostate cancer Quality of life is assessed at baseline and then at 1, 3, 5 and 7 years Participants are followed annually
Participants	Healthy male volunteers. A total of 32,400 participants (8100 per prevention arm) will be accrued for this study within 5 years
Interventions	Dietary supplement: selenium Dietary supplement: vitamin E
Outcomes	Primary outcome measures: Effect on the clinical incidence of cancer Effect on cancer-free survival, overall survival and serious cardiovascular events Quality of life Association of biological molecular markers with cancer risk Relationship between effects on cancer risk and genetic factors Effects in terms of intake of other nutrients, foods and dietary supplements Effect of other dietary nutrients and dietary patterns on cancer risk Effects on the reduction of Alzheimer's disease incidence Reduction in the risk of age-related macular degeneration or cataract
Starting date	July 2001
Contact information	-
Notes	http://clinicaltrials.gov/show/NCT00006392

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

WACS (*Continued*)

Interventions	2 x 2 x 2 x 2 factorial design: Vitamin E (600 IU on alternate days) Vitamin C (500 mg daily) Beta-carotene (5 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	http://clinicaltrials.gov/show/NCT00000541

AMD: age-related macular degeneration

DATA AND ANALYSES

Comparison 1. Any antioxidant versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AMD	4	62520	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.08]
2 Advanced AMD	4	62520	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.80, 1.39]

Comparison 2. Alpha-tocopherol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AMD	3	40887	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.09]
2 Advanced AMD	3	40887	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.84, 2.14]

Comparison 3. Beta-carotene versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AMD	2	21589	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]
2 Advanced AMD	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 AMD.

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

Comparison: 1 Any antioxidant versus placebo

Outcome: 1 AMD

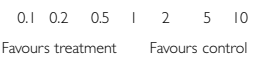
Study or subgroup	Antioxidant n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	216/728	53/213		10.8 %	1.19 [0.92, 1.54]
PHS I	275/10585	274/10557		36.1 %	1.00 [0.85, 1.18]
VECAT	92/504	92/512		12.0 %	1.02 [0.78, 1.32]
WHS	280/19697	313/19724		41.1 %	0.90 [0.76, 1.05]
Total (95% CI)	**31514**	**31006**		**100.0 %**	**0.98 [0.89, 1.08]**

Total events: 863 (Antioxidant), 732 (Placebo)

Heterogeneity: $Chi^2 = 3.55$, df = 3 (P = 0.31); $I^2 = 16\%$

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

Test for subgroup differences: Not applicable

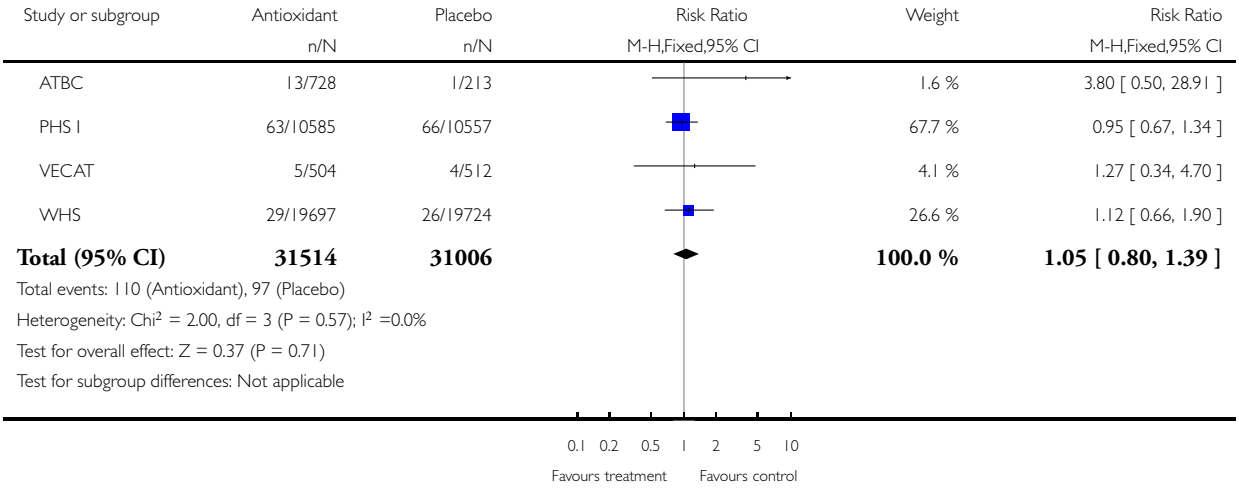


Analysis 1.2. Comparison 1 Any antioxidant versus placebo, Outcome 2 Advanced AMD.

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

Comparison: 1 Any antioxidant versus placebo

Outcome: 2 Advanced AMD



Analysis 2.1. Comparison 2 Alpha-tocopherol versus placebo, Outcome 1 AMD.

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

Comparison: 2 Alpha-tocopherol versus placebo

Outcome: 1 AMD

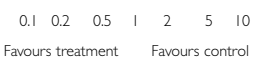
Study or subgroup	Alpha-tocopherol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	75/237	53/213		12.1 %	1.27 [0.94, 1.72]
VECAT	92/504	92/512		19.8 %	1.02 [0.78, 1.32]
WHS	280/19697	313/19724		68.0 %	0.90 [0.76, 1.05]
Total (95% CI)	**20438**	**20449**		**100.0 %**	**0.97 [0.85, 1.09]**

Total events: 447 (Alpha-tocopherol), 458 (Placebo)

Heterogeneity: Chi^2 = 4.25, df = 2 (P = 0.12); I^2 =53%

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

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Alpha-tocopherol versus placebo, Outcome 2 Advanced AMD.

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

Comparison: 2 Alpha-tocopherol versus placebo

Outcome: 2 Advanced AMD

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	8/237	1/213		3.4 %	7.19 [0.91, 57.01]
VECAT	5/504	4/512		12.8 %	1.27 [0.34, 4.70]
WHS	29/19697	26/19724		83.8 %	1.12 [0.66, 1.90]
Total (95% CI)	**20438**	**20449**		**100.0 %**	**1.34 [0.84, 2.14]**

Total events: 42 (Alpha-tocopherol), 31 (Placebo)

Heterogeneity: Chi^2 = 3.00, df = 2 (P = 0.22); I^2 =33%

Test for overall effect: Z = 1.24 (P = 0.21)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Beta-carotene versus placebo, Outcome 1 AMD.

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

Comparison: 3 Beta-carotene versus placebo

Outcome: 1 AMD

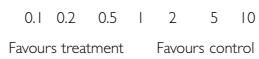
Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATBC	68/234	53/213		16.8 %	1.17 [0.86, 1.59]
PHS 1	275/10585	274/10557		83.2 %	1.00 [0.85, 1.18]
Total (95% CI)	**10819**	**10770**		**100.0 %**	**1.03 [0.89, 1.19]**

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)

Test for subgroup differences: Not applicable

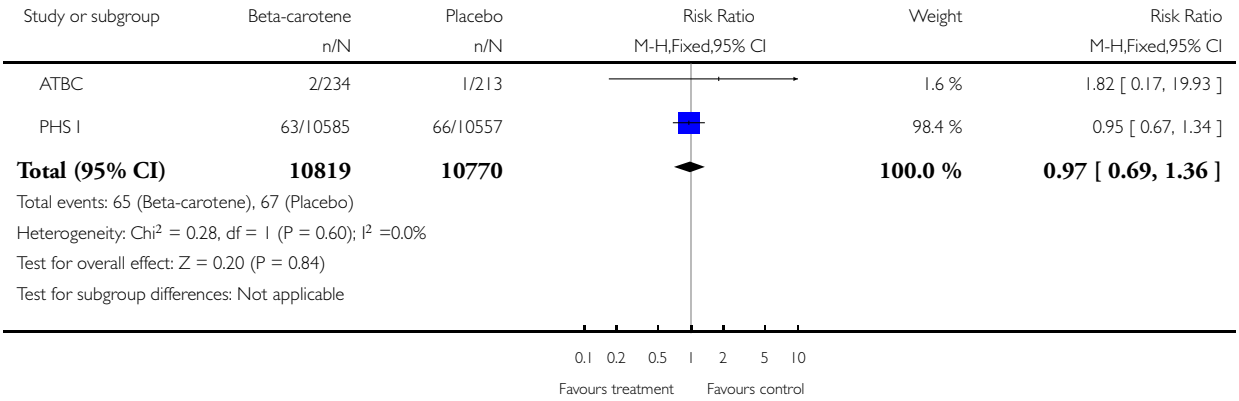


Analysis 3.2. Comparison 3 Beta-carotene versus placebo, Outcome 2 Advanced AMD.

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

Comparison: 3 Beta-carotene versus placebo

Outcome: 2 Advanced AMD



APPENDICES

Appendix 1. CENTRAL search strategy

#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 (macula* or retina* or choroid*) near/4 degenerat*
#8 (macula* or retina* or choroid*) near/4 neovascul*
#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 (OvidSP) search strategy

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 (OvidSP) search strategy

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. AMED (OvidSP) search strategy

1. exp eye disease/
2. exp vision disorders/
3. exp retinal disease/
4. maculopath$.tw.
5. ((macul$ or retina$ or choroid$) adj3 degenerat$).tw.
6. ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
7. or/1-6
8. exp vitamins/
9. vitamin A.tw.
10. retinol$.tw.
11. exp carotenoids/
12. caroten$.tw.
13. exp ascorbic acid/
14. ascorbic acid$.tw.
15. vitamin C.tw.
16. vitamin E.tw.
17. alpha tocopherol$.tw.
18. vitamin B12.tw.
19. cobalamin$.tw.
20. exp antioxidants/
21. ((antioxidant$ or anti) adj1 oxidant$).tw.
22. zinc/
23. zinc$.tw.
24. riboflavin$.tw.
25. selenium/
26. selenium$.tw.
27. lutein$.tw.
28. xanthophylls.tw.
29. zeaxanthin$.tw.
30. or/8-29
31. 7 and 30

Appendix 5. Open Grey search strategy

macular degeneration AND antioxidant

Appendix 6. *meta*Register of Controlled Trials search strategy

(macular degeneration) AND (antioxidant or vitamin or carotene or selenium or tocopherol)

Appendix 7. ClinicalTrials.gov search strategy

(Macular Degeneration) AND (Antioxidant OR Vitamin OR Carotene OR Selenium OR Tocopherol)

Appendix 8. ICTRP search strategy

Macular Degeneration = Condition AND Antioxidant OR Vitamin OR Carotene OR Selenium OR Tocopherol = Intervention

Appendix 9. MEDLINE (OvidSP) adverse effects search strategy

1. exp retinal degeneration/
2. retinal neovascularization/
3. choroidal neovascularization/
4. exp macula lutea/
5. (macula$ adj2 lutea).tw.
6. ((macul$ or retina$ or choroid$) adj4 degener$).tw.
7. ((macul$ or retina$ or choroid$) adj4 neovasc$).tw.
8. (AMD or ARMD or CNV).tw.
9. maculopath$.tw.
10. or/1-9
11. exp vitamins/
12. vitamin A.tw.
13. retinol$.tw.
14. (caroten$ or betacaroten$).tw.
15. ascorbic acid$.tw.
16. vitamin C.tw.
17. alpha?tocopherol$.tw.
18. alpha tocopherol$.tw.
19. vitamin E.tw.
20. ((antioxidant$ or anti) adj1 oxidant$).tw.
21. zinc/
22. zinc$.tw.
23. or/11-22
24. 10 and 23
25. ae.fs.
26. 24 and 25
27. limit 26 to (meta analysis or randomized controlled trial or "review")

WHAT'S NEW

Last assessed as up-to-date: 26 January 2012.

Date	Event	Description
19 April 2012	New search has been performed	Issue 6 2012: New searches yielded one new trial. New 'Risk of bias' grading and a 'Summary of findings' table have been included
19 April 2012	New citation required but conclusions have not changed	Issue 6 2012: The author byline has changed. Katherine Henshaw has been replaced by a new author, John Lawrenson

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 4, 1999

Date	Event	Description
28 August 2008	Amended	Converted to new review format.
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 risk of bias, extracted data, entered data and wrote the text of the review.

JL assessed studies for inclusion/exclusion, assessed risk of bias, extracted data, and reviewed and commented on the text of the review.

DECLARATIONS OF INTEREST

None known.

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- NIHR/Department of Health, UK.

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External sources

- No sources of support supplied

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