Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration (Review)
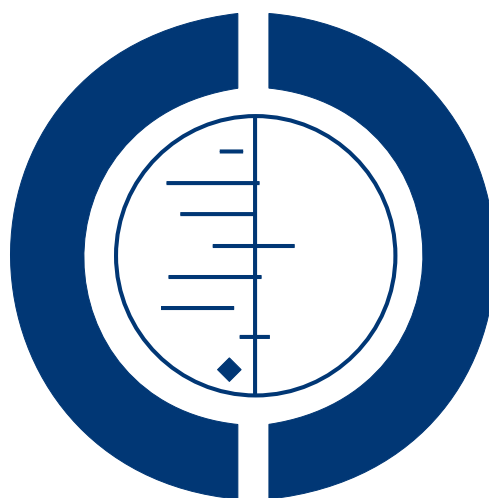
Evans JR

THE COCHRANE
COLLABORATION®

WILEY

TABLE OF CONTENTS

[Intervention Review]

Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Jennifer R Evans[1]

[1]Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, London, UK

Contact address: Jennifer R Evans, Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. jennifer.evans@lshtm.ac.uk.

A B S T R A C T

Background

It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption.

Objectives

The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of age-related macular degeneration (AMD).

Search methods

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 We contacted investigators and experts in the field for details of unpublished studies.

Selection criteria

We included randomised trials comparing antioxidant vitamin or mineral supplementation (alone or in combination) to a control intervention in people with AMD.

Data collection and analysis

The author extracted data and assessed trial quality. Where appropriate, data were pooled using a random-effects model unless three or fewer trials were available in which case a fixed-effects model was used.

Main results

Nine trials were included in this review. The majority of people were randomised in one trial (AREDS in the USA) that found a beneficial effect of antioxidant (beta-carotene, vitamin C and vitamin E) and zinc supplementation on progression to advanced AMD (adjusted odds ratio 0.68, 99% confidence interval 0.49 to 0.93). People taking supplements were less likely to lose 15 or more letters of visual acuity (adjusted odds ratio 0.77, 99% confidence interval 0.58 to 1.03). Hospitalisation for genito-urinary problems was more common in people taking zinc and yellowing of skin was more common in people taking antioxidants. The other trials were, in general, small and the results were inconsistent.

Authors' conclusions

The evidence as to the effectiveness of antioxidant vitamin and mineral supplementation in halting the progression of AMD comes mainly from one large trial in the USA. The generalisability of these findings to other populations with different nutritional status is not known. Further large, well-conducted randomised controlled trials in other populations are required. Long-term harm from supplementation cannot be ruled out. Beta-carotene has been found to increase the risk of lung cancer in smokers; vitamin E has been associated with an increased risk of heart failure in people with vascular disease or diabetes.

PLAIN LANGUAGE SUMMARY

Antioxidant vitamins and mineral supplements to slow down the progression 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. It has been suggested that progression of the disease may be slowed down in people who eat a diet rich in antioxidant vitamins (carotenoids, vitamins C and E) or minerals (selenium and zinc). The author identified nine randomised controlled trials; four trials based in the USA, four in Australia, Austria, Switzerland and the UK and one in China. The review of trials found that supplementation with antioxidants and zinc may be of modest benefit in people with AMD. Long-term harm from these supplements cannot be ruled out. Large well-conducted trials in a range of populations and with different nutritional status are required.

BACKGROUND

Introduction

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

Presentation and epidemiology

The early stages of the disease are in general asymptomatic. In the later stages there may be considerable distortion of vision and complete loss of visual function, particularly in the central area of vision. Population-based studies suggest that in people 75 years and older, approximately 30% have early signs of the disease and

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

Treatment options

Currently there is no treatment that can restore vision in AMD. Photoreceptors in the retina are subject to oxidative stress throughout life due to combined exposures to light and oxygen. It has been proposed that antioxidants may prevent cellular damage in the retina by limiting the damaging effects of free radicals produced in the process of light absorption (for a review see Christen 1996). Antioxidant vitamin and mineral supplements are increasingly being marketed for use in age-related eye disease, including AMD.

OBJECTIVES

The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation, alone or in combination, on the progression of AMD.

M E T H O D S

Criteria for considering studies for this review

Types of studies

This review included randomised controlled trials.

Types of participants

Participants in the trials were people with AMD in one or both eyes.

Types of interventions

We included trials in which antioxidant vitamin or mineral supplementation, alone or in combination, was compared to placebo or no intervention. 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. The following were considered: vitamin C, vitamin E, carotenoids, selenium and zinc.

Types of outcome measures

Primary outcomes

The primary outcome for this review was vision.
As one of the consequences of AMD is a progressive loss of vision the preferred outcome was dichotomous (loss of three or more lines of visual acuity) which, if measured on a logMAR chart, reflects a doubling of the visual angle. This is a meaningful clinical change for patients. However, some studies report vision as a continuous measure so I also looked at the mean difference. If there were studies that used different ways of measuring vision (for example, some may report vision at the end of the study, some may report change) I calculated a standardised mean difference. Snellen values were converted to logMAR to ensure that there was consistency in the direction of effect (higher Snellen values reflect better vision, higher logMAR values reflect poorer vision).

Secondary outcomes

Secondary outcomes included progression of the disease. There are several ways of measuring this. I decided to use progression as defined by the study investigators as the outcome. This was usually reported as a dichotomous outcome.
Other outcomes included contrast sensitivity, which is measured on a continuous scale, analysed as a mean difference or standardised mean difference if different measurement scales were used. Quality of life was also to be assessed if data were available.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in *The Cochrane Library*, MEDLINE, EMBASE, National Research Register (NRR), PubMed, Allied & Complementary Medicine (AMED), SIGLE. The searches in *The Cochrane Library*, MEDLINE, EMBASE and NRR were last updated on 2 August 2007. There were no language or date restrictions in the searches.
See: Appendices for details of search strategies for each database. All possible AMD trials were examined for trials of vitamin and mineral supplements.

Searching other resources

We searched the reference lists of identified trial reports to find additional trials. The Science Citation Index was used to find studies that cite the identified trials. We contacted investigators of included studies to identify additional published and unpublished studies.

Data collection and analysis

Selection of trials

The author assessed the titles and abstracts of all reports of trials identified by the electronic searching. The full texts of possibly relevant trials were obtained. Relevant studies were selected according to the definitions in the 'Criteria for considering studies for this review'.

Assessment of methodological quality

The author assessed trial quality according to methods set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). Five parameters were considered: allocation concealment, method of allocation to treatment, documentation of exclusions, masking of outcome assessment and completeness of follow up.
Each parameter of trial quality was graded: A, low risk of bias; B moderate risk of bias; or C high risk of bias. The author was not masked to the report authors or the trial results. The a priori criterion for exclusion was that trials scoring C on allocation concealment (that is, where allocation was not concealed properly) were excluded.

Data collection

The author extracted data using a standardised form developed by the Cochrane Eyes and Vision Group. These data were sent for verification to the trial investigators of all studies included in the review.

Analysis strategy

Previous versions of this review did not include statistical analyses because only a small number of trials were identified and variable methods of collecting and presenting outcome data were used. More trials in this area have become available and new developments in statistical software and Cochrane guidelines mean that the analysis section was substantially revised for later versions of the review.

The following plan was set out (and reviewed by the statistical editorial team) in September 2005, before re-doing the analyses. It should be noted that this plan was developed with knowledge of the trials and the results included in previous versions of this review. However, every effort has been taken to base judgements as to the analysis on methodological grounds without reference to the results of the individual trials.

Comparisons

The overall objective of the review was to assess the impact of antioxidant vitamin and mineral supplements on the progression of AMD. Trials in this area fall into two broad categories: those evaluating a single vitamin or mineral (for example, vitamin E or zinc) and those investigating a broad spectrum formulation (for example, Ocuguard). The following comparisons were considered in this review.

(1) Broad-spectrum formulation versus placebo. Within this category fall all the broad-spectrum formulations which include one or more antioxidant vitamins or minerals.

(2) Single-component formulations versus placebo. Currently only vitamin E, zinc and lutein have been studied as single formulations, however, it is likely that in future other trials will be published which investigate individual components.

(3) All trials of broad-spectrum or single component studies together.

The traditional study design method in this area is parallel group randomised controlled trials. Cluster randomised trials are unlikely but would still be considered. Cross-over studies would not be appropriate in this area because of the uncertain and complex natural history of AMD. If such studies are reported the first phase only would be used.

Some studies report findings on right eyes and left eyes separately. As there is no hypothesis that the effect of antioxidant supplements should differ according to eye, I have made the a priori decision to consider right eyes only.

Which measure of effect?

In general the risk ratio is to be preferred when the proportion of the control group experiencing the event of interest is greater than 10%. However, in this particular case the main trial from which over 80% of the information on this topic is available reported odds ratios and their confidence intervals only (derived from repeated measures logistic regression). For this reason, I have analysed the data using the generic inverse variance method with the main effect measure being the odds ratio. The standard error was calculated from the confidence interval from each study. In discussion of the results of the review, where possible, I have converted the pooled odds ratio back to the risk ratio to ensure that any estimates of effect are not exaggerated. The risk ratio was calculated using the following formula: $RR = OR/[(1-P_0)+(P_0 x OR)]$ where P^0 is the incidence of the outcome of interest in the control group.

How will the decision be made as to whether it is appropriate to pool data?

I considered how similar the trials were and looked at the forest plot to see whether the effect measures for the different studies were in the same direction and of a similar order of effect. I then examined the I^2 value. A value of 50% or more was taken to indicate considerable inconsistency of results such that a pooled result may be inaccurate and should not be reported.

Which model will I use?

I used a random-effects model, unless there were three or fewer trials in which case I used a fixed-effect model. I compared fixed and random-effects models to see how robust the result was.

How will clinical and methodological diversity be addressed? How will these be incorporated into the analysis strategy?

The main clinical diversity was with respect to the type of supplement. This is incorporated into the analysis strategy by considering the formulations by type (*see* Comparisons 1 and 2). Again with methodological diversity, the type of study design was fairly standard and straightforward, however, the methodological quality of the studies was reported and used to interpret the results (*see* below).

How will the quality of included studies be addressed in the analysis section?

Currently there are not enough published studies to enable sensitivity analysis. However, should enough studies become available in the future, the proposal would be to repeat the analysis including only high quality studies. All studies included in the review were randomised controlled trials. The main quality attributes in this area are: (i) whether or not the randomisation was properly concealed, (ii) whether or not the participants were masked, (iii) whether or not the outcome assessment was masked, and (iv) extent of follow up in the study groups. In practice, most studies compare the supplements versus placebo and report that the masking was adequate, that is that the tablets were similar etc. It is likely that the main quality attributes that may differ between studies will be allocation concealment and follow up.

Pre-specify characteristics of the studies that may be examined as potential causes of heterogeneity

Currently there are not enough studies to perform any sub-group analyses and these are not proposed for this version of the review. One characteristic that may be important is the type of AMD or severity of AMD. Subgroup analyses on type or severity of AMD may be considered in future.

How will missing data be handled?

It was proposed to do an available case analysis.

Currently only one study (Stur 1996) specifically excluded people who experienced a neovascular event (one component of late stage AMD) from the analyses. The published report did not give enough information to include these people in the analyses.

If missing data should prove to be a problem in the constituent studies, that is if follow up was less than 80% for trials contributing more than 50% of the data for the analysis, I will do a sensitivity analysis considering outcome in the people lost to follow up as either 'all OK' or 'all not OK' to see the range within which the true result might lie. However, currently this was not considered to necessary as the largest trial in the area had follow up of nearly 98%.

Whether or how evidence of possible publication or reporting biases will be sought

Currently there are not enough studies to examine this formally, however, I reviewed the forest plots to see if there was any sign that this might be happening i.e. whether smaller studies were reporting larger effects.

RESULTS

Description of studies

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

Results of the search

The original electronic searches identified 577 reports of possible AMD trials of which five reports (four trials) were of antioxidant interventions (AMDSG; Kaiser 1995; Newsome 1988; Stur 1996). These four trials met the inclusion criteria for this review. Contact with a trial author identified an additional trial of zinc supplementation that has been published in abstract form only (Holz 1993).

In October 2001, the result of the Age-Related Eye Disease Study (AREDS) was published. The reference list of this study report identified that the Vitamin E, Cataract and Age-related Maculopathy Study (VECAT) had been published in abstract form. Searching the reference lists of trial reports located one further possible relevant trial (Vannas 1958). This study was not included in the review because there was no evidence from the report that the comparison groups (heparin, vitamin A and E, Hydergin therapy and placebo) were randomly allocated or that the allocation was concealed in any way. As the trial was conducted in 1958, no further attempt was made to clarify this.

A trial of zinc supplementation (30 mg daily) of people with neovascular AMD in one eye and drusen in the other (n = 170) has been conducted and is as yet unpublished (France 1998). This trial is listed as 'Awaiting assessment' in this review.

Searches were first performed in August 1997 and repeated in October 1998, December 1999, September 2000, November 2001 and May 2005. Two further trials were identified: Veterans LAST study and a trial published in Chinese which is currently awaiting assessment (Wang 2004). The searches were updated in January 2006 and August 2007 but no new trials were identified.

Included studies

Below is a summary of the eight trials included in this review. See 'Characteristics of included studies' for detailed information about the trials.

Types of participants

The average age of people participating in the trials was 70 years. Slightly more women than men were recruited with the exception of AMDSG and Veterans LAST study where predominantly men were enrolled. In AREDS it was noted that people taking part in the trial were relatively well-nourished compared to the general population.

People taking part in the trials were identified by referral from local ophthalmologists (Kaiser 1995; Newsome 1988), from people attending Department of Veterans Medical Centers (AMDSG; Veterans LAST study), from retinal specialty clinics and general population volunteers (AREDS), from an eye outpatient clinic (Stur 1996; Wang 2004) and from the general population (VECAT).

The trials enrolled groups of people with AMD at different stages of the disease: AMDSG and Veterans LAST study considered people with early macular degeneration only; Newsome 1988 examined people with both early and late-stage disease; Stur 1996 enrolled only people with late-stage disease in one eye; Kaiser 1995 recruited only people with geographic AMD. In AREDS participants had a range of disease from mild or borderline features to advanced AMD which was defined as geographic atrophy involving the centre of the macula or features of choroidal neovascularisation. The majority of the participants in VECAT had no or mild age-related maculopathy.

Types of intervention

Three trials compared zinc sulfate 200 mg daily versus placebo (Holz 1993; Newsome 1988; Stur 1996). Two trials compared a broad-spectrum antioxidant complex versus placebo (AMDSG -

Ocuguard; Kaiser 1995 - Visaline). VECAT compared vitamin E (500 international units (IU) daily) with placebo. In AREDS a 2x2 factorial design was used. Participants were randomised into four groups: placebo, zinc alone (80 mg daily), antioxidants (vitamin C 500 mg, vitamin E 400 IU and beta-carotene 15 mg) alone and zinc plus antioxidants. In AREDS 67% of participants took other multivitamin supplements to recommended daily allowance levels (Centrum). The Veterans LAST study compared lutein 10 mg daily to lutein plus a broad-spectrum antioxidant (OcuPower). The duration of supplementation in these trials ranged from six months to seven years. The Chinese trial studied zinc oxide (80 mg daily), vitamin C (dose unknown) and vitamin E (dose unknown).

Types of outcome measures

All the trials used different outcome measures for visual function and progression of disease. AMDSG and Veterans LAST study measured vision using Snellen acuity and converted the score into logMAR units. Newsome 1988 and AREDS used the visual acuity chart developed as part of the Early Treatment of Diabetic Retinopathy Study (ETDRS 1980). Stur 1996 and VECAT used Bailey-Lovie Charts #4 and #5 (National Vision Research Institute, Australia). Some studies have presented vision as a continuous outcome (AMDSG; Kaiser 1995; Stur 1996), others have used a cut-off of loss of 10 (Newsome 1988) or 15 letters of acuity (AREDS). A loss of 15 letters of acuity is equivalent to a loss of three lines of vision read on the chart and is the same as experiencing a doubling of the visual angle.

In most studies disease progression was assessed by grading stereoscopic colour photographs of the retina. Stur 1996 used the Wisconsin Age-Related Maculopathy Grading System (Klein 1991); AMDSG used the grading system developed as part of the Chesapeake Bay Waterman Study (Bressler 1989); VECAT used the International Grading System (ARMSG 1995); AREDS adapted the Wisconsin system. The Wisconsin, AREDS and International Systems are closely related; the latter was published after the two former systems were in use. All these grading systems involve classification into categories according to the number and type of drusen, pigmentary abnormalities and presence of geographic atrophy or neovascularisation. In AMDSG and Stur 1996 these categories were accorded a score which was analysed as a continuous measure. Newsome 1988 recorded the number of cases of increased drusen, pigment abnormalities and atrophy. Kaiser 1995 did not include any measures of progression of AMD.

AREDS reported data for three categories of participant: (i) mild or borderline AMD features (n = 1063); (ii) AMD but not advanced AMD (n = 1621) and (iii) advanced AMD or reduced visual acuity due to AMD in one eye (n = 956). Advanced AMD was defined as signs of geographic atrophy involving the centre of the macula or signs of choroidal neovascularisation (defined as the presence of fluid, blood or fibrovascular tissue under the retina or retinal pigment epithelium).

The study followed up 90% of the cohort by the end of five years; the mean follow-up time was 6.3 years. On the basis of having missed the last two consecutive study visits, 2.4% were defined as lost to follow up. In the borderline AMD group, 1.3% progressed to advanced AMD by five years (15 AMD events); in the advanced AMD category, 43% progressed to advanced AMD (in the other eye) by five years and 18% progressed in the intermediate group. At five year follow up 71% of participants were taking 75% or more of their tablets.

The investigators found that individuals with outcomes such as signs of advanced AMD and visual acuity loss of 15 or more letters could recover later on. Approximately 8% of the identified cases of advanced AMD, based on central grading of colour stereo photographs, apparently recovered as the AMD lesions were not seen on subsequent yearly photographs. The report did not distinguish between grading errors and verified disappearance of lesion. For this reason they used repeated measures logistic regression which counts each event but also allows for the fact that the event could 'recover'.

Outcomes were not clearly defined for the Chinese trials (Wang 2004).

Risk of bias in included studies

Most of the trials were small. The number of participants for which data were analysed ranged from 20 to 151. In only one trial (Stur 1996) was an a priori sample size estimate reported but the trial was terminated early when follow up of the first 40 patients showed no detectable trend. The more recent trials, AREDS and VECAT, were larger at 3640 and 1204 participants respectively and were based on prior sample size calculations. In the case of VECAT, however, sample size was based on estimated prevalence and incidence of cataract rather than age-related maculopathy. In addition, most of the 1204 participants did not have signs of AMD at the beginning of the study and were, therefore, are also included in the related Cochrane review on prevention of AMD (Evans 2008).

In most trials randomisation appeared to have been executed properly, that is, an unpredictable sequence of treatment allocation was concealed adequately from people recruiting participants into the trial. As Holz 1993 has only been published in abstract form to date the details of randomisation were not clear. In AMDSG more people in the placebo group withdrew (six) compared to the treatment group (one). The description of the tablets cannot exclude the possibility that there were detectable differences between treatment and placebo that may mean that some participants in the study were unmasked. In AREDS four people were documented as being unmasked to study group. More people in the antioxidant group (8.3%) reported changes in skin colour (yellowing) than in the placebo group (6.0%, P < 0.01) and more people in the zinc groups reported difficulty swallowing the study tablets (17.8% versus 15.3%, P = 0.04). However, there was little evi-

dence of unmasking when at the end of the study participants were asked to guess their treatment assignment. The percentages of participants who guessed correctly, by treatment assignment, were: placebo 17%, antioxidants alone 16%; zinc alone 18%; and antioxidants plus zinc 16%.

In the Veterans LAST study the tablets were apparently identical in appearance but it was not clear whether taste or systemic effects differed between the different groups.

In Stur 1996 analysis of the main outcome measures (visual function and progression of disease) was not done on a strictly intention-to-treat basis as anyone experiencing the endpoint of late-stage AMD (neovascularisation) was withdrawn from the study. Contact with the trial investigator revealed that all of these participants ended up with visual acuity of 20/200 or less and that these participants were excluded because the investigators wished to detect functional changes caused by degeneration of the retinal pigment epithelium and the sensory retina and not vision losses caused by choroidal neovascularisation.

There was not enough information available for the trial conducted in China (Wang 2004) to assess study quality (*see* 'Characteristics of included studies' table).

Effects of interventions

Table 1 provides more information on the outcomes and follow-up times relating to the data included in these analyses.

Comparison 1: multivitamin supplement versus placebo

These analyses were restricted to trials of multivitamin and mineral supplements: AREDS (vitamins C, E, beta-carotene and zinc), AMDSG (Ocuguard), Kaiser 1995 (Visaline) and Veterans LAST study (Ocupower). *See* 'Characteristics of included studies' for details of vitamins and minerals included in Ocuguard, Visaline and Ocupower.

Outcome 1 distance visual acuity: loss of three or more lines

Only AREDS reported visual acuity data in a dichotomous format. People who received antioxidant vitamins plus zinc were less likely to lose 15 or more letters of visual acuity. The odds ratio (OR) adjusted age,sex, race, AMD category and baseline smoking status was 0.77, 95% CI 0.62 to 0.96.

Outcome 2 distance visual acuity: mean

Trials reporting visual acuity in continuous format were smaller and had shorter treatment and follow-up durations (6 months to 18 months) (AMDSG; Kaiser 1995; Veterans LAST study). A total of 69 people were randomised to treatment and 62 to placebo in pooled analyses of all three trials. The results of these trials were

consistent I^2 = 0. Little effect of treatment on visual acuity was seen from these analyses. The pooled standardised mean difference was 0.16 (95% CI -0.19 to 0.51) (Analysis 1.1).

Outcome 3 progression AMD: dichotomous

Only the AREDS trial contributed to this outcome. People taking antioxidant vitamins plus zinc were less likely to progress to advanced AMD. The OR adjusted for age, sex, race, AMD category and baseline smoking status was 0.68, 95% CI 0.53 to 0.87.

Outcome 4 progression AMD: continuous

Only one trial reported the progression of AMD in a continuous format (AMDSG), with 25 people randomised to treatment and 24 to control. There was little evidence of any effect of treatment at 18 months (mean difference -0.06, 95% CI -0.62 to 0.50). The power of the study was low.

Comparison 2: zinc versus placebo

Four trials have investigated the effect of zinc supplementation (AREDS; Holz 1993 (published in abstract form only); Newsome 1988; Stur 1996). In addition there is one unpublished study for which we have no data (France 1998).

Outcome 1, distance visual acuity: loss of three or more lines

Two trials reported visual acuity data in this format (AREDS; Newsome 1988). The pooled analyses include a total of 984 people randomised to zinc supplementation and 974 to placebo. The trials were consistent I^2 = 0%. There was a modest beneficial effect of treatment on visual acuity (pooled OR 0.81, 95% CI 0.66 to 0.99). (Analysis 2.1)

Outcome 2 distance visual acuity: mean

Two trials provided data for this outcome (Newsome 1988; Stur 1996). A total of 77 people were randomised to zinc supplementation and 78 to placebo in these two trials which had a maximum treatment and follow-up duration of 24 months. The results of these trials were less consistent, I^2 = 56.6% (Analysis 2.2). Newsome 1988 found that there was more visual acuity loss in the control group than the treatment group although this did not reach statistical significance. Stur 1996 found little difference between the two groups with respect to mean visual acuity at the end of the study.

In Stur 1996 the primary outcome was incidence of choroidal neovascularisation (CNV) in all patients. During the treatment period, a CNV developed in the study eye in 14 patients (nine in the treatment group, five in the placebo group). People who experienced a CNV were not included in the analyses of visual acuity.

Outcome 3 progression AMD: dichotomous

Three trials provided data for this outcome (AREDS; Holz 1993; Stur 1996). A total of 969 people were randomised to zinc supplementation and 974 to placebo. Overall, there was a modest benefit of treatment (Analysis 2.3). The pooled OR was 0.73 (95% CI 0.58 to 0.93). Stur 1996 had quite different results to the other two trials. Over the treatment period, nine people experienced a CNV in the study eye in the zinc group compared to five people in the placebo group. This may have been a chance finding, however. The OR for that trial (2.31) had wide confidence intervals and the results are therefore also consistent with a protective effect of treatment (95% CI 0.58 to 9.26). Overall, the I^2 value was 29.0%. Holz 1993 has been published in abstract form only so we have little information about this trial.

Comparison 3: any multivitamin or single component antioxidant supplement versus placebo

Outcome 1, distance visual acuity: loss of 15 or more letters

Three trials contributed to this analysis (AREDS; Newsome 1988; VECAT) . The trials were reasonably consistent (I^2 = 27.7%) (Analysis 3.1). Overall there was a small beneficial effect of supplementation (pooled OR fixed-effect model 0.81, 95% CI 0.67 to 0.98, P = 0.03). A random-effects model gave a different result (pooled OR 0.83, 95% CI 0.63 to 1.09, P = 0.18). The difference in these two models reflects the difference in weighting given to the largest trial (AREDS) - 75% in the fixed-effect model versus 63% in the random-effects model.

Outcome 2, distance visual acuity: mean

Not all trials reported visual acuity data in a dichotomous format. Some trials reported average distance visual acuity at the end of the follow-up period or the mean change in visual acuity.
Five trials contributed to this analysis (AMDSG; Kaiser 1995; Newsome 1988; Stur 1996; Veterans LAST study). A total of 146 people were randomised to treatment and 140 to control. The results of the different studies were consistent (I^2 = 0%) (Analysis 3.2). There was little evidence of any benefit of treatment. The pooled standardised mean difference (random-effects model) was 0.02 (95% CI -0.21 to 0.26). A fixed-effect model gave identical results. Duration of treatment and follow up in these trials ranged from 6 to 24 months.

Outcome 3, progression AMD: dichotomous

Data on the progression of AMD was not reported or was reported in such a way as to make it difficult to extract data for this review in three studies (Kaiser 1995; Newsome 1988; Veterans LAST study).

Four trials contributed data on the progression of AMD as a dichotomous outcome (AREDS; Holz 1993; Stur 1996; VECAT) (Analysis 3.3). The results of the trials were inconsistent (I^2 = 64.2%) with the ORs for the individual studies ranging from 0.50 to 2.31. Estimating a pooled OR, therefore, was not of value in this case. Moreover, these trials were quite different in terms of the interventions studied, follow-up period and method of evaluating progression of AMD. (*See* Table 1).

Outcome 4, progression AMD: continuous

One study (AMDSG) reported data on the progression of AMD in a continuous format. There was little evidence for any benefit of treatment (mean difference -0.06, 95% CI -0.62 to 0.50). The number of participants in this analysis was small with 35 in the treatment group and 24 in the control group.
There was limited information from the Chinese trial (Wang 2004), particularly about the definitions of the outcome. However, the authors reported that supplementation with zinc, vitamin E and vitamin C over 24 months had no effect on the progression of early ARM (chi-squared test P > 0.05) but had a beneficial effect on the progression of the disease in people with advanced AMD. 12/124 people receiving supplements who had large drusen, geographic atrophy or neovascularisation in one eye progressed to "advanced AMD" (not defined but perhaps comparable to the AREDS definitions) compared to 36/124 in the placebo group (chi-squared P < 0.05).

Comparison 4: Vitamin E versus placebo

There has only been one trial investigating vitamin E alone (VECAT). This trial randomised 587 participants to vitamin E supplementation and 592 to placebo and followed them up for four years on average.

Outcome 1 distance visual acuity: loss of three or more lines

Outcome 2 progression of AMD

There was no evidence of any effect of treatment either on visual acuity (OR 1.05, 95% CI 0.70 to 1.57) or progression of AMD (OR 1.11, 95% CI 0.80 to 1.55). Over 80% of participants in this trial did not have signs of ARM or AMD.

Comparison 5: lutein or zeaxanthin versus placebo

Outcome 1 distance visual acuity: mean

There has only been one trial published to date comparing supplementation with lutein versus placebo (Veterans LAST study). The trial was small with a total of 25 people randomised to lutein

supplementation and 27 to placebo; the treatment duration and follow up was 12 months. The only outcome of relevance to this review, for which data could be extracted, was mean visual acuity at the end of the study. This showed little evidence of any effect of treatment: mean difference logMAR acuity 0.04 (95% CI -0.15 to 0.23). The power of the study was low.

Quality of life

None of the trials have reported on quality of life.

Adverse effects

The main reported adverse effect leading to withdrawal from the studies was gastrointestinal symptoms. Of 286 people randomised into trials of zinc sulfate supplementation compared to placebo, 5/146 zinc-treated people withdrew due to gastrointestinal symptoms compared to 2/140 controls. No-one developed copper-deficiency anaemia.

In AMDSG one person developed an 'allergic reaction' although it was not clear whether or not this was related to the treatment. AREDS considered a number of safety outcomes. They conducted over 100 comparisons of zinc versus no zinc and antioxidants versus no antioxidants. Participants in the antioxidant arms more frequently reported yellow skin (8.3% versus 6.0%, P = 0.008). Participants in the zinc arms reported more anaemia (13.2% versus 10.2%, P = 0.004), however, serum haematocrit levels were the same. They found that participants taking zinc had a lower mortality. Later follow-up of the cohort of people taking part in the AREDS study found that there was a significant increase in hospital admissions due to genitourinary diseases in people taking zinc supplements (11.1% versus 7.6% P = 0.0003) (Johnson 2007).

DISCUSSION

The trials contributing to this review fall into two categories. There are two large trials with reasonably long treatment duration and follow up of four to six years (AREDS; VECAT). The other six trials are smaller (ranging from 20 to 151 participants) and have shorter duration of treatment and follow up (6 to 24 months).

The large trials provide reasonably clear answers to different questions. The AREDS trial provides evidence that long-term supplementation with vitamins C, E, beta-carotene and zinc, in people with AMD, reduced the risk of progression of the disease and visual acuity loss. The overall benefit is modest with a risk reduction in the order of 20% to 25%. However, given that treatment options for AMD are limited, and vision loss is rarely recovered, this is of interest to people with AMD.

The VECAT study suggests that the general population should not take vitamin E with a view to preventing the incidence or progression of AMD. However, the study was underpowered to answer the question as to whether people with signs of AMD, such as those participating in the AREDS study, should take vitamin E. Currently VECAT is the only published trial on vitamin E supplementation and AMD.

The other trials of multivitamin preparations, Ocuguard (AMDSG), Ocupower (Veterans LAST study) and Visaline (Kaiser 1995) are too small to provide evidence either way. Pooling results, where possible, did not provide evidence of any benefit of supplementation. However, these trials were of relatively short duration.

A total of five trials investigated zinc supplementation (AREDS; France 1998; Holz 1993; Newsome 1988; Stur 1996). The AREDS study indicated that the beneficial effect of zinc supplementation was of a similar order to that of vitamin supplementation. The other trials provide more conflicting evidence. Newsome 1988 found a reduction in the risk of visual acuity loss with supplementation over 12 to 24 months. However, Stur 1996 found no effect of treatment. Unfortunately Stur 1996, which was planned to recruit 500 participants, was terminated early because the results of the first 40 patients at 24 months indicated no benefit of treatment. The other two trials of zinc supplementation are as yet unpublished, although limited results from Holz 1993 were published in abstract form and are included here. The trialists have been contacted with a view to including unpublished data in future versions of this review.

The main evidence that antioxidant vitamin and mineral supplementation is of benefit comes from the AREDS trial. As AREDS is a large well-conducted randomised study, potential biases will have been minimised. The only area where bias may have been introduced is if there were different systemic effects of the antioxidant and zinc supplementation (for example, yellowing of skin or difficulty swallowing tablets) which led the participants to guess which group they were in or alternatively, the retinal fundus photographs might have been different in some way such that the graders response was affected by treatment group. There is little evidence that this was a problem in the study.

AREDS was the only study to examine in detail the question of safety. They found little evidence of harm, however, recent follow-up of the cohort suggests an increased risk of hospital admission due to genitourinary complications in people taking the zinc supplements. The safety of some of the components of the AREDS formulation have been questioned in other studies. Two large randomised controlled trials have indicated that smokers who take beta-carotene may be at increased risk of developing lung cancer (ATBC; Omenn 1996). The Heart Outcomes Prevention Evaluation (HOPE) Study found that, among people with vascular disease or diabetes, vitamin E supplementation was associated with a higher risk of heart failure (Hope 2005).

AUTHORS' CONCLUSIONS

Implications for practice

People with AMD may experience modest delay in progression of the disease with antioxidant vitamin and mineral supplementation. This finding is drawn from one large trial conducted in a relatively well-nourished American population. Until it is replicated by other large-scale trials in other populations we will not know whether these findings can be applied more generally.

Antioxidant vitamin and mineral supplements are readily available for purchase without prescription in many countries. The decision as to whether to take these supplements is at the discretion of the person with AMD. The following benefits and harms need to be considered. People with AMD may delay the progression of their condition if they take antioxidant vitamins and zinc at the levels described in this review. Given that there are few other interventions that offer much in the way of disease prevention or cure this is an important consideration. However, harmful effects associated with long-term vitamin supplementation, particularly in smokers and people with vascular disease, cannot be ruled out. A healthy diet with a variety of fresh fruit and vegetables will have many benefits and is unlikely to be harmful. It may be difficult, however, to consume as part of a normal diet the levels of antioxidants and zinc described in the trials included in this review . For example, one orange provides 80 mg of vitamin C; this is a relatively high amount. However, one would need to eat six to seven oranges daily to obtain 500 mg vitamin C.

There is currently considerable interest in the potential role of lutein and zeaxanthin supplementation in AMD. This review includes only one small equivocal trial on lutein. Such supplements currently cannot be recommended.

Implications for research

Trials in other populations, preferably with a variety of nutritional status, are required. These trials should have a large enough sample size to demonstrate effects that are meaningful for people and should also include a component on quality of life. It is likely that AMD develops over many years. Three categories of people may be identified: healthy people at risk because of age or genetic factors; people with early stages of the disease; people with intermediate or late-stage disease. There are likely to be differences in the potential protective effect of antioxidant supplementation depending on the stage of the disease.

REFERENCES

References to studies included in this review

AMDSG *{published data only}*
Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study-part 1: design, subjects and procedures. *Journal of the American Optometric Association* 1996;**67**:12–29.
* Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study-part 2: antioxidant intervention and conclusions. *Journal of the American Optometry Association* 1996;**67**:30–49.

AREDS *{published data only}*
* Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report No. 8. *Archives of Ophthalmology* 2001;**119** (10):1417–36.
Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS) system for classifying age-related macular degeneration from stereoscopic color fundus photographs: The Age-Related Eye Disease Study Report No. 6. *American Journal of Ophthalmology* 2001; **132**:668–81.
Clemons TE, Kurinji N, Sperduto RD, AREDS Research

Group. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. *Archives of Ophthalmology* 2004;**122**:716–26.

Johnson AR, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *The Journal of urology* 2007;**177**(2):639–43.

Moriarty-Craige SE, Ha KN, Sternberg P, Lynn M, Bressler S, Gensler G, et al.Effects of long-term zinc supplementation on plasma thiol metabolites and redox status in patients with age-related macular degeneration. *American journal of ophthalmology* 2007;**143**(2):206–11.

The Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): Design Implications AREDS Report No. 1. *Controlled Clinical Trials* 1999;**20**:573–600.

Holz 1993 *{published data only}*
Holz FG, Wolfensberger TJ, Piguet B, Gross-Jendroska M, Arden GB, Bird AC. Oral zinc-therapy in age-related macular degeneration: a double-blind study (abstract). *German Journal of Ophthalmology* 1993;**2**:391.

Kaiser 1995 *{published and unpublished data}*
Kaiser HJ, Flammer J, Stumpfig D, Hendrickson P. Visaline in the treatment of age-related macular degeneration: a pilot study. *Ophthalmologica* 1995;**209**:302–5.

Newsome 1988 *{published data only}*
Newsome DA, Swartz M, Leone NC, Elston RC, Miller E. Oral zinc in macular degeneration. *Archives of Ophthalmology* 1988;**106**:192–8.

Stur 1996 *{published data only}*
Stur M, Tittl M, Reitner A, Meisinger V. Oral zinc and the second eye in age-related macular degeneration. *Investigative Ophthalmology & Visual Science* 1996;**37**:1225–35.

VECAT *{unpublished data only}*
* Garrett SKM, McNeil JJ, Silagy C, Sinclair M, Thomas AP, Robman LD, et al.Methodology of the VECAT study: vitamin E intervention in cataract and age-related maculopathy. *Ophthalmic Epidemiology* 1999;**6**:195–208.

Robman LD, Tikellis G, Garrett SKM, Harper CA, McNeil JJ, Taylor HR, et al.Baseline ophthalmic findings in the vitamin E, cataract and age-related maculopathy (VECAT) study. *Australian and New Zealand Journal of Ophthalmology* 1999;**27**:410–6.

Taylor HR, Tikellis G, Robman LD, McCarty CA, McNeil. Vitamin E supplementation and age-related maculopathy (abstract). Investigative Ophthalmology & Visual Science. 2001; Vol. 42:S311.

Veterans LAST study *{published data only}*
Richer S, Devenport J, Lang JC. LAST II: Differential temporal responses of macular pigment optical density in patients with atrophic age-related macular degeneration to dietary supplementation with xanthophylls. *Optometry* 2007;**78**:213–9.

Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D, et al.Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation

in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 2004;**75**:216–30.

Wang 2004 *{published data only}*
Wang H, Li R-X, Wang M-F. Effects of zinc and antioxidant on visual function of patients with age-related macular degeneration. *Zhongguo Linchuant Kangfu* 2004;**8**:1290–1.

References to studies excluded from this review

Bahrami 2006 *{published data only}*
Bahrami H, Melia M, Dagnelie G. Lutein supplementation in retinitis pigmentosa: PC-based vision assessment in a randomized double-masked placebo-controlled clinical trial. *BMC Ophthalmology* 2006;**6**:23.

Barakat 2006 *{published data only}*
Barakat MR, Metelitsina TI, DuPont JC, Grunwald JE. Effect of niacin on retinal vascular diameter in patients with age-related macular degeneration. *Current Eye Research* 2006;**31**(7-8):629–34.

Benzie 2006 *{published data only}*
Benzie IF, Chung WY, Wang J, Richelle M, Bucheli P. Enhanced bioavailability of zeaxanthin in a milk-based formulation of wolfberry (Gou Qi Zi; Fructus barbarum L.). *The British Journal of Nutrition* 2006;**96**(1):154–60.

Bone 2007 *{published data only}*
Bone RA, Landrum JT, Cao Y, Howard AN, Alvarez-Calderon F. Macular pigment response to a supplement containing meso-zeaxanthin, lutein and zeaxanthin. *Nutrition & Metabolism* 2007;**4**:Article Number: 12.

Cangemi 2007 *{published data only}*
Cangemi FE. TOZAL Study: an open case control study of an oral antioxidant and omega-3 supplement for dry AMD. *BMC Ophthalmology* 2007;**7**:3.

Christen 2007 *{published data only}*
Christen WG, Manson JE, Glynn RJ, Gaziano JM, Chew EY, Buring JE, et al.Beta carotene supplementation and age-related maculopathy in a randomized trial of US physicians. *Archives of Ophthalmology* 2007;**125**(3):333–9.

Cumurcu 2006 *{published data only}*
Cumurcu T, Mendil D, Etikan I. Serum zinc and copper level in age-related macular degeneration. *Trace Elements & Electrolytes* 2006;**23**(2):103–7.

Franciose 2006 *{published data only}*
Franciose JL, Askew EW, Lang JC, Bernstein PS. Serum and macular responses to antioxidant supplementation versus a carotenoid-rich dietary intervention in the elderly. *Current Topics in Nutraceuticals Research* 2006;**4**(1):69–78.

Goodrow 2006 *{published data only}*
Goodrow EF, Wilson TA, Houde SC, Vishwanathan R, Scollin PA, Handelman G, et al.Consumption of one egg per day increases serum lutein and zeaxanthin concentrations in older adults without altering serum lipid and lipoprotein cholesterol concentrations. *The Journal of Nutrition* 2006;**136**(10):2519–24.

Kamburoglu 2006 *{published data only}*
Kamburoglu G, Gumus K, Kadayifcilar S, Eldem B. Plasma homocysteine, vitamin B12 and folate levels in age-related macular degeneration. *Graefes Archive for Clinical & Experimental Ophthalmology* 2006;**244**(5):565–9.

Khachik 2006 *{published data only}*
Khachik F, de Moura FF, Chew EY, Douglass LW, Ferris FL, Kim J, et al.The effect of lutein and zeaxanthin supplementation on metabolites of these carotenoids in the serum of persons aged 60 or older. *Investigative Ophthalmology & Visual Science* 2006;**47**(12):5234–42.

Kopsell 2006 *{published data only}*
Kopsell DA, Lefsrud MG, Kopsell DE, Wenzel AJ, Gerweck C, Curran-Celentano J. Spinach cultigen variation for tissue carotenoid concentrations influences human serum carotenoid levels and macular pigment optical density following a 12-week dietary intervention. *Journal of Agricultural and Food Chemistry* 2006;**54**(21):7998–8005.

Lim 2006 *{published data only}*
Lim JI, Walonker AF, Levin L, Mahmoud M, Sadda S, Flaxel CJ, et al.One-year results of a pilot study using oral 13-cis retinoic acid as a treatment for subfoveal predominantly occult choroidal neovascularization in patients with age-related macular degeneration. *Retina* 2006;**26**(3):314–21.

LUNA study *{published data only}*
* Trieschmann M, Beatty S, Nolan JM, Hense HW, Heimes B, Austermann U, et al.Changes in macular pigment optical density and serum concentrations of its constituent carotenoids following supplemental lutein and zeaxanthin: the LUNA study. *Experimental Eye Research* 2007;**84**(4): 718–28.

LUXEA *{published data only}*
Kvansakul J, Rodriguez-Carmona M, Edgar DF, Barker FM, Kopcke W, Schalch W, et al.Supplementation with the carotenoids lutein or zeaxanthin improves human visual performance. *Ophthalmic & Physiological Optics* 2006;**26** (4):362–71.
Rodriguez-Carmona M, Kvansakul J, Harlow JA, Köpcke W, Schalch W, Barbur JL. The effects of supplementation with lutein and/or zeaxanthin on human macular pigment density and colour vision. *Ophthalmic & Physiological Optics* 2006;**26**(2):137–47.
* Schalch W, Cohn W, Barker FM, Köpcke W, Mellerio J, Bird AC, et al.Xanthophyll accumulation in the human retina during supplementation with lutein or zeaxanthin - the LUXEA (LUtein Xanthophyll Eye Accumulation) study. *Archives of biochemistry and biophysics* 2007;**458**(2):128–35.

Moeller 2006 *{published data only}*
Moeller SM, Parekh N, Tinker L, Ritenbaugh C, Blodi B, Wallace RB, et al CAREDS Research Study Group. Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-related Eye Disease Study (CAREDS): ancillary study of the Women's Health Initiative. *Archives of Ophthalmology* 2006;**124**(8):1151–62.

Nolan 2006 *{published data only}*
Nolan J, Stack J, Mellerio J, Godhinio M, O'Donovan O, Neelam K, et al.Monthly consistency of macular pigment optical density and serum concentrations of lutein and zeaxanthin. *Current Eye Research* 2006;**31**(2):199–213.

Nolan 2007 *{published data only}*
Nolan JM, Stack J, O' Donovan O, Loane E, Beatty S. Risk factors for age-related maculopathy are associated with a relative lack of macular pigment. *Experimental Eye Research* 2007;**84**(1):61–74.

Nussenblatt 2006 *{published data only}*
Nussenblatt RB, Kim J, Thompson DJ, Davis MD, Chew E, Ferris FL, Buggage R. Vitamin E in the treatment of uveitis-associated macular edema. *American Journal of Ophthalmology* 2006;**141**(1):193–4.

Owsley 2006 *{published data only}*
Owsley C, McGwin G, Jackson GR, Heimburger DC, Piyathilake CJ, Klein R, et al.Effect of short-term, high-dose retinol on dark adaptation in aging and early age-related maculopathy. *Investigative Ophthalmology & Visual Science* 2006;**47**(4):1310–8.

Rosenthal 2006 *{published data only}*
Rosenthal JM, Kim J, de Monasterio F, de Monastario F, Thompson DJ, Bone RA, et al.Dose-ranging study of lutein supplementation in persons aged 60 years or older. *Investigative Ophthalmology & Visual Science* 2006;**47**(12): 5227–33.

Vannas 1958 *{published data only}*
Vannas S, Orma H. On the treatment of arteriosclerotic chorioretinopathy. *Acta Ophthalmologica Copenhagen* 1958; **36**:601–12.

Wang 2007 *{published data only}*
Wang W, Connor SL, Johnson EJ, Klein ML, Hughes S, Connor WE. Effect of dietary lutein and zeaxanthin on plasma carotenoids and their transport in lipoproteins in age-related macular degeneration. *American Journal of Clinical Nutrition* 2007;**85**(3):762–9.

Wenzel 2006 *{published data only}*
Wenzel AJ, Gerweck C, Barbato D, Nicolosi RJ, Handelman GJ, Curran-Celentano J. A 12-wk egg intervention increases serum zeaxanthin and macular pigment optical density in women. *Journal of Nutrition* 2006;**136**(10):2568–73.

Zhao 2006 *{published data only}*
Zhao DY, Bhosale P, Bernstein PS. Carotenoids and ocular health. *Current Topics in Nutraceuticals Research* 2006;**4**(1): 53–68.

References to studies awaiting assessment

France 1998 *{unpublished data only}*
Professor Soubrane. Zinc supplementation. Universitaire de Creteil, France.

Additional references

ARMSG 1995
The International ARM Epidemiological Study Group. An international classification and grading system for age-

related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surveys of Ophthalmology* 1995;**39**:367–74.

ATBC

The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine* 1994;**330**: 1029–35.

Bressler 1989

Bressler NM, Bressler SB, West SK, Fine SL, Taylor HR. The grading and prevalence of macular degeneration in Chesapeake Bay watermen. *Archives of Ophthalmology* 1989; **107**:847–52.

Christen 1996

Christen WG, Glynn RJ, Hennekens CH. Antioxidants and age-related eye disease. Current and future perspectives. *Annals of Epidemiology* 1996;**Jan 6**(1):60–6.

ETDRS 1980

Early Treatment Diabetic Retinopathy Study Research Group. *Early Treatment Diabetic Retinopathy Study Manual of Operations*. Baltimore: ETDRS Co-ordinating Center, 1980:1–15.

Evans 1996

Evans JR, Rooney C, Dattani N, Ashwood F, Wormald RPL. Causes of blindness and partial sight in England and Wales. *Health Trends* 1996;**28**:5–12.

Evans 2008

Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD000253.pub2]

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE:

ten years on. *Journal of the Medical Library Association* 2006; **94**(2):130–6.

Higgins 2006

Higgins JPT, Green S, editors. Assessment of study quality. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 6. In: The Cochrane Library, Issue 4, 2006. John Wiley & Sons, Ltd. Chichester, UK.

Hope 2005

The HOPE and HOPE-TOO trial investigators. Effects of long term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005;**293**:1338–47.

Johnson 2007

Johnson AR, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *Journal of Urology* 2007;**177**:639–43.

Klein 1991

Klein R, Davis MD, Magli YL, Segal P, Klein BEK, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology* 1991;**98**:1128–34.

Klein 1992

Klein R, Klein BEK, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992;**99**:933–43.

Omenn 1996

Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al.Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New England Journal of Medicine* 1996;**334**: 1189–90.

* *Indicates the major publication for the study*

Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

13

CHARACTERISTICS OF STUDIES

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

AMDSG

Methods	Method of allocation: Sponsor prepared coded tablets. Masking: Participant - not clear; Provider - yes; Outcome - yes. Losses to follow up: 4 died (2 treatment, 2 control); 1 adverse effect withdrawn (treatment); 7 lost to follow up (1 treatment, 6 control)
Participants	Country: USA. Number of participants randomised: 71 veterans. Age: Average age 72 years. Sex: 66 male 5 female. Inclusion criteria: People with a monocular one line drop in Snellen visual acuity not attributable to cataract, amblyopia, systemic or ophthalmic disease AND clinically observable drusen, RPE disruption and loss of macular reflex. Exclusion criteria: Greater than one year use of vitamins; ex-prisoners of war, chronic alcoholics with tobacco/nutritional amblyopia or gastrointestinal absorption disorders
Interventions	Treatment: Ocuguard (Twin Lab Inc, Ronkonkoma, NY) broad spectrum antioxidant: beta carotene 20,000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercitin (bioflavonoid) 50 mg, bilberry extract (bioflavonoid) 5 mg, rutin (bioflavonoid) 50 mg, zinc picolinate 12.5 mg, selenium 50 mcg, taurine 100 mg, n-acetyl cysteine 100mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 mcg. Control: Starch placebo. Duration: 18 months.
Outcomes	Snellen acuity with best refraction converted to logMAR units for analysis; Near vision M units with dual sided Bailey-Lovie chart; Contrast sensitivity; Retinal grading score (adapted from Chesapeake Bay Study); Subjective perception of vision; Adverse gastrointestinal reactions
Notes	Treatment and placebo may not have been identical. Funders: Twin Laboratories Inc, Ronkokoma NY; Stereo Optical Inc, Chicago, IL.; Eye Communications Inc, Upland, CA; Illinois College of Optometry, Chicago, IL; Pacific University College of Optometry, Forest Grove, OR; Ezell Foundation, American Academy of Optometry, Rockville, MD

Risk of bias

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

AREDS

Methods	Method of allocation: Coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow-up: 2.4% balanced across study groups.
Participants	Country: USA. Number of participants randomised: 3640. Age: Average age 69 years (range 55 to 80). Sex: 56% female. Inclusion criteria: 20/32 or better in at least one eye; ocular media clear and therefore able to obtain adequate stereoscopic fundus photographs; at least one eye free from eye disease that could complicate assessment of AMD. Exclusion criteria: Illness or disorders that would make long term follow-up or compliance with study protocol unlikely or difficult
Interventions	Treatment: Antioxidants (500mg vitamin C, 400IU vitamin E, 15mg beta carotene) zinc (80mg of zinc as zinc oxide and 2mg of copper as cupric oxide). Control: Placebo identical in external appearance and similar in internal appearance and taste. Duration: 7 years.
Outcomes	Primary outcomes: (1) progression to advanced AMD and (2) 15 letter or more decrease in visual acuity score. AMD assessed using stereoscopic fundus colour photograph; visual acuity measured using EDTRS logMAR chart. Safety outcomes included: reported adverse events; serum levels of haemoglobin; hospitalisations and mortality
Notes	2x2 factorial design. 67% participants took additional supplements to RDA levels (Centrum). In 1996 current smokers offered option of discontinuing supplementation; 2% of participants and 18% of smokers did so. A further 2.3% reassigned to no beta-carotene group. Intention to treat analysis maintained

Risk of bias

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

Holz 1993

Methods	Method of allocation: Not known. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow-up: Not known.
Participants	Country: UK. Number of participants randomised: 58. Age: 55 - 82, mean 68.
Interventions	Treatment: 100mg zinc sulfate twice daily. Control: Placebo. Duration: 12 to 24 months.

Holz 1993 *(Continued)*

Outcomes	Visual acuity; Contrast sensitivity; Dark adaptation; Stereo fundus photographs and fluorescein angiograms
Notes	Data available from abstract only.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kaiser 1995

Methods	Method of allocation: Sponsor prepared coded tablets. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow-up: None.
Participants	Country: Switzerland. Number of participants randomised: 20. Age: over 50. Average age 72 in treatment group, 74 in control group. Sex: 7 male, 20 female. Inclusion criteria: People with nonserous AMD. All participants had regional atrophy of the pigment epithelium. Corrected visual acuity was between 20/100 and 20/25 with distance correction of less than four dioptres. Exclusion criteria: People with diabetes mellitus, endocrine problems, cardiac dysrhythmia, cardial infarction or hypotension, other ocular disorders
Interventions	Treatment: Visaline (Novopharma Cham, Switzerland). Each tablet contains 1.5mg buphenine HCl, 10 mg beta-carotene, 10 mg tocopherol acetate, and 50 mg ascorbic acid. Participants took 2 tablets in the morning and at night, daily except for Saturdays and Sundays. Control: Placebo resembling active treatment prepared by sponsor. Duration: 6 months.
Outcomes	Only one eye per person was evaluated. In cases of bilateral AMD, the eye with better visual acuity was selected. Distance and near visual acuity; Intraocular pressure; Visual fields; Lens opacity; Retinal visual acuity; Colour vision; Contrast sensitivity
Notes	

Risk of bias

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

Newsome 1988

Methods	Method of allocation: Computer generated table of random numbers. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: 23 (10 treatment, 13 placebo).
Participants	Country: USA. Number of participants randomised: 174. Age: 42 to 89. Sex: 61 men 113 women. Inclusion criteria: Macular degeneration: clinically visible drusen with varying degrees of pigmentary change with visual acuity in one eye of 20/80 or better. Exclusion criteria: Cataract reducing vision more than one line; other known serious eye disease; diabetes mellitus; other known systematic/metabolic disease or congenital condition which might interfere with results
Interventions	Treatment: Zinc sulfate 100mg twice daily. Control: Identical tablets with lactose and fructose. Duration: 1 to 2 years.
Outcomes	Pinhole corrected visual acuity using ETDRS charts; Changes in visible pigment, drusen or atrophy from grading of macular photographs; Adverse effects of zinc including copper deficiency anaemia
Notes	Funders: Research Fund, Department of Veterinary Science, Utah State University, Logan; James L Shupe, DVM; Mary Katherine Peterson Foundation, Houston

Risk of bias

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

Stur 1996

Methods	Method of allocation: sponsor prepared coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow-up: 6 withdrawn due to adverse gastrointestinal effects (4 treatment, 2 control); 14 withdrawn when developed neovascularisation (9 treatment, 5 control); 14 lost to follow up (6 treatment, 8 control)
Participants	Country: Austria. Number of participants randomised: 112. Age: 50 plus. Sex: 48 men, 64 women. Inclusion criteria: Exudative AMD in one eye (defined as angiographic evidence of classic or occult choroidal neovascularisation or RPE detachment) and early ARM with visual acuity 20/40 or better in other eye (early ARM: macular drusen with no angiographic evidence of exudative lesion). Exclusion criteria: Dense senile cataract; any other eye disease which could produce significant and permanent loss of visual acuity during follow up; physical status that could prevent follow up; history of serious systemic or metabolic disease

Stur 1996 (*Continued*)

Interventions	Treatment: Zinc sulfate 200 mg once daily. Lemon flavoured effervescent tablet made of citric acid containing saccharine and sorbitol. Control: As treatment but without zinc sulfate. Duration: 24 months.
Outcomes	Best corrected LogMAR visual acuity measured using Bailey-Lovie chart; Contrast sensitivity; Incidence of choroidal neovascularisation; Progression of disease (Wisconsin Age-related Maculopathy Grading System); Copper deficiency anaemia
Notes	A priori sample size estimate was 500 patients but trial stopped early because interim analysis showed no detectable trend. Funders: Astra, Linz, Austria; Austrian Foundation for the Propagation of Scientific Research

Risk of bias

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

VECAT

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

Risk of bias

Item	Authors' judgement	Description

Allocation concealment?	Yes	A - Adequate

Veterans LAST study

Methods	Method of allocation: Coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: 7 withdrew, 4 lost to follow-up, 3 died. Slightly lower % follow up in group 2 (lutein/antioxidant) 80% compared to other 2 group (lutein alone 86% placebo 87%)
Participants	Country: USA. Number of participants randomised: 90. Approximate average age 75 years. Sex: 86/90 male. Inclusion criteria: Atrophic AMD diagnosed by ophthalmoscopy and at least one visual abnormality: reduced contrast sensitivity, photo-stress glare recovery deficit or deficit on Amsler grid. Clear ocular media, free of any other ocular/systemic disease that could affect central or parafoveal macular visual function. Exclusion criteria: Cataract or retinal surgery within 6 months, photosensitizing drugs, taken lutein supplements within the previous six months
Interventions	Treatment: Group 1 L: Lutein 10mg non-esterified lutein (FloraGlo from Kemin Foods International, Des Moines, Iowa); Group 2 L/A: Lutein plus additional antioxidants and nutrients (OcuPower (see below) from Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida) Group 3 P: maltodextrin. Duration: 12 months Ocupower had a range of nutrients including lutein , vitamin A, betacarotene, vitamins C, D3, E, B1, B2, B3, B5, B6, B12, folic acid, biotin, calcium, magnesium, iodine, zinc copper, manganese, selenium, chromium, molybdenum, lycopene, bilberry extract, alpha lipoic acid, N-acetyl cysteine, quercetin, rutin, citrus bioflavonoids, plant enzymes, black pepper extract, malic acid, taurine, L-glycine, L-glutathione, boron
Outcomes	The following clinical measurements were made: Lens opacity; retinal images; Macular Pigment Optical Density (MPOD); visual acuity (Snellen) distance and near; glare testing; glare recovery; contrast sensitivity; VFQ-14 (activities of daily living, night driving, glare recovery symptoms) ; Amsler grid; self-reported vision
Notes	It was difficult to extract data on outcomes of relevance to this review: i.e. visual acuity and progression of AMD

Risk of bias

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

Wang 2004

Methods	Method of allocation: Unknown. Masking: Participant - unknown; Provider - unknown; Outcome - unknown. Losses to follow up: unknown
Participants	Country: China Number of participants randomised: 400 188 men / 212 women aged 52 to 76, average age 65
Interventions	Treatment: zinc oxide 80mg daily, vitamin C, vitamin E. Control: placebo Duration 24 to 32 months.
Outcomes	Outcomes: visual acuity
Notes	Limited information available on this trial. AMD patients were stratified in early and late stage disease

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

AMD: age-related macular degeneration
ETDRS: Early Treatment Diabetic Retinopathy Study
RPE: retinal pigment epithelium
MPOD: macular pigment optical density

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

Study	Reason for exclusion
Bahrami 2006	Not AMD.
Barakat 2006	Not antioxidant vitamin.
Benzie 2006	Bioavailability study
Bone 2007	Bioavailability study.
Cangemi 2007	No control group.
Christen 2007	RCT in healthy population group. Included in Cochrane review on prevention of AMD with antioxidant supplements
Cumurcu 2006	Not RCT.

Franciose 2006	Bioavailability study.
Goodrow 2006	Bioavailability study.
Kamburoglu 2006	Not RCT, not antioxidant
Khachik 2006	Bioavailability study.
Kopsell 2006	Bioavailability study.
Lim 2006	Not antioxidant
LUNA study	Bioavailability study.
LUXEA	MPOD only measured; no clinical outcomes.
Moeller 2006	Not RCT.
Nolan 2006	Not RCT.
Nolan 2007	Not RCT.
Nussenblatt 2006	Not AMD.
Owsley 2006	Not antioxidant.
Rosenthal 2006	Small dose ranging study. Data on vision only collected for nine months and not possible to extract from report
Vannas 1958	Allocation concealment inadequate.
Wang 2007	Bioavailability study.
Wenzel 2006	Bioavailability study.
Zhao 2006	Bioavailability study.

AMD: age-related macular degeneration
MPOD: macular pigment optical density
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Multivitamin supplement versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity: mean	3	131	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.19, 0.51]
1.1 Mean visual acuity at end of study	3	131	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.19, 0.51]

Comparison 2. Zinc versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity: loss of 3 or more lines	2	1958	Odds ratio (Fixed, 95% CI)	0.81 [0.66, 0.99]
2 Distance visual acuity: mean	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Mean visual acuity at end of study	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Change in visual acuity	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Progression AMD: dichotomous	3	1943	Odds ratio (Fixed, 95% CI)	0.73 [0.58, 0.93]

Comparison 3. Any multivitamin or single component antioxidant supplement versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity: loss of 3 or more lines	3	4970	Odds ratio (Fixed, 95% CI)	0.81 [0.67, 0.98]
2 Distance visual acuity: mean	5	286	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.21, 0.26]
2.1 Mean visual acuity at end of study	3	157	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.21, 0.42]
2.2 Change in visual acuity	2	129	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.66, 0.59]
3 Progression AMD: dichotomous	4		Odds ratio (Random, 95% CI)	Totals not selected

Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration (Review)   **22**

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.1. Comparison 1 Multivitamin supplement versus placebo, Outcome 1 Distance visual acuity: mean.

Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 1 Multivitamin supplement versus placebo

Outcome: 1 Distance visual acuity: mean

Study or subgroup	Antioxidant		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Mean visual acuity at end of study							
AMDSG	35	0.33 (0.41)	24	0.29 (0.24)		44.4 %	0.11 [-0.41, 0.63]
Kaiser 1995	9	0.17 (0.7)	11	0.22 (0.66)		15.5 %	-0.07 [-0.95, 0.81]
Veterans LAST study	25	-0.03 (0.242347)	27	-0.14 (0.437431)		40.1 %	0.30 [-0.24, 0.85]
Total (95% CI)	**69**		**62**			**100.0 %**	**0.16 [-0.19, 0.51]**

Heterogeneity: Chi² = 0.56, df = 2 (P = 0.76); I² =0.0%

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable

```
          -10    -5     0     5    10
           Favours treatment   Favours control
```

Analysis 2.1. Comparison 2 Zinc versus placebo, Outcome 1 Distance visual acuity: loss of 3 or more lines.

Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 2 Zinc versus placebo

Outcome: 1 Distance visual acuity: loss of 3 or more lines

Study or subgroup	Zinc	Placebo	log [Odds ratio]	Odds ratio	Weight	Odds ratio
	N	N	(SE)	IV,Fixed,95% CI		IV,Fixed,95% CI
AREDS	904	903	-0.1985 (0.1045)		97.2 %	0.82 [0.67, 1.01]
Newsome 1988	80	71	-0.8159 (0.6123)		2.8 %	0.44 [0.13, 1.47]
Total (95% CI)					**100.0 %**	**0.81 [0.66, 0.99]**

Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² =0.0%

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable

```
      0.001 0.01  0.1   1   10  100 1000
          Favours treatment   Favours control
```

Analysis 2.2. Comparison 2 Zinc versus placebo, Outcome 2 Distance visual acuity: mean.

Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 2 Zinc versus placebo

Outcome: 2 Distance visual acuity: mean

Study or subgroup	Zinc		Placebo		Std. Mean Difference	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
1 Mean visual acuity at end of study						
Stur 1996	37	0.05 (0.12)	41	0.03 (0.14)		0.15 [-0.29, 0.60]
2 Change in visual acuity						
Newsome 1988	40	0.08 (0.12)	37	0.14 (0.22)		-0.34 [-0.79, 0.11]

-10   -5   0   5   10

Favours treatment   Favours control

Analysis 2.3. Comparison 2 Zinc versus placebo, Outcome 3 Progression AMD: dichotomous.

Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 2 Zinc versus placebo

Outcome: 3 Progression AMD: dichotomous

Study or subgroup	Zinc N	Placebo N	log [Odds ratio] (SE)	Odds ratio IV,Fixed,95% CI	Weight	Odds ratio IV,Fixed,95% CI
AREDS	904	903	-0.3425 (0.1266)		95.8 %	0.71 [0.55, 0.91]
Holz 1993	28	30	-0.6931 (1.1533)		1.2 %	0.50 [0.05, 4.79]
Stur 1996	37	41	0.8391 (0.7073)		3.1 %	2.31 [0.58, 9.26]
Total (95% CI)					**100.0 %**	**0.73 [0.58, 0.93]**

Heterogeneity: Chi² = 2.82, df = 2 (P = 0.24); I² =29%

Test for overall effect: Z = 2.50 (P = 0.012)

Test for subgroup differences: Not applicable

```
        0.001 0.01  0.1    1    10  100 1000
        Favours treatment      Favours control
```

Analysis 3.1. Comparison 3 Any multivitamin or single component antioxidant supplement versus placebo, Outcome 1 Distance visual acuity: loss of 3 or more lines.
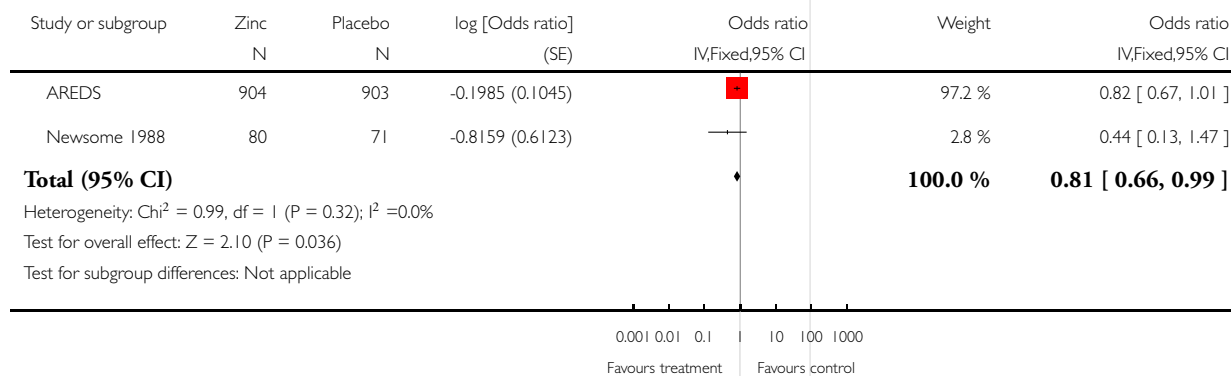
Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 3 Any multivitamin or single component antioxidant supplement versus placebo

Outcome: 1 Distance visual acuity: loss of 3 or more lines

Study or subgroup	Antioxidant N	Placebo N	log [Odds ratio] (SE)	Odds ratio IV,Fixed,95% CI	Weight	Odds ratio IV,Fixed,95% CI
AREDS	2737	903	-0.2614 (0.1113)		75.4 %	0.77 [0.62, 0.96]
Newsome 1988	80	71	-0.8159 (0.6123)		2.5 %	0.44 [0.13, 1.47]
VECAT	587	592	0.0477 (0.2053)		22.1 %	1.05 [0.70, 1.57]
Total (95% CI)					**100.0 %**	**0.81 [0.67, 0.98]**

Heterogeneity: Chi² = 2.77, df = 2 (P = 0.25); I² =28%

Test for overall effect: Z = 2.14 (P = 0.032)

Test for subgroup differences: Not applicable

```
        0.001 0.01  0.1    1    10  100 1000
        Favours treatment      Favours control
```

Analysis 3.2. Comparison 3 Any multivitamin or single component antioxidant supplement versus placebo, Outcome 2 Distance visual acuity: mean.
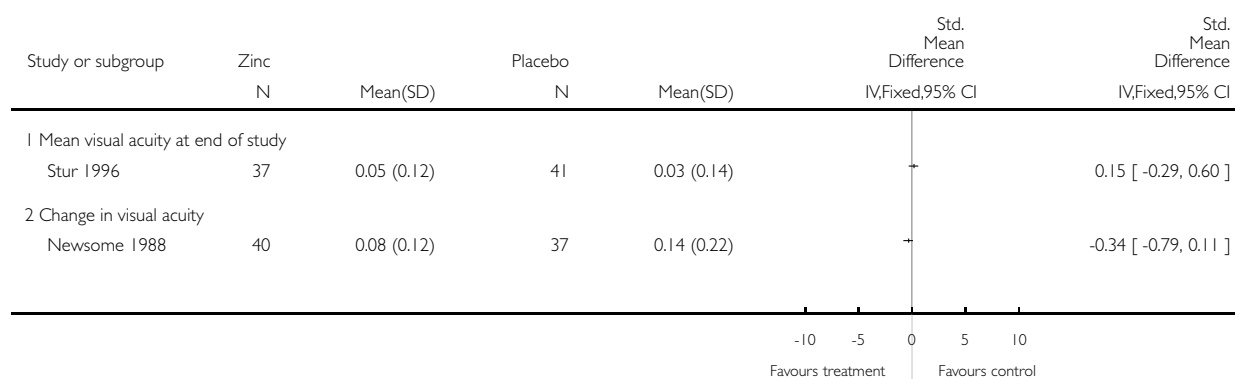
Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 3 Any multivitamin or single component antioxidant supplement versus placebo

Outcome: 2 Distance visual acuity: mean

Study or subgroup	Antioxidant N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Mean visual acuity at end of study							
AMDSG	35	0.33 (0.41)	24	0.29 (0.24)		20.2 %	0.11 [-0.41, 0.63]
Kaiser 1995	9	0.17 (0.7)	11	0.22 (0.66)		7.0 %	-0.07 [-0.95, 0.81]
Stur 1996	37	0.05 (0.12)	41	0.03 (0.14)		27.6 %	0.15 [-0.29, 0.60]
Subtotal (95% CI)	**81**		**76**			**54.8 %**	**0.11 [-0.21, 0.42]**
Heterogeneity: Tau² = 0.0; Chi² = 0.19, df = 2 (P = 0.91); I² =0.0%							
Test for overall effect: Z = 0.67 (P = 0.50)							
2 Change in visual acuity							
Newsome 1988	40	0.08 (0.12)	37	0.14 (0.22)		26.9 %	-0.34 [-0.79, 0.11]
Veterans LAST study	25	-0.03 (0.25)	27	-0.14 (0.44)		18.2 %	0.30 [-0.25, 0.85]
Subtotal (95% CI)	**65**		**64**			**45.2 %**	**-0.04 [-0.66, 0.59]**
Heterogeneity: Tau² = 0.14; Chi² = 3.12, df = 1 (P = 0.08); I² =68%							
Test for overall effect: Z = 0.12 (P = 0.90)							
Total (95% CI)	**146**		**140**			**100.0 %**	**0.02 [-0.21, 0.26]**
Heterogeneity: Tau² = 0.0; Chi² = 3.94, df = 4 (P = 0.41); I² =0.0%							
Test for overall effect: Z = 0.19 (P = 0.85)							

```
            -10    -5     0     5    10

          Favours treatment    Favours control
```

Analysis 3.3.   Comparison 3 Any multivitamin or single component antioxidant supplement versus placebo, Outcome 3 Progression AMD: dichotomous.
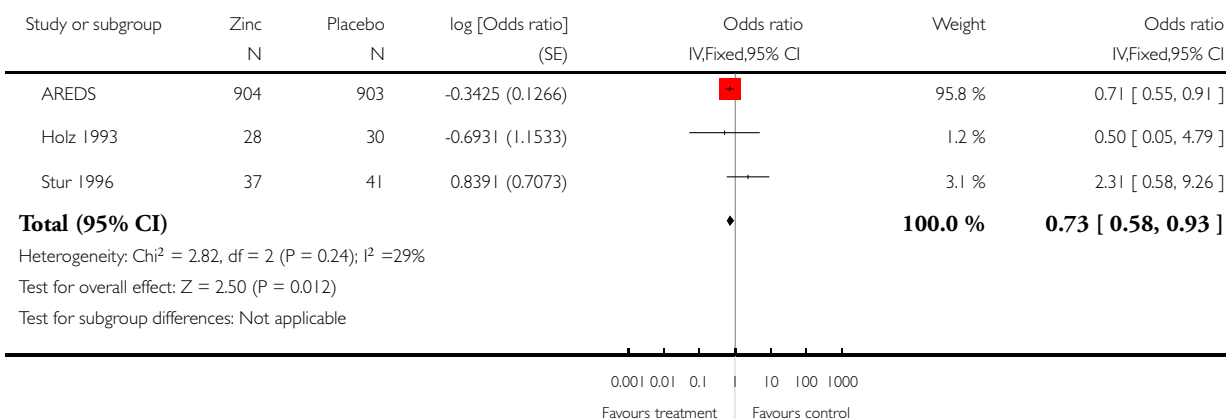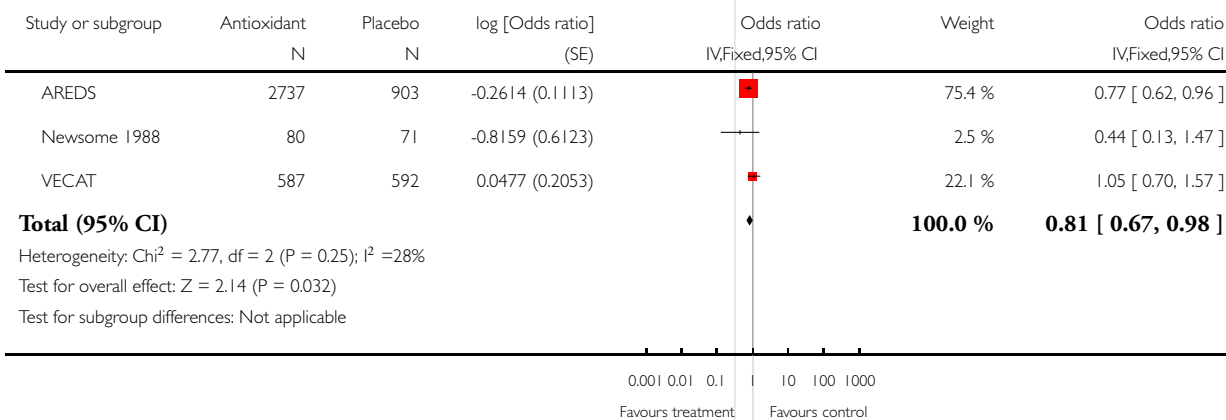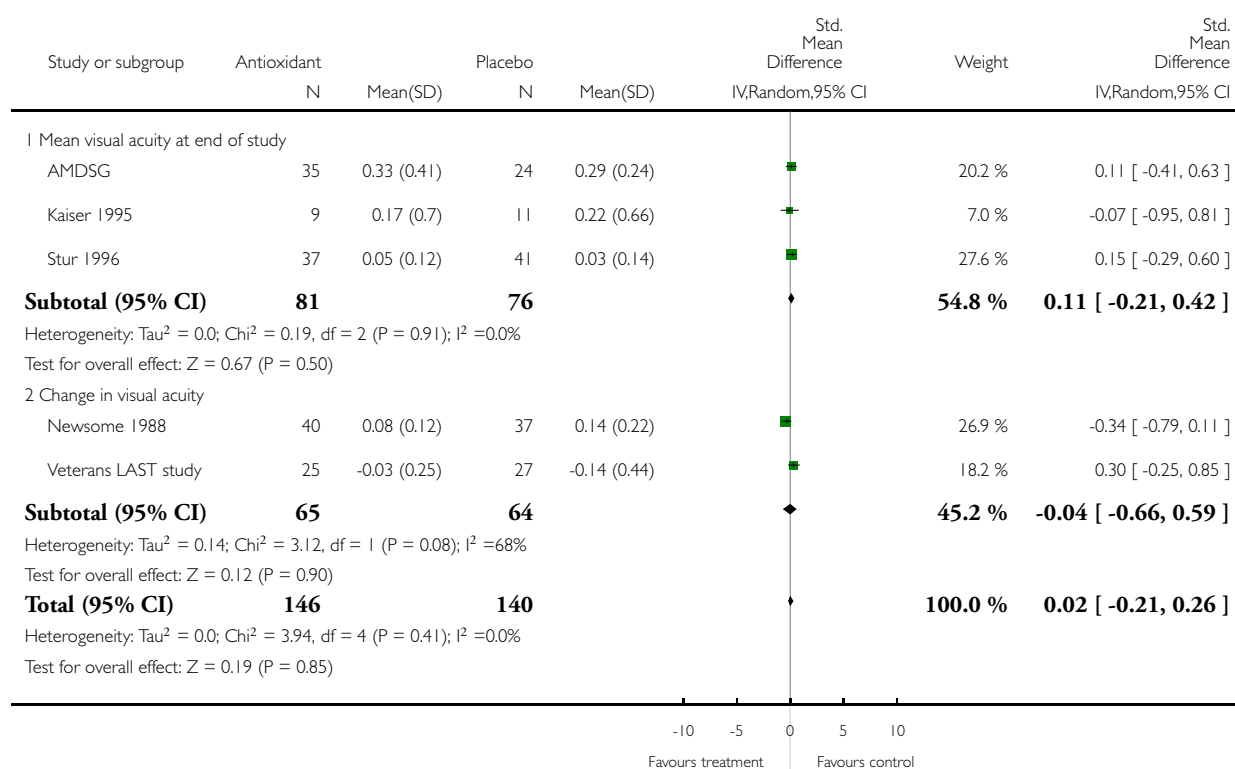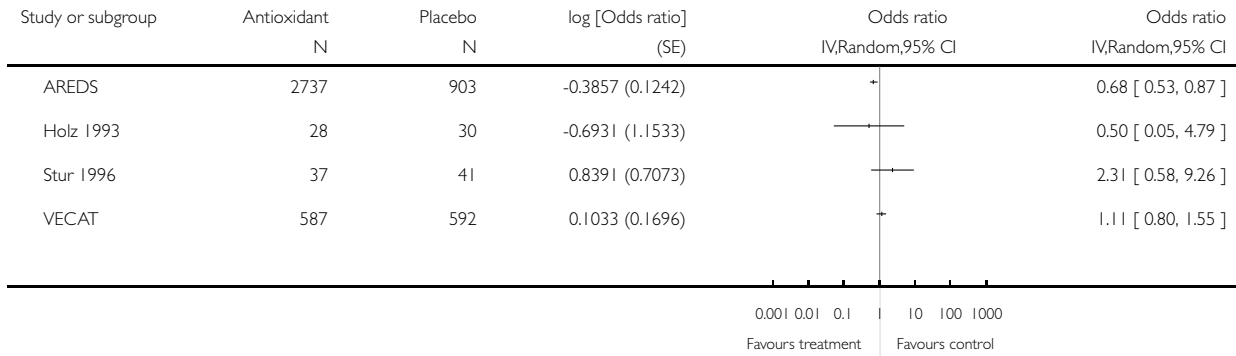
Review: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Comparison: 3 Any multivitamin or single component antioxidant supplement versus placebo

Outcome: 3 Progression AMD: dichotomous

Study or subgroup	Antioxidant N	Placebo N	log [Odds ratio] (SE)	Odds ratio IV,Random,95% CI	Odds ratio IV,Random,95% CI
AREDS	2737	903	-0.3857 (0.1242)		0.68 [0.53, 0.87]
Holz 1993	28	30	-0.6931 (1.1533)		0.50 [0.05, 4.79]
Stur 1996	37	41	0.8391 (0.7073)		2.31 [0.58, 9.26]
VECAT	587	592	0.1033 (0.1696)		1.11 [0.80, 1.55]

0.001 0.01 0.1 1 10 100 1000

Favours treatment   Favours control

ADDITIONAL TABLES

Table 1.   Supplementary information on trials

Study	Type of AMD	Treatment	Treatment duration	Follow up	Visual acuity	Progression AMD	Notes
AMDSG	Early ARM	Ocuguard	18 months	18 months	Snellen converted to log-MAR: continuous score	Based on Chesapeake Bay grading but using indirect ophthalmoscopy: expressed as an average grade	
AREDS	ARM & VA 20/32 or better in one eye. 956/3640 had AMD.	Vitamin C, E, beta-carotene, zinc. Factorial design	Average duration 6.3 years	Average follow-up 6.3 years, 2.4% lost to follow up	Loss of 3 or more lines VA (equivalent to doubling visual angle)	Progression to advanced AMD: photocoagulation or other treatment for CNV; GA involving center of the macula,	

Table 1. Supplementary information on trials (*Continued*)

						RPE detachment, hemorrhage under the retina, subretinal fibrosis. Color fundus photography	
Holz 1993	People with drusen	Zinc	Not stated but assume same as follow-up duration	12-24	Not reported	"Incidence of new exudative or dry macula lesions"	
Kaiser 1995	"Nonserous AMD"	Visaline	6	6	Average Snellen score reported, converted to logMAR for this review	Not reported	
Newsome 1988	Drusen and/or pigmentary change, VA 20/80 or better	Zinc	12-24	12-24	Number of letters lost on logMAR chart, converted to logMAR score for this review	Difficult to extract data on this. Reported number with increased pigment, drusen and atrophy for two observers. In general found results favouring the zinc treated group	
Stur 1996	Neovascular AMD in one eye, VA better than 20/40 in other eye	Zinc	24	24	Mean logMAR score NOTE: patients with neovascular event excluded from this outcome	Incidence of neovascular lesion in study eye	Original trial of n = 500 terminated ?by sponsor (Astra) because statistical evaluation of first 40 patients at 24 months follow up

Table 1. **Supplementary information on trials** *(Continued)*

							"did not show any treatment benefit"
VECAT	Early AMD (18%) Late AMD (0. 5%). Rest presumably had no signs of ARM	Vitamin E	48	48	Loss of more than 9 letters on logMAR chart (two lines)	Investigators defined six stages of AMD progression and defined progression as movement from a lower stage to a higher stage in their worst eye	
Veterans Last study	Atrophic AMD and reduced vision	Lutein and/or Ocupower	12	12	Change in logMAR score	Data not reported	

A P P E N D I C E S

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

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

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

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

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

27. exp beta carotene/
28. caroten$.tw.
29. exp ascorbic acid/
30. ascorbic acid$.tw.
31. vitamin C.tw.
32. exp Vitamin E/
33. exp alpha tocopherol/
34. alpha?tocopherol$.tw.
35. alpha tocopherol$.tw.
36. vitamin E.tw.
37. exp Vitamin B12/
38. vitamin B12.tw.
39. cobalamin$.tw.
40. exp antioxidants/
41. ((antioxidant$ or anti) adj1 oxidant$).tw.
42. exp carotenoids/
43. carotenoid$.tw.
44. exp zinc/
45. zinc$.tw.
46. exp riboflavin/
47. riboflavin$.tw.
48. exp selenium/
49. selenium$.tw.
50. exp lutein/
51. lutein$.tw.
52. exp xanthophylls/
53. xanthophyll.tw.
54. zeaxanthin$.tw.
55. or/23-54
56. 22 and 55
57. 12 and 56
The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

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

We used the following strategy to search EMBASE on OVID to August 2007.
1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.

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

70. lutein$.tw.
71. xanthophyll.tw.
72. or/43-71
73. 42 and 72

Appendix 4. PubMed search strategy used on 24 January 2006 (last 60 days)

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

Appendix 5. AMED search strategy used up to January 2006

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

Appendix 6. SIGLE search strategy used up to March 2005

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

WHAT'S NEW

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

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

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 1, 1998

Date	Event	Description
12 August 2007	New search has been performed	Issue 1 2008: Results of trial from China (Wang et al) added. Report from AREDS study on risk of hospital admission due to genitourinary complications in people taking high dose zinc. Graphs with only one trial have been deleted and results have been reported in the text
19 January 2006	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Moorfields Eye Hospital NHS Trust, UK.

External sources

- Guide Dogs for the Blind Association, UK.

N O T E S

The Cochrane Eyes and Vision Group editorial team is aware that there has been some criticism of one trial included in this review (AREDS). We welcome comments and criticisms on the review through the feedback system of The Cochrane Library.

I N D E X   T E R M S

Medical Subject Headings (MeSH)

*Dietary Supplements; Antioxidants [*therapeutic use]; Macular Degeneration [*prevention & control]; Minerals [*therapeutic use]; Randomized Controlled Trials as Topic; Vitamins [*therapeutic use]

MeSH check words

Aged; Humans