Evans, Jennifer R; Lawrenson, John G; (2012) Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. The Cochrane database of systematic reviews, 6 (6). CD000253-. ISSN 1469-493X DOI: https://doi.org/10.1002/14651858.CD000253.pub3

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

Evans JR, Lawrenson JG

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Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration.
DOI: 10.1002/14651858.CD000253.pub3.

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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: New search for studies and content updated (no change to conclusions), published in Issue 6, 2012.

Citation: Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD000253. DOI: 10.1002/14651858.CD000253.pub3.

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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 metaRegister of Controlled Trials (mRCT) (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**

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

* 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.
B A C K G R O U N D

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).

O B J E C T I V E S
To determine whether antioxidant vitamin and/or mineral supplementation prevents the development of AMD.

M E T H O D S

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 metaRegister of Controlled Trials (mRCT) (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), mRCT (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 \( \chi^2 \) 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.

<table>
<thead>
<tr>
<th>Risk of Bias Item</th>
<th>ATBC</th>
<th>PHSI</th>
<th>VECAT</th>
<th>WHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias): AMD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Blinding of outcome assessment (performance bias): AMD</td>
<td>+</td>
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<tr>
<td>Blinding of outcome assessment (detection bias): AMD</td>
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<td>+</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>+</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
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

**Antioxidant supplement compared with placebo for prevention of AMD**

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
<th>GRADE Working Group grades of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AMD</td>
<td>180 per 1000</td>
<td>193 per 1000</td>
<td>RR 1.03 (0.89 to 1.19)</td>
<td>21,589 (3)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
<td>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Advanced AMD</td>
<td>6 per 1000</td>
<td>6 per 1000</td>
<td>RR 0.97 (0.69 to 1.36)</td>
<td>21,589 (3)</td>
<td>⊕⊕⊕⊕ high</td>
<td></td>
<td>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
</tbody>
</table>

* 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

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

Acknowledgements

We are grateful to:

- the Systematic Review Training Unit at the 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.

We thank Katherine Henshaw who was an author on the original review. The Cochrane Eyes and Vision Group editorial team prepared and executed the electronic searches for this review. We are grateful to Anupa Shah and Iris Gordon for their assistance with the review process.

Richard Wormald (Co-ordinating Editor for CEVG) acknowledges financial support for his CEVG research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health.

References to studies included in this review

ATBC [published data only]


Liede KE, Alfthan G, Hietanen JH, Haukka JK, Saxen LM, Heinonen OP. Beta-carotene concentration in buccal mucosal cells with and without dysplastic oral leukoplakia...


**PHS I (published data only)**


References to studies excluded from this review

ADSC [published data only]

Andrews 1969 [published data only]

AREDS [published data only]

Benner 1994 [published data only]

Benton 1995 [published data only]

Blok 1997 [published data only]

Bogden 1990 [published data only]

Bone 2010 [published data only]

Brewer 1997 [published data only]

Brown 1998 [published data only]

Bussey 1982 [published data only]

Caligiuri 1997 [published data only]

CARET [published data only]

CARMIS [published data only]
Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (Review)

CCSG  [published data only]

Chandra 1992  [published data only]

CHAOS  [published data only]

Clausen 1989  [published data only]

Constans 1996  [published data only]

Constantino 1988  [published data only]

Cucinotta 1994  [published data only]

DATATOP  [published data only]

DeCosse 1989  [published data only]

de Klerk 1998  [published data only]

Dobson 1984  [published data only]

ECP-IM  [published data only]

EUROSCAN  [published data only]

Fairley 1996  [published data only]

Fonzhal 1995  [published data only]

Galán 1997  [published data only]

Garawal 1995  [published data only]

GISSI  [published data only]

HOPE  [published data only]
Gerstein HIC, Bosch J, Pogue J, Taylor DW, Zipman B, Yusuf S. Rationale and design of a large study to evaluate

Johnson 1997 [published data only]

Jyothirmayi 1996 [published data only]

Kuklinski 1994 [published data only]

Kvansakul 2006 [published data only]

Leng 1997 [published data only]

Li 1992 [published data only]

LINXIAN [published data only]


Mayne 1998 [published data only]

McKeown 1988 [published data only]

Meyskens 1994 [published data only]

Munoz 1987 [published data only]

Munoz 1996 [published data only]

Nambour 1995 [published data only]

NCT00718653 [published data only]

NCT01208948 [published data only]

Newsome, 2008 [published data only]

NPCSG [published data only]

Pastorino 1991 [published data only]

Pemp 2010 [published data only]
Peng 1993  {published data only}

PPP  {published data only}

PPSG  {published data only}

Prasad 1995  {published data only}

REACT  {published data only}

Recchia 1995  {published data only}

Rein 2007  {published data only}

Ret Pig 1993  {published data only}

Rodriguez-Carmona 2006  {published data only}

SAINTS  {published data only}

SCPS 1989  {published data only}

Shandong 1998  {published data only}

Sharma 1989  {published data only}

Steiner 1995  {published data only}

SUVIMAX  {published data only}

SECURE  {published data only}
Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (Review)

References to ongoing studies

AREDS2 [published data only]

LIMPIA [published data only]

PHS II [published data only]

SELECT [published data only]

WACS [unpublished data only]

Additional references

AREDS 2001a

AREDS 2001b

ATBC 1994
Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (Review)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Characteristics of included studies  
*ordered by study ID*

#### ATBC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>“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...</td>
</tr>
</tbody>
</table>

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

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### ATBC

#### 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

---

### 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)

| 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)

| 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)

| 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 |

---

**Annals of Epidemiology** 1994;4: page 1

Characteristics, and compliance.

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**PHS I**

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

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
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

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>“The PHS I was a randomized, double-masked, placebo controlled trial...” Page 334 Christen et al 2007</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>“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</td>
</tr>
</tbody>
</table>
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  

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

<table>
<thead>
<tr>
<th>Sex: 56% female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: lens and retina of at least one eye available for documentation</td>
</tr>
<tr>
<td>Exclusion criteria: previous cataract surgery or advanced cataract in both eyes; steroid or anticoagulation use; serious disease; regular use or sensitivity to vitamin E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Vitamin E 500 IU per day: natural vitamin E in soybean oil medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Placebo identical in sight, taste and smell</td>
</tr>
<tr>
<td>Duration</td>
<td>4 years</td>
</tr>
</tbody>
</table>

| Outcomes | 2 m logMAR visual acuity; clinical examination; colour stereoscopic fundus photographs graded using International Grading Scheme |

<table>
<thead>
<tr>
<th>Notes</th>
<th>Worse eye used as the study eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methodology published but results available from abstract only</td>
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</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>“This random allocation was performed by using a “permuted blocks” allocation scheme” Page 2</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>“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</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Visual acuity</td>
<td>Low risk</td>
<td>“Participants randomly received either 500 IU natural vitamin E (335 mg dlα-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</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>“Participants randomly received either 500 IU natural vitamin E (335 mg dα 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</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Visual acuity</td>
<td>Low risk</td>
<td>“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</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) AMD</td>
<td>Low risk</td>
<td>“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</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>“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...”</td>
</tr>
</tbody>
</table>
VECAT  (Continued)

| 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**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Method of allocation: Masking: participant: yes; provider: yes; outcome: yes  Losses to follow-up: not known</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>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</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Vitamin E (600 IU on alternate days) or placebo</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Self report and review of medical records</th>
</tr>
</thead>
</table>

| Notes | NCT00000161 |

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

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

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Study Area</th>
<th>Risk</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low</td>
<td>“The WHS was a randomized, double-blind, placebo-controlled, 2x2 factorial trial. ..” Page 1163</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low</td>
<td>“The WHS was a randomized, double-blind, placebo-controlled, 2x2 factorial trial. ..” Page 1163</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low</td>
<td>“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</td>
</tr>
<tr>
<td>Visual acuity</td>
<td></td>
<td>“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</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low</td>
<td>“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</td>
</tr>
<tr>
<td>AMD</td>
<td></td>
<td>“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</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low</td>
<td>“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</td>
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<td>Visual acuity</td>
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<td>“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</td>
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<tr>
<td>AMD</td>
<td></td>
<td>“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</td>
</tr>
</tbody>
</table>
Incomplete outcome data (attrition bias)

<table>
<thead>
<tr>
<th>All outcomes</th>
<th>Low risk</th>
</tr>
</thead>
</table>

“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)

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADSC</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Andrews 1969</td>
<td>No published data on age-related macular degeneration. Unable to contact author</td>
</tr>
<tr>
<td>AREDS</td>
<td>Age-related maculopathy outcomes for people without age-related maculopathy at baseline were not reported</td>
</tr>
<tr>
<td>Benner 1994</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Benton 1995</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Blok 1997</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
</tbody>
</table>

**AMD**: age-related macular degeneration

**ETDRS**: Early Treatment Diabetic Retinopathy Study

**IU**: international units

**RPE**: retinal pigment epithelium
<table>
<thead>
<tr>
<th>Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bogden 1990</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Bone 2010</td>
<td>Biological availability study only</td>
</tr>
<tr>
<td>Brewer 1997</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Brown 1998</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Bussey 1982</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Caligiuri 1997</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>CARET</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>CARMIS</td>
<td>Study on people with AMD (non-advanced AMD) therefore not on prevention in healthy people</td>
</tr>
<tr>
<td>CCSG</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Chandra 1992</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>CHAOS</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Clausen 1989</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Constans 1996</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Constantino 1988</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Cucinotta 1994</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>DATATOP</td>
<td>No published data on age-related macular degeneration. Unable to contact author</td>
</tr>
<tr>
<td>de Klerk 1998</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>DeCosse 1989</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Dobson 1984</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>ECP-IM</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>EUROSCAN</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Fairley 1996</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Falsani 2010</td>
<td>Participants had early AMD</td>
</tr>
<tr>
<td>Study Name</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fontham 1995</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Galan 1997</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Garawal 1995</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>GISSI</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>HOPE</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Johnson 1997</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Jyothirmayi 1996</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Kuklinski 1994</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Kvansakul 2006</td>
<td>No AMD outcomes</td>
</tr>
<tr>
<td>Leng 1997</td>
<td>No published data on age-related macular degeneration. Unable to contact author</td>
</tr>
<tr>
<td>Li 1992</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>LINXIAN</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Mayne 1998</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>McKeown 1988</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Meyskens 1994</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Munoz 1987</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Munoz 1996</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Nambour 1995</td>
<td>No follow-up data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>NCT00718653</td>
<td>Study of macular pigment only</td>
</tr>
<tr>
<td>NCT01208948</td>
<td>No AMD outcomes</td>
</tr>
<tr>
<td>Newsome, 2008</td>
<td>Study on people with AMD</td>
</tr>
<tr>
<td>NPCSG</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Pastorino 1991</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Pemp 2010</td>
<td>Study of ocular blood flow and endothelial function only in model of oxidative stress in health volunteers</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Peng 1993</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>PPP</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>PPSG</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Prasad 1995</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>REACT</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Recchia 1995</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Rein 2007</td>
<td>Study not a randomised controlled trial</td>
</tr>
<tr>
<td>Ret Pig 1993</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Rodriguez-Carmona 2006</td>
<td>No AMD outcomes</td>
</tr>
<tr>
<td>SAINTS</td>
<td>Study on people with AMD</td>
</tr>
<tr>
<td>SCPS 1989</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>SECURE</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Shandong 1998</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Sharma 1989</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Steiner 1995</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>SUVIMAX</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>SWSCPSG</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Takamatsu 1995</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Tomoeo 1995</td>
<td>No published data on age-related macular degeneration. No response from author</td>
</tr>
<tr>
<td>Tsunobono 1997</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>WAFACS</td>
<td>Reported on folic acid, pyridoxine and cyanocobalamin combination treatment</td>
</tr>
<tr>
<td>Wahlqvist 1994</td>
<td>No data on age-related macular degeneration collected</td>
</tr>
<tr>
<td>Wong 2010</td>
<td>Participants had geographic atrophy</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies  
*ordered by study ID*

#### AREDS2

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>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</td>
</tr>
<tr>
<td>Participants</td>
<td>Participants were enrolled on the basis of the AREDS Simplified Severity Scale for defining risk categories for development of advanced age-related macular degeneration</td>
</tr>
</tbody>
</table>
| 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)**

<table>
<thead>
<tr>
<th>Contact information</th>
<th>See: <a href="http://clinicaltrials.gov/show/NCT00345176">http://clinicaltrials.gov/show/NCT00345176</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
<td>-</td>
</tr>
</tbody>
</table>

**LIMPIA**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Lutein influence on macula of persons issued from AMD parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Multicentre, double-masked, randomised clinical trial of supplementation with 'Nutrof Total' (lutein and zeaxanthin) versus placebo</td>
</tr>
<tr>
<td>Participants</td>
<td>People at high genetic risk for AMD because their parents had AMD. Age 40 to 70 years</td>
</tr>
<tr>
<td>Interventions</td>
<td>Nutrof Total or placebo</td>
</tr>
</tbody>
</table>
| 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](http://clinicaltrials.gov/show/NCT01269697) |

**PHS II**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Physician's Health Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>Participants</td>
<td>15,000 physicians aged 55 or older</td>
</tr>
</tbody>
</table>
| 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 | -                                                                 |
## SELECT

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Selenium and Vitamin E Cancer Prevention Trial (SELECT) for prostate cancer</th>
</tr>
</thead>
</table>
| 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](http://clinicaltrials.gov/show/NCT00006392) |

## WACS

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Women's Antioxidant Cardiovascular Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>-</td>
</tr>
<tr>
<td>Participants</td>
<td>8171 female health professionals aged 40 plus with pre-existing cardiovascular disease (CVD) or high risk for developing CVD</td>
</tr>
</tbody>
</table>
### 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

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

### Comparison 2. Alpha-tocopherol versus placebo

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

### Comparison 3. Beta-carotene versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AMD</td>
<td>2</td>
<td>21589</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.03 [0.89, 1.19]</td>
</tr>
<tr>
<td>2 Advanced AMD</td>
<td>2</td>
<td>21589</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.97 [0.69, 1.36]</td>
</tr>
</tbody>
</table>
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

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

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

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### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antioxidant n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed(95% CI)</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC</td>
<td>13/728</td>
<td>1/213</td>
<td>1.6 % 3.80 [ 0.50, 28.91 ]</td>
<td>68.7</td>
<td>0.95 [ 0.67, 1.34 ]</td>
</tr>
<tr>
<td>PHS I</td>
<td>63/10585</td>
<td>66/10557</td>
<td>67.7 % 1.27 [ 0.34, 4.70 ]</td>
<td>4.1</td>
<td>1.12 [ 0.66, 1.90 ]</td>
</tr>
<tr>
<td>VECAT</td>
<td>5/504</td>
<td>4/512</td>
<td>26.6 % 1.12 [ 0.66, 1.90 ]</td>
<td>1.0</td>
<td>1.05 [ 0.80, 1.39 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 31514 31006

Total events: 110 (Antioxidant), 97 (Placebo)

Heterogeneity: Chi² = 2.00, df = 3 (P = 0.57); I² = 0.0%

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable
### 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

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

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alpha-tocopherol</th>
<th>Placebo</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC</td>
<td>8/237</td>
<td>1/213</td>
<td>3.4 % 7.19 [ 0.91, 57.01 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VECAT</td>
<td>5/504</td>
<td>4/512</td>
<td>12.8 % 1.27 [ 0.34, 4.70 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHS</td>
<td>29/19697</td>
<td>26/19724</td>
<td>83.8 % 1.12 [ 0.66, 1.90 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20438</strong></td>
<td><strong>20449</strong></td>
<td>100.0 % 1.34 [ 0.84, 2.14 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Total events: 343 (Beta-carotene), 327 (Placebo)

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 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

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

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

Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² =0.0%

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

Test for subgroup differences: Not applicable

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

Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (Review) 42

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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.
22. or/13-21
23. exp vitamins/
24. exp vitamin A/
25. vitamin A.tw.
26. retinol$.tw.
27. exp beta carotene/
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$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
14. ((singl$ 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. ((macula$ or retina$ or choroid$) adj3 degener$).tw.
39. ((macula$ 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.
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. metaRegister 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. ac.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.

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

**HISTORY**


Review first published: Issue 4, 1999

<table>
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<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tr>
<td>28 August 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>8 November 2007</td>
<td>New citation required and conclusions have changed</td>
<td>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’</td>
</tr>
</tbody>
</table>

**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.

SOURCES OF SUPPORT

Internal sources
- NIHR/Department of Health, UK.
JE was funded by NIHR during the updating of this review (Issue 6, 2012)

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