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

Evans JR

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ABSTRACT

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

Objectives
The objective of this review is to assess the effects of antioxidant vitamin and/or mineral supplementation on the progression of age-related macular degeneration.

Search strategy
The Cochrane Controlled Trials Register - CENTRAL/CCTR, which contains the Cochrane Eyes and Vision Group specialised register (Cochrane Library Issue 3 2001), MEDLINE (1966 to August 2001), EMBASE (1980 to September 2001), the Science Citation Index, and the reference lists of relevant articles were searched. Investigators of included studies were contacted for further information.

Selection criteria
Randomised trials comparing an antioxidant vitamin and/or mineral supplement (alone or in combination) to control in people with age-related macular degeneration are included in this review.

Data collection and analysis
The reviewer extracted data and assessed trial quality. Due to the variable methods of collecting and presenting outcome data, no statistical summary measure was calculated.

Main results
Seven trials, which randomised 4119 people with signs of age-related macular degeneration, are included in this review. One unpublished trial of zinc supplementation (170 participants) is awaiting assessment. The majority of people (88%) were randomised in one trial that found a modest beneficial effect of antioxidant and zinc supplementation on progression to advanced age-related macular degeneration (odds ratio 0.72, 99% confidence interval 0.52 to 0.98). People supplemented with antioxidants and zinc were less likely to lose 15 or more letters of visual acuity (equivalent to a doubling of the visual angle) (odds ratio 0.79, 99% confidence interval 0.60 to 1.04). This effect was seen more strongly in people with moderate to severe disease. There were few events in people with early signs of the disease. The trial evaluated many safety outcomes, of which hospitalisation for genitourinary problems was more common in people taking zinc and yellowing of skin was more common in people taking antioxidant micronutrients. The other six trials in this review were 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 age-related macular degeneration is dominated by one large trial that showed modest benefit in people with moderate to severe signs of the disease. There is no evidence at present that people with early signs of the disease should take supplementation, however, current studies are underpowered to answer that question. Long term harm from supplementation cannot be ruled out, particularly in smokers. The

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generalisability of these findings to other populations with different nutritional statuses is not known. Further large well-conducted randomised controlled trials in other populations are required.

PLAIN LANGUAGE SUMMARY

Antioxidant vitamin or mineral supplementation in people with moderate to severe age-related macular degeneration may have modest benefits in delaying the progression of the disease

The retina (the light sensitive layer at the back of the eye) can deteriorate with age. Some people get lesions called 'age-related macular degeneration' 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 review of trials found that supplementation with antioxidants and zinc may be of modest benefit in people with moderate to severe disease. Long term harm from these supplements cannot be ruled out. More trials in other populations are required.

BACKGROUND

Age-related macular degeneration 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 age-related macular degeneration). Haemorrhage can occur which often results in increased scarring of the retina.

The early stages of the disease are in general asymptomatic. In the later stages there may be considerable distortion 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 per cent have early signs of the disease and seven per cent have late stage disease (Klein 1992). It is the most common cause of blindness and visual impairment in industrialised countries. In the UK for example, over 30,000 people are registered as blind or partially sighted annually, half of whom have lost their vision due to macular degeneration (Evans 1996). Currently there is no treatment that can restore vision in age-related macular degeneration.

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 age-related macular degeneration.

OBJECTIVES

The objective of this review is to assess the effects of antioxidant vitamin and/or mineral supplementation on the progression of age-related macular degeneration.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

This review includes only randomised controlled trials.

Types of participants

Participants in the trials were people with age-related macular degeneration in one or both eyes.

Types of intervention

Trials in which antioxidant vitamin and/or mineral supplementation was compared to placebo or no intervention are included. 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

The following outcomes were used:

(1) number of participants with disease progression,
(2) number of participants with new visual loss due to age-related macular degeneration,
(3) quality of life measures,
(4) any adverse outcomes as reported in trials.

The following definitions were used:

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- Age-related macular degeneration: this was taken as defined by trial investigators. It is commonly defined as: in the macular area 3000 microns diameter from fovea: drusen with or without pigmentary abnormalities or geographic atrophy or characteristic choroidal neovascularisation with no other cause.
- Progression of disease: development of drusen, geographic atrophy or growth or progression of new vessels in the retina.
- Visual loss: any well-defined outcome based on visual acuity was used depending on the way in which authors presented trial data. Other validated measures of visual loss, such as contrast sensitivity, were used where available.
- Quality of life: any validated measurement scale.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Trials were identified from the Cochrane Controlled Trials Register - CENTRAL/CCTR (which contains the Cochrane Eyes and Vision Group specialised register) on the Cochrane Library, MEDLINE and EMBASE.

The following strategy was used to search CENTRAL Issue 3 2001:

#1 MACULAR-DEGENERATION:ME
#2 RETINAL-DEGENERATION:ME
#3 NEOVASCULARIZATION-PATHOLOGIC*:ME
#4 ((((((MACULA or MACULAR) or RETINA) or RETINAL) or CHOROID) or CHOROIDAL) near (DEGENERATION or NEOVASCULARIZATION) or NEOVASCULARISATION)
#5 MACULOPATHY
#6 ((((#1 or #2) or #3) or #4) or #5)
#7 ((((AGE next RELATED) or AGE-RELATED) or AGEING) or AGING)
#8 (#6 AND #7)

The following strategy was used to search MEDLINE on SilverPlatter to August 2001:

#1 "MACULAR-DEGENERATION"/ all subheadings
#2 "RETINAL-DEGENERATION"/ all subheadings
#3 "NEOVASCULARIZATION,-PATHOLOGIC"/ all subheadings
#4 "RETINAL-NEOVASCULARIZATION"/ all subheadings
#5 "CHOROIDAL-NEOVASCULARIZATION"/ all subheadings
#6 #1 or #2 or #3 or #4 or #5
#7 (MACUL* or RETINA* or CHOROID*) near (DEGENER* or NEOVASC*) in TI,AB
#8 MACULOPATHY in TI,AB
#9 (AGE or AG?ING or AGE?RELATED or SENIL*) in TI,AB
#10 (#6 or #7 or #8) and #9

To identify randomised controlled trials, this search was combined with the Cochrane Highly Sensitive Search Strategy phases one and two as contained in the Cochrane Reviewers' Handbook (Clarke 2000).

The following strategy was used to search EMBASE on SilverPlatter to September 2001:

#1 explode "RETINA-MACULA-DEGENERATION"/ all subheadings
#2 "RETINA-DEGENERATION"/ all subheadings
#3 "NEOVASCULARIZATION-(PATHOLOGY)"/ all subheadings
#4 "SUBRETINAL-NEOVASCULARIZATION"/ all subheadings
#5 ((MACUL* or RETINA* or CHOROID*) near (DEGENER* or NEOVASC*)) in TI,AB
#6 MACULOPATHY in TI,AB
#7 (AGE?RELATED or AGE RELATED OR AG?ING OR SENIL*) IN TI,AB
#8 (#1 or #2 or #3 or #4 or #5 or #6) and #7

To identify randomised controlled trials, this search was combined with the following search:

#1 "RANDOMIZED-CONTROLLED-TRIAL"/ all subheadings
#2 "RANDOMIZATION"/ all subheadings
#3 "CONTROLLED-STUDY"/ all subheadings
#4 "MULTICENTER-STUDY"/ all subheadings
#5 "PHASE-3-CLINICAL-TRIAL"/ all subheadings
#6 "PHASE-4-CLINICAL-TRIAL"/ all subheadings
#7 "DOUBLE-BLIND-PROCEDURE"/ all subheadings
#8 "SINGLE-BLIND-PROCEDURE"/ all subheadings
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* in TI,AB
#11 (SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*) in TI,AB
#12 #9 or #10 or #11
#13 HUMAN in DER
#14 (ANIMAL or NONHUMAN) in DER
#15 #13 and #14
#16 #14 not #15
#17 #12 not #16

No additional search terms for antioxidant vitamin and mineral supplements were used. All possible age-related macular degeneration trials were examined for trials of vitamin and mineral supplements.

The reference lists of identified trial reports were searched to find additional trials. The Science Citation Index was used to find studies that cite the identified trials. Investigators of included

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studies were contacted to identify additional published and unpublished studies.

Searches were first performed in August 1997 and repeated in October 1998, December 1999, September 2000 and November 2001.

METHODS OF THE REVIEW

Selection of trials
The reviewer assessed the titles and abstracts of all reports of trials identified by the electronic searching. The full text hard copies of possible trials of antioxidant vitamin and/or mineral supplements were obtained. Relevant studies were selected according to the definitions in the 'Criteria for considering studies for this review'.

Assessment of methodological quality
Trial quality was assessed according to methods set out in section 6 of the Cochrane Reviewer's Handbook. Five parameters were considered: allocation concealment, method of allocation to treatment, documentation of exclusions, masking of outcome assessment and completeness of follow-up.

Each parameter of trial quality was graded: A - low risk of bias; B - moderate risk of bias; and C - high risk of bias. The assessor was not masked to the report authors and 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 reviewer 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.

Data synthesis
Due to the small number of trials identified, and variable methods of collecting and presenting outcome data, no summary measure was calculated.

DESCRIPTION OF STUDIES

Finding the trials
The original electronic searches identified 577 reports of possible age-related macular degeneration (AMD) trials of which five reports (four trials) were of antioxidant interventions (Newsome 1988; Kaiser 1995; AMDSG; 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 & 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 milligrams (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.

See the Table of Included Studies for detailed information about the seven trials included in this review.

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 the AMDSG where predominantly men were enrolled. In the AREDS study it was noted that people taking part in the trial were relatively well-nourished compared to the general population. This is commonly found in clinical trials.

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

The trials enrolled groups of people with AMD at different stages of the disease: the AMDSG 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 the AREDS study 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 neovascularization. The majority of the participants in the VECAT study had no or mild age-related maculopathy.

Types of intervention
Three trials compared zinc sulfate 200 milligrams daily versus placebo (Newsome 1988; Holz 1993; Stur 1996). Two trials compared a broad-spectrum antioxidant complex versus placebo (AMDSG - Ocuguard; Kaiser 1995 - Visaline). The VECAT study 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. 67% of

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participants in AREDS took additional multivitamin supplements to recommended daily allowance levels (Centrum).

The duration of supplementation in these trials ranged from six months to seven years.

Types of outcome measures

All the trials used different outcome measures for visual function and progression of disease. The AMDSG 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 (ARM Study Group 1995); AREDS adapted the Wisonsin system. The Wisconsin, AREDS and International Systems are closely related; the latter was published after the two former 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 and atrophy. Kaiser 1995 did not include any measures of progression of AMD.

METHODOLOGICAL QUALITY

All of the five trials that were published before 2001 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 age-related macular degeneration at the beginning of the study and are therefore included in the related Cochrane review on prevention of AMD (Evans 2001).

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 one trial (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 arms reported difficulty swallowing the study tablets (17.8% versus 15.3%, $P = 0.04$). However, there was little evidence of unmasking - 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 one trial (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 age-related macular degeneration (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.

RESULTS

The results of the studies could not be summarised meaningfully because measures of vision and disease progression were presented in different ways. The largest trial (AREDS) only presented odds ratios derived from repeated measures logistic regression so these could not be included in the graphical displays. The following description highlights the main results from each study.

The AMDSG found an effect on visual acuity in the left eye only ($P = 0.03$). The average visual acuity (logMAR score) of the left eye of people in the placebo group was 0.24 (standard error 0.03) at baseline and 0.40 (standard error 0.10) 18 months later; in the antioxidant treatment group vision in the left eye remained stable at 0.19 (standard error 0.03). There was no evidence of any beneficial effect of antioxidant supplementation on progression of the disease. However, more people in the control group (9/24) than the intervention group (5/35) reported their vision had declined at 18 months.

Kaiser 1995 found no difference between treatment and control in objective measures of visual functioning although more people in

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the control group (3/10) than the treatment group (0/8) reported deterioration in visual function.

Newsome 1988 found a clear effect on both vision and progression of disease. People in the zinc treated group were less likely to lose 10 or more letters on the ETDRS chart than controls (odds ratio 0.33, 95% confidence interval 0.15 to 0.69) (equivalent to a loss of two lines on the chart); there was evidence of slower progression of disease in the treatment group. Stur 1996 showed no evidence of any beneficial effect of zinc supplementation on visual function or progression of age-related macular degeneration, similarly, Holz 1993 showed no difference in the incidence of new exudative or dry lesions (four versus two per group).

None of these trials contained information on quality of life and they were too small to look for serious 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 the AMDSG trial, one person developed an 'allergic reaction' although it was not clear whether or not this was related to the treatment.

The results of VECAT have only been published in abstract form at present. Although 1204 people were randomised initially, only 102 of those followed up to four years had early age-related maculopathy (ARM) at baseline. Of these 44 experienced worsening of ARM over the study period but there was no evidence of any benefit from vitamin E supplementation. There was also little evidence of a reduction in the incidence of ARM in people previously without the disease but these data are considered in the Cochrane review on prevention of age-related macular degeneration (Evans 2001).

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 beneath the retinal pigment epithelium of sensory retina of fluid, blood or fibrovascular or fibrous tissue).

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 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'. A summary of their results is shown in Table 02 and Table 03.

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 none of the individual treatments, when compared with placebo, statistically significantly reduced or increased the risk of mortality although the estimate is in the direction of harm for participants who had never smoked. The trial was not designed or powered to investigate effects on mortality and therefore interpretation of this sub-group analysis should be measured.

DISCUSSION

Prior to 2001 there was little evidence as to the benefits and harms of antioxidant supplementation in age-related macular degeneration. Previous versions of this review concluded that 'currently available trials do not answer the question as to whether people with age-related macular degeneration should take antioxidant vitamin and mineral supplements in order to halt the progression of the disease' and that two large trials were ongoing in USA and Australia. These trials have now been published (one in abstract form) and are included in this review.

Table 01 shows the sample size and number of events in the trials included in this review. There have been 4119 people with signs of age-related macular degeneration randomised into trials of antioxidant vitamin and mineral supplementation producing in the region of 814 events. The majority of people (88%) have been randomised in the AREDS trial which has produced the majority of the events (88%). There is one additional trial of zinc supplementation (30 milligrams) in 170 participants that has not yet been published and is awaiting assessment in this review.

AREDS found a modest beneficial effect of antioxidant and zinc supplementation on progression to advanced AMD. This effect was seen most strongly in people with moderate or advanced signs of the disease. They also found that people with moderate or advanced signs of the disease supplemented with antioxidants and zinc were less likely to develop reduced vision. There were only 15

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'events' in people with mild or borderline signs of the disease at five years follow-up and this study was underpowered to answer the question as to whether people with early stages of the disease might experience modest benefit from vitamin and/or mineral supplementation.

Visual acuity fluctuates over time and clinical signs of AMD change, sometimes for the better. The analysis of AREDS took this variability into account using repeated measures logistic regression. The advantage of this technique is that it takes into account all the experiences of the participants over time. The disadvantage is that some of the transient events counted may be due to errors in grading retinal photographs which may not be the most relevant outcome for the patient. From the patients' point of view, the most relevant outcome is the risk of developing permanent visual loss and established advanced AMD. However, defining 'permanent' can be problematic. On request, AREDS supplied unpublished data on AMD and visual acuity outcomes for the five year follow-up in a format more suitable for incorporation into this review. However, this did not include information on confirmed cases prior to the five year follow-up. As this provides less information than the measures presented in the published report of the study, I decided not to include these data in the review.

Another difficulty with logistic regression is that the effect measures are all presented as odds ratios. These have convenient mathematical properties but are not always easily interpreted. Most people tend to think in terms of the relative risk or risk ratio. The odds ratio approximates the risk ratio when the event rate is low (less than 10 per cent), but at higher event rates such as seen in this study the odds ratio exaggerates the benefits (or harms) of treatment. It is possible to calculate risk ratios directly from the report and the authors report that the risk reduction in progression to AMD for people with moderate or severe disease is 25% (compare with odds ratio of 0.66 and therefore odds reduction of 34%).

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 (e.g., yellowing of skin or difficulty swallowing tablets) which lead 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.

The other trials included in this review add little to the discussion of this topic. They were too small on their own to provide definitive answers and the variety of ways in which outcomes were measured and reported means that meta-analysis, or pooling of their results, is impossible.

The three trials of daily supplementation with 200 mg zinc sulfate were small (less than 200 participants). The results of these trials were inconsistent - one found a beneficial effect whilst the others did not. This may reflect differences in the populations studied: the positive result was looking at progression from early stages of the disease, whilst the other took people with established neovascular disease and followed-up the second eye. It is difficult to rule out competing explanations for the effects observed. The study with negative findings may not have had enough power to detect a difference; the study with positive findings may have had imbalances in the two groups studied. There is one unpublished trial on zinc supplementation that is not yet included in this review (170 participants).

The AMDSG trial of broad-spectrum antioxidant supplementation was too small (59 participants) to detect important effects and its results must be described as equivocal. The authors reported a positive finding but the size of the effect was small and was limited to distance visual acuity in the left eye only. As many parameters were analysed for right and left eyes, this may be a chance finding. No effect was seen on other measures of visual function or progression of the disease, with the exception of subjective perception of vision. Similarly the Kaiser 1995 trial of Visaline was too small to detect differences in visual function (20 participants) but participants in the control group were more likely to report worsening of visual function.

None of the trials identified have published data on quality of life as yet. These data were collected in AREDS and will be published shortly.

AREDS was the only study to examine effectively the question of safety. They found little evidence of harm, although in a post-hoc analysis non-smokers taking antioxidants had a non-significant increased risk of death. Smokers are at increased risk of developing advanced AMD, however, the current consensus is that smokers who take beta-carotene may be at increased risk of developing lung cancer (ATBC; Omenn 1996).

AUTHORS' CONCLUSIONS

Implications for practice

People with moderate to severe age-related macular degeneration 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. There is no evidence that people with early signs of the disease would benefit from antioxidant supplementation. Current studies have been underpowered to address that question.

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

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the person with age-related macular degeneration. The following benefits and harms need to be considered. People with moderate or severe disease 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, 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. However, it may be difficult to consume safely 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.

Implications for research

Trials in other populations, preferably with a variety of nutritional statuses, are required. These trials should have a large enough sample size to demonstrate effects that are meaningful for patients and should also include a component on quality of life.

It is likely that age-related macular degeneration 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.

NOTES

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.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	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.

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	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.
Allocation concealment	A

Study	**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 55-80). 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.

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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.
Allocation concealment	A

Study	**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.
Outcomes	Visual acuity. Contrast sensitivity. Dark adaptation. Stereo fundus photographs and fluorescein angiograms.
Notes	Data available from abstract only.
Allocation concealment	B

Study	**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.

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	Intraocular pressure. Visual fields. Lens opacity. Retinal visual acuity. Colour vision. Contrast sensitivity.
Notes	
Allocation concealment	A

Study	**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: 1-2 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.
Allocation concealment	A

Study	**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).

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	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.
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.
Allocation concealment	A

Study	**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.
Allocation concealment	A

AMD - Age-related macular degeneration
RPE - Retinal pigment epithelium

Characteristics of excluded studies

Study	**Reason for exclusion**
Vannas 1958	Allocation concealment inadequate.

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Characteristics of excluded studies (*Continued*)

ADDITIONAL TABLES

Table 01. Trials

Trial	Intervention	Number randomised	Outcome	Duration	Number with outcome
Newsome 1988	Zinc	174	Loss of acuity 10 letters or more	24	35
Kaiser 1995	Antioxidants	20	Subjective assessment	6	3
AMDSG	Antioxidants plus zinc	71	Acuity and retinal grading score	18	?
Stur 1996	Zinc	112	Development of new vessels	24	?
AREDS	Antioxidants plus zinc	3640	Progression to advanced AMD	60*	718
VECAT	Vitamin E	102**	Worsening of age-related maculopathy	48	44

*study follow up was to 7 years but data on number of events only reported for five years.

**1204 randomised but only 102 people followed up had age-related maculopathy at baseline

Table 02. AREDS: Effect of treatment on risk of progression to advanced AMD

Comparison	OR (All groups)	99% CI	OR (mod & severe)	99% CI
Antioxidant versus no antioxidant	0.87	0.70 to 1.09	0.83	0.66 to 1.06
Zinc versus no zinc	0.82	0.66 to 1.03	0.79	0.62 to 0.99
Antioxidant versus placebo	0.80	0.59 to 1.09	0.76	0.55 to 1.05
Zinc versus placebo	0.75	0.55 to 1.03	0.71	0.52 to 0.99
Antioxidant plus zinc versus placebo	0.72	0.52 to 0.98	0.66	0.47 to 0.91

Table 03. AREDS: Effect of treatment on risk of loss of visual acuity score of 15 letters

Comparison	OR (all groups)	99% CI	OR (mod & severe)	99% CI
Antioxidant versus no antioxidant	0.90	0.74 to 1.09	0.86	0.70 to 1.07
Zinc versus no zinc	0.88	0.73 to 1.07	0.84	0.68 to 1.04
Antioxidant versus placebo	0.88	0.67 to 1.15	0.85	0.63 to 1.14

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Table 03. AREDS: Effect of treatment on risk of loss of visual acuity score of 15 letters (*Continued*)

Comparison	OR (all groups)	99% CI	OR (mod & severe)	99% CI
Zinc versus placebo	0.87	0.66 to 1.13	0.83	0.62 to 1.11
Antioxidant plus zinc versus placebo	0.79	0.60 to 1.04	0.73	0.54 to 0.99

ANALYSES

Comparison 01. ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Increased pigment			Odds Ratio (Fixed) 95% CI	Totals not selected
02 Increased drusen			Odds Ratio (Fixed) 95% CI	Totals not selected
03 Increased atrophy			Odds Ratio (Fixed) 95% CI	Totals not selected
04 Development of new CNV			Odds Ratio (Fixed) 95% CI	Totals not selected
05 Loss of 10 or more letters (ETDRS chart)			Odds Ratio (Fixed) 95% CI	Totals not selected
06 Visual acuity (logMAR)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
07 Contrast sensitivity 3 cycles/degree			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
08 Contrast sensitivity 18 cycles/degree			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 02. OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Visual acuity (logMAR) right eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Visual acuity (logMAR) left eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Near vision (m print) right eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Near vision (m print) left eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
05 Contrast sensitivity 6 cc/degree right eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
06 Contrast sensitivity 6 cc/degree left eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
07 Subjective perception that vision declined			Odds Ratio (Fixed) 95% CI	Totals not selected
08 Retinal photography grading results right eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
09 Retinal photography grading results left eyes			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

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Comparison 03. VISALINE (TM) VERSUS PLACEBO

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Visual acuity			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Near vision			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Subjective assessment vision declined			Odds Ratio (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

COVER SHEET

Title	Antioxidant vitamin and mineral supplements for age-related macular degeneration
Authors	Evans JR
Contribution of author(s)	Information not supplied by author
Issue protocol first published	1997/3
Review first published	1998/1
Date of most recent amendment	28 May 2003
Date of most recent SUBSTANTIVE amendment	26 February 2002
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	29 October 2001
Date authors' conclusions section amended	29 October 2001
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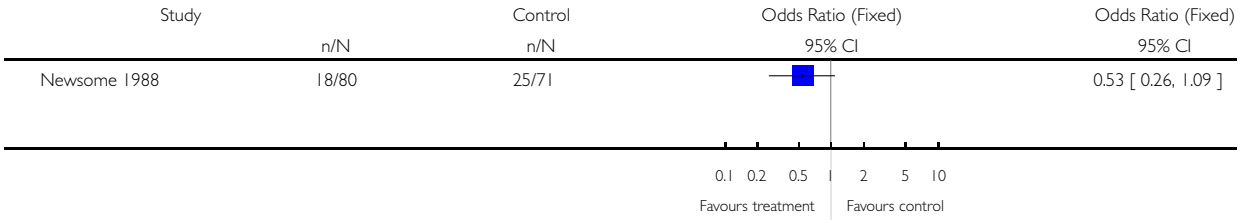
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 01 Increased pigment

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 01 Increased pigment

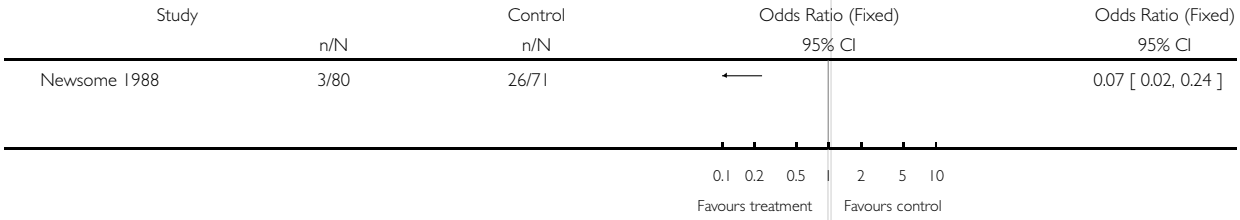


Analysis 01.02. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 02 Increased drusen

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 02 Increased drusen



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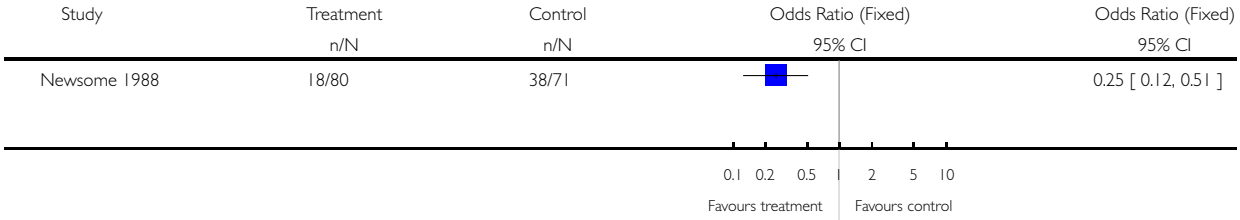
Analysis 01.03. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 03 Increased atrophy

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 03 Increased atrophy

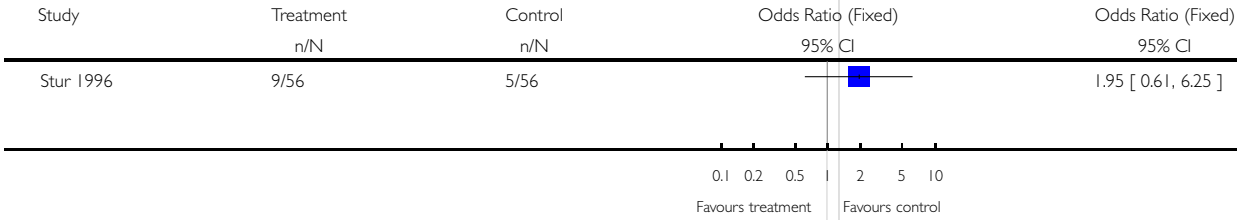


Analysis 01.04. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 04 Development of new CNV

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 04 Development of new CNV

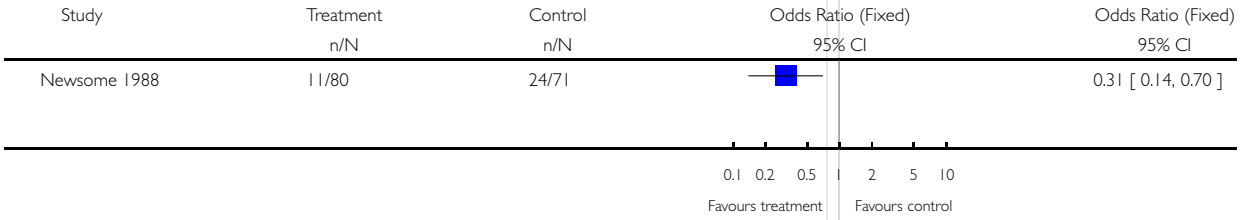


Analysis 01.05. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 05 Loss of 10 or more letters (ETDRS chart)

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 05 Loss of 10 or more letters (ETDRS chart)



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Analysis 01.06. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 06 Visual acuity (logMAR)

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 06 Visual acuity (logMAR)

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Stur 1996	37	0.05 (0.12)	41	0.03 (0.14)		0.02 [-0.04, 0.08]

Analysis 01.07. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 07 Contrast sensitivity 3 cycles/degree

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 07 Contrast sensitivity 3 cycles/degree

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Stur 1996	37	71.90 (32.20)	41	70.70 (31.90)		1.20 [-13.05, 15.45]

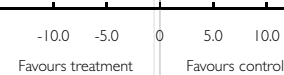
Analysis 01.08. Comparison 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO, Outcome 08 Contrast sensitivity 18 cycles/degree

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

Comparison: 01 ZINC SULFATE 200mg DAILY VERSUS PLACEBO

Outcome: 08 Contrast sensitivity 18 cycles/degree

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Stur 1996	37	12.80 (11.00)	41	14.60 (14.70)		-1.80 [-7.53, 3.93]



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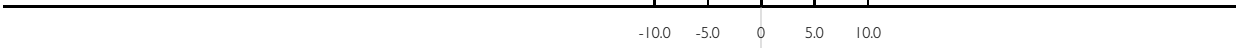
Analysis 02.01. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 01 Visual acuity (logMAR) right eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 01 Visual acuity (logMAR) right eyes

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
AMDSG	35	0.33 (0.41)	24	0.29 (0.24)		0.04 [-0.13, 0.21]



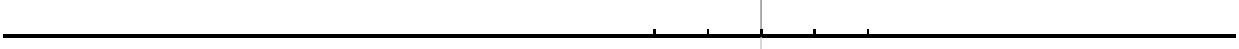
Analysis 02.02. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 02 Visual acuity (logMAR) left eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 02 Visual acuity (logMAR) left eyes

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
AMDSG	35	0.19 (0.24)	24	0.40 (0.49)		-0.21 [-0.42, 0.00]



Analysis 02.03. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 03 Near vision (m print) right eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 03 Near vision (m print) right eyes

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
AMDSG	35	1.13 (1.36)	24	1.04 (0.69)		0.09 [-0.44, 0.62]

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Analysis 02.04. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 04 Near vision (m print) left eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 04 Near vision (m print) left eyes

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
AMDSG	35	0.86 (0.59)	24	1.90 (3.87)		-1.04 [-2.60, 0.52]

Analysis 02.05. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 05 Contrast sensitivity 6 cc/degree right eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 05 Contrast sensitivity 6 cc/degree right eyes

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
AMDSG	35	5.50 (2.37)	24	5.70 (1.96)		-0.20 [-1.31, 0.91]

Analysis 02.06. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 06 Contrast sensitivity 6 cc/degree left eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 06 Contrast sensitivity 6 cc/degree left eyes

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
AMDSG	35	6.20 (1.77)	24	5.63 (2.84)		0.57 [-0.71, 1.85]

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Analysis 02.07. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 07 Subjective perception that vision declined

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 07 Subjective perception that vision declined

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Odds Ratio (Fixed) 95% CI
AMDSG	5/35	9/24		0.28 [0.08, 0.98]

Analysis 02.08. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 08 Retinal photography grading results right eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 08 Retinal photography grading results right eyes

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
AMDSG	35	3.08 (1.22)	24	3.31 (1.08)		-0.23 [-0.82, 0.36]

Analysis 02.09. Comparison 02 OCUGUARD (TM) DAILY VERSUS PLACEBO, Outcome 09 Retinal photography grading results left eyes

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

Comparison: 02 OCUGUARD (TM) DAILY VERSUS PLACEBO

Outcome: 09 Retinal photography grading results left eyes

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
AMDSG	35	3.08 (1.22)	24	3.53 (0.87)		-0.45 [-0.98, 0.08]

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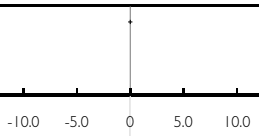
Analysis 03.01. Comparison 03 VISALINE (TM) VERSUS PLACEBO, Outcome 01 Visual acuity

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

Comparison: 03 VISALINE (TM) VERSUS PLACEBO

Outcome: 01 Visual acuity

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Kaiser 1995	9	0.67 (0.20)	11	0.60 (0.22)		0.07 [-0.11, 0.25]



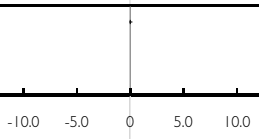
Analysis 03.02. Comparison 03 VISALINE (TM) VERSUS PLACEBO, Outcome 02 Near vision

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

Comparison: 03 VISALINE (TM) VERSUS PLACEBO

Outcome: 02 Near vision

Study	Treatment		Control		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Kaiser 1995	9	0.62 (0.14)	11	0.55 (0.23)		0.07 [-0.09, 0.23]



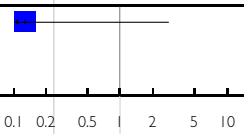
Analysis 03.03. Comparison 03 VISALINE (TM) VERSUS PLACEBO, Outcome 03 Subjective assessment vision declined

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

Comparison: 03 VISALINE (TM) VERSUS PLACEBO

Outcome: 03 Subjective assessment vision declined

Study	Treatment	Control	Odds Ratio (Fixed)	Odds Ratio (Fixed)
	n/N	n/N	95% CI	95% CI
Kaiser 1995	0/8	3/10		0.13 [0.01, 2.86]



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