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

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TABLE OF CONTENTS

[Intervention Review]

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

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ABSTRACT

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. Higher dietary levels of antioxidant vitamins and minerals may reduce the risk of progression of age-related macular degeneration (AMD).

Objectives

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

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 8), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2012), EMBASE (January 1980 to August 2012), Allied and Complementary Medicine Database (AMED) (January 1985 to August 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 20 August 2012. We searched the reference lists of identified reports and the Science Citation Index. We contacted investigators and experts in the field for details of unpublished studies. We also searched for systematic reviews of harms of vitamin supplements.

Selection criteria

We included randomised trials comparing antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention in people with AMD.

Data collection and analysis

Two authors assessed risk of bias and extracted data from the included trials. Where appropriate, we pooled data using a random-effects model unless three or fewer trials were available in which case we used a fixed-effect model.

Main results

Thirteen trials (6150 participants) were included in this review. Over half the participants (3640) were randomised in one trial (AREDS in the USA), which found a beneficial effect of antioxidant (beta-carotene, vitamin C and vitamin E) and zinc supplementation on progression to advanced AMD (adjusted odds ratio (OR) 0.68, 95% confidence interval (CI) 0.53 to 0.87) over an average of 6.3 years. People taking supplements were less likely to lose 15 or more letters of visual acuity (adjusted OR 0.77, 95% CI 0.62 to 0.96). The other trials, in general, had shorter follow-up (less than two years). No evidence for an effect of supplementation was seen in these smaller trials of shorter duration. Overall we considered the strength of the evidence to be moderate. We did not consider included trials, in general, to be at risk of bias, although we found it difficult to assess reporting biases. The main reason for downgrading the strength of the evidence was because, for several analyses, only one trial was included and therefore consistency of the findings could not be assessed. The included trials reported the following adverse effects: hospitalisation for genito-urinary problems was more common in people taking zinc and yellowing of skin was more common in people taking antioxidants. Systematic searching of the literature identified other potential harms of vitamin supplementation, in particular an increased risk of lung cancer in smokers associated with beta-carotene supplements, but we were unable to identify a good systematic review of the evidence for harms of nutritional supplementation.

Authors' conclusions

People with AMD may experience 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. The generalisability of these findings to other populations is not known. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed.

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). We identified 13 randomised controlled trials that included 6150 participants; five trials based in the USA, two in the UK, two trials in Austria, and one trial in each of a further four countries (Australia, China, Italy and Switzerland). The review of trials found that supplementation with antioxidants and zinc may be of modest benefit in people with AMD. This was mainly seen in one large trial that followed up participants for an average of six years. The other smaller trials with shorter follow-up do not provide evidence of any benefit. Large well-conducted trials in a range of populations and with different nutritional status are required. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Multivitamin antioxidant vitamin or mineral supplement for age-related macular degeneration

Patient or population: patients with age-related macular degeneration
Settings: community
Intervention: multivitamin antioxidant vitamin or mineral supplement
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Multivitamin antioxidant vitamin or mineral supplement				
Distance visual acuity (loss of 3 or more lines) LogMAR Follow-up: mean 6.3 years	**Moderate**		**OR 0.77** (0.62 to 0.96)	3640 (1 study)	⊕⊕⊕○ **moderate**[1]	
	300 per 1000	**248 per 1000** (210 to 291)				
Progression to advanced AMD Grading of fundus photographs Follow-up: mean 6.3 years	**Moderate**		**OR 0.68** (0.53 to 0.87)	3640 (1 study)	⊕⊕⊕○ **moderate**[1]	
	300 per 1000	**226 per 1000** (185 to 272)				

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

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

[1] Downgraded for inconsistency: only one study so not possible to assess consistency of findings.

BACKGROUND

Description of the condition

Age-related macular degeneration (AMD) is a disease affecting the central area of the retina (macula). In the early stages of the disease lipid material accumulates in deposits underneath the retinal pigment epithelium. These deposits are known as drusen and can be seen as pale yellow spots on the retina. The pigment of the retinal pigment epithelium may become disturbed with areas of hyperpigmentation and hypopigmentation. In the later stages of the disease the retinal pigment epithelium may atrophy completely. This loss can occur in small focal areas or can be widespread (geographic). In some cases new blood vessels grow under the retinal pigment epithelium and occasionally into the subretinal space (exudative or neovascular AMD). 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 older people (80 years and above) approximately one in three people have early signs of the disease (Klein 1992) and one in eight people have late-stage disease (Owen 2012)). It is the most common cause of blindness and visual impairment in industrialised countries (Bunce 2010).

Description of the intervention

Photoreceptors in the retina are subject to oxidative stress throughout life due to combined exposures to light and oxygen. It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals produced in the process of light absorption (Christen 1996). Antioxidants are any vitamin or mineral which is known to have antioxidant properties in vivo or which has been shown to be an important component of an antioxidant enzyme present in the retina. The following vitamins and minerals are usually considered to be 'antioxidant': vitamin C, vitamin E, carotenoids, selenium and zinc.

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

How the intervention might work

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.

Why it is important to do this review

People with AMD need to have reliable information in order to decide whether or not to take vitamin supplements.

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.

METHODS

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 (including the macular pigment carotenoids lutein and zeaxanthin), selenium and zinc.

Types of outcome measures

Primary outcomes

The primary outcome for this review was visual acuity.
As one of the consequences of AMD is a progressive loss of vision, our primary outcome was loss of 3 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. We also report visual acuity as a continuous measure as this was often reported by the included trials, however, this was not defined a priori.

Secondary outcomes

Secondary outcomes included progression of the disease as defined by study investigators. This was usually reported as a dichotomous outcome.
We also planned to assess quality of life and adverse effects, if data were available.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 8, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 20 August 2012), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2012), EMBASE (January 1980 to August 2012), Allied and Complementary Medicine Database (AMED) (January 1985 to August 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 20 August 2012.
See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), AMED (Appendix 4), OpenGrey (Appendix 5), *m*RCT (Appendix 6), ClinicalTrials.gov (Appendix 7) and the ICTRP (Appendix 8).
For the update in 2012 we specifically looked for adverse effects using a simple search aimed to identify systematic reviews of adverse effects of vitamin supplements, see Appendix (Appendix 9) for search strategy.

Searching other resources

We searched the reference lists of identified trial reports to find additional trials. We used the Science Citation Index 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 studies

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

Data extraction and management

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 two 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.

We extracted data using a standardised form developed by the Cochrane Eyes and Vision Group. For the initial review we sent these data for verification to the trial investigators of all studies included in the review. In the update (2012) data were extracted by both authors, compared, disagreements resolved by discussion, and data cut and pasted into Revman by one author and checked by the other.

Assessment of risk of bias in included studies

We assessed risk of bias using The Cochrane Collaboration's tool for assessing the risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment 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 most of the information on this topic is available) reported odds ratios (OR) and their confidence intervals only (derived from repeated measures logistic regression) and therefore we used the OR as the main measure of effect. We entered the data into Revman using the generic inverse variance method. We calculated the standard error from the confidence interval from each study. In discussion of the results of the review, where possible, we converted the pooled OR back to the risk ratio (RR) using the following formula: RR = OR/1-ACR*(1-OR) where ACR is the assumed risk in the control group as given in Chapter 12.5.4.4. of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

For continuous outcomes we used the standardised mean difference (SMD) as outcomes were measured on different scales. For visual acuity outcomes, we corrected for differences in direction between Snellen and logMAR scales by multiplying the Snellen decimal values by -1. Where possible, we checked for skewness using methods outlined in Chapter 9.4.5.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Unit of analysis issues

The main study design method in this area is the parallel-group randomised controlled trial. 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. Currently no such studies have been identified, but if they are in the future, we will only use data from the first phase.

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, we only included data for right eyes in the analyses.

Dealing with missing data

The data included in the review represent an 'available case analysis'. The majority of the data in the current review come from one large trial which had a follow-up of nearly 98%.

Currently 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.

Assessment of heterogeneity

We assessed heterogeneity by looking at the forest plots to see whether the effect measures for the different studies were in the same direction and of a similar order of effect. An I^2 statistic 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.

The main clinical heterogeneity is the type of supplement. This is incorporated into the analysis strategy by considering the formulations by type.

Assessment of reporting biases

In future versions of this review, when sufficient trials are included in the meta-analyses (10 or more), we plan to examine the funnel plot to assess whether there is any evidence that smaller studies are reporting larger effects, which may indicate publication bias.

We completed an outcome reporting matrix for the current review (following the methods of Kirkham 2010) to assess the potential for selective outcome reporting bias.

Data synthesis

We pooled data using a random-effects model because it is likely that the effects of antioxidant vitamin and mineral supplementation may vary in different population groups (for example, by age, sex, stage of disease, nutritional status etc). When there were three or fewer trials we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Currently there are not enough studies to perform useful subgroup 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.

Sensitivity analysis

A sensitivity analysis was not planned.

RESULTS

Description of studies

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

Results of the search

See Appendix 11 for details of searches run previously for this review.

An update search was done in August 2012 which yielded 640 records. The Trials Search Co-ordinator scanned the search results

and removed 335 references which were not relevant to the scope of the review. We screened the title and abstracts of the remaining 305 references. We rejected 277 references as not eligible for inclusion in the review. We assessed the hard copies of 28 reports of 27 studies and categorised them as follows:

- We included four new trials (Bartlett 2007; CARMIS; LISA; Newsome 2008: see 'Characteristics of included studies').
- We excluded 14 studies (Connolly 2011; ISRCTN35481392; ISRCTN57556290; ISRCTN81595685; Landrum 2012; NCT00121589; NCT00006202; NCT00718653; NCT00563979; NCT00564902; Nolan 2012; PHS II; Sasamoto 2011; Vidal 2011: see 'Characteristics of excluded studies').
- We identified three studies that have been completed but not yet published (CARMA; Falsini 2010; NCT00800995: see 'Characteristics of studies awaiting classification'). We will assess these studies when data become available.
- One study is awaiting assessment because it requires translating (Dawczynski 2012).
- We identified four ongoing studies (AREDS2; NCT00879671; NCT00893724; NCT01048476: see 'Characteristics of ongoing studies').
- One study was not eligible but described possible adverse effects (Eller 2012).

Included studies

Below is a summary of the 13 trials included in this review. See 'Characteristics of included studies' for detailed information on individual trials.

Types of participants

The average age of people participating in the trials was 72 years (median from included trials that reported age). On average, slightly more women than men were recruited (median percentage female 56%) 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). Bartlett 2007 recruited by sending letters to "*local optometrists, ophthalmologists and a specialist centre for rehabilitation of people with sight loss*" and then patients were seen at the University research centre. In CARMIS, Holz 1993, LISA and Newsome 2008 it was not clear how participants were identified.

The trials enrolled groups of people with AMD at different stages of the disease: AMDSG, CARMIS, Bartlett 2007, Holz 1993; Newsome 2008 and Veterans LAST study considered people with early macular degeneration only; Newsome 1988 and Wang 2004 examined people with both early and late-stage disease; Stur 1996 enrolled only people with late-stage disease in one eye; Kaiser 1995 recruited people with "non-serous" 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. LISA recruited individuals in categories 2, 3 and 4 according to AREDS criteria (similar to the participants in AREDS).

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 2 x 2 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). Bartlett 2007 compared an antioxidant formulation containing lutein 6 mg, retinol 750 μg, vitamin C 250 mg, vitamin E 34 mg, zinc 10 mg and copper 0.5 mg to placebo. CARMIS compared a similar formulation (vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg) and astaxanthin (4 mg)) to no intervention. Newsome 2008 investigated 25 mg of zinc-monocysteine supplement. The Chinese trial studied zinc oxide (80 mg daily), vitamin C (dose unknown) and vitamin E (dose unknown) (Wang 2004). LISA compared lutein (Lutamax, 20 mg once daily for three months followed by 10 mg once daily for three months) versus placebo, The duration of supplementation in these trials ranged from six months to seven years.

Types of outcome measures

The trials used a variety of different ways of measuring and reporting outcomes. AMDSG and Veterans LAST study measured visual acuity using a Snellen chart and converted the score into logMAR units. AREDS, CARMIS, Bartlett 2007, LISA, Newsome 1988 and Newsome 2008 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 reported visual acuity as a continuous outcome (AMDSG; CARMIS; Bartlett 2007; Kaiser 1995; Newsome 2008; Stur 1996), others used a cut-off of loss of 10 (Newsome 1988) or

15 letters of acuity (AREDS). A loss of 15 letters of acuity on the EDTRS chart is equivalent to a loss of 3 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 and this adapted system was also used by Bartlett 2007 and LISA. The Wisconsin, AREDS and International Systems are closely related, but the AREDS grading system is the most widely adopted at present. 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 Bartlett 2007 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 and Newsome 2008 did not include any measures of progression of AMD. CARMIS included a fundus examination at follow-up examinations but did not report 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 lesions. 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 trial (Wang 2004).

Excluded studies

Details of excluded studies are provided in 'Characteristics of excluded studies'.

Risk of bias in included studies

Figure 1 and Figure 2 summarise the 'Risk of bias' assessment. Overall we considered the trials to be generally at low risk of bias for the main types of bias, in particular selection bias (allocation sequence generation and concealment) and performance and detection bias. This is because all trials (with the exception of CARMIS) had a placebo control. Two trials were not well reported (Holz 1993; Wang 2004).

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

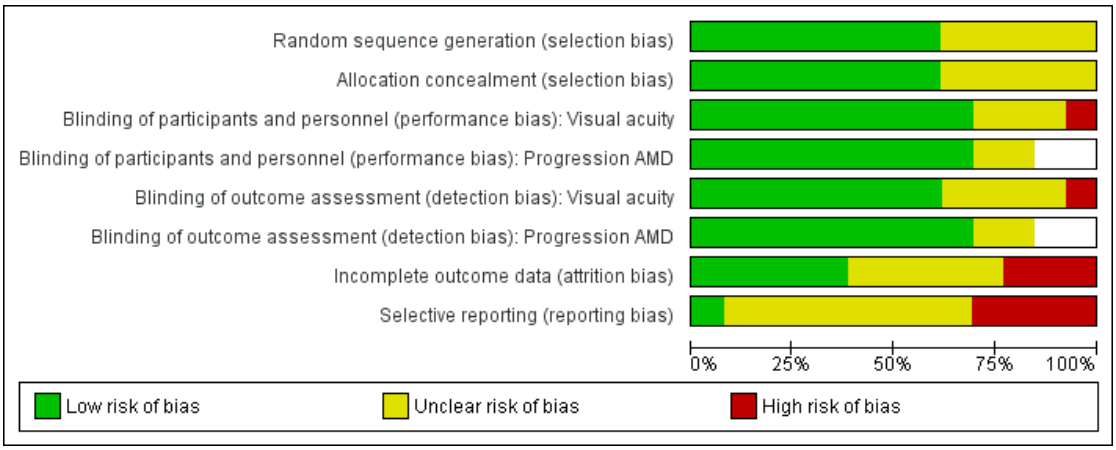
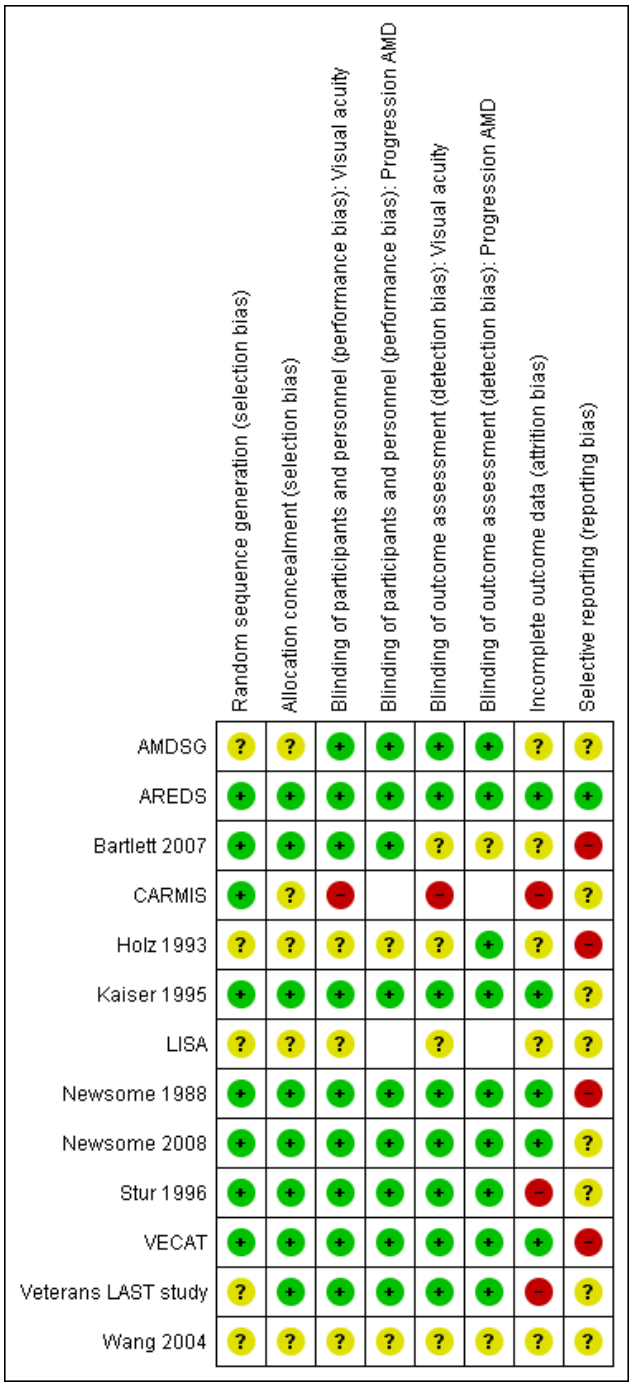


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

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).

Blinding

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 evidence 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.

Incomplete outcome data

Information on attrition bias was not so clearly reported and it was difficult to assess how likely this bias was.

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 study 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.

Selective reporting

See the outcome reporting matrix (Table 1). In general there was little evidence of selective outcome reporting. The exception was for visual acuity. In two studies, visual acuity data were not reported but it was stated that there were no significant differences between groups (Holz 1993; VECAT) and in one further study visual acuity was measured and not reported and we judged it likely that this was because no statistically significant differences were found (Wang 2004).

Effects of interventions

See: **Summary of findings for the main comparison** Multivitamin antioxidant vitamin or mineral supplement for age-related macular degeneration; **Summary of findings 2** Zinc for age-related macular degeneration; **Summary of findings 3** Vitamin E for age-related macular degeneration; **Summary of findings 4** Lutein for age-related macular degeneration

Table 2 provides more information on the outcomes and follow-up times relating to the data included in these analyses.

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), Bartlett 2007 (lutein, retinol, vitamin C, E, zinc), CARMIS (lutein, zeaxanthin, astaxanthin, vitamin C, E, zinc), 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. Currently data for CARMIS are not available in a form suitable for inclusion in the analyses in this review but have been requested from the study investigators; the trial publication reported stabilisation of visual acuity in the treated group compared to the non-treated group.

Distance visual acuity: loss of 3 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 for age, sex, race, AMD category and baseline smoking status was 0.77 (95% confidence interval (CI) 0.62 to 0.96).

Distance visual acuity: mean

Trials reporting visual acuity in continuous format were smaller and had shorter treatment and follow-up durations (six months to 18 months) (AMDSG; Bartlett 2007, Kaiser 1995; Veterans LAST study). A total of 89 people were randomised to treatment and 72 to placebo in pooled analyses of all four 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 (SMD) was 0.17 (95% CI -0.14 to 0.49) (Analysis 1.1).

Progression of 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).

Progression of AMD: continuous

Two trials reported the progression of AMD in a continuous format (AMDSG; Bartlett 2007), with 48 people randomised to treatment and 32 to control. There was little evidence of any effect of treatment (Analysis 1.2).

Zinc and zinc-monocysteine 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 we are aware of one unpublished study for which we have no data (France 1998). One trial has investigated zinc-monocysteine (Newsome 2008).

Distance visual acuity: loss of 3 or more lines

Two trials reported visual acuity data in this format (AREDS; Newsome 1988). The pooled analyses include a total of 977 people randomised to zinc supplementation and 965 to placebo. The trials were consistent I^2 = 0%. There was a beneficial effect of treatment on visual acuity (pooled OR 0.81, 95% CI 0.66 to 0.99) (Analysis 2.1).

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.

Progression of 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 an observed 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.

Only one trial has investigated zinc-monocysteine to date (Newsome 2008). At six months, people taking zinc-monocysteine read more letters (distance visual acuity). In people treated with zinc-moncysteine, the mean (SD) number of letters read correctly on an EDTRS charts with best correction was 39.027 (0.672) at baseline and 43.432 (0.784) at six months in their right eyes. In people taking placebo the values were 40.297 (0.649) at baseline and 39.243 (0.921) in their right eyes. Differences between the groups were statistically significant. Similar findings were seen for the left eye.

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. Over 80% of participants in this trial did not have signs of AMD.

There was no evidence of any effect of treatment on visual acuity; 59 people in the vitamin E group and 57 people in the placebo group lost more than nine letters of acuity (equivalent to 2 or more lines) on the Bailey-Lovie chart (OR 1.05, 95% CI 0.71 to 1.54). Similarly there was no evidence of effect on the progression of AMD; on grading of photographs 95 of 491 people in the vitamin E group showed progression compared with 90 of 506 people in the placebo group (OR 1.11, 95% CI 0.81 to 1.53). The results of clinical grading were that 40 of 508 people in the vitamin E group and 31 of 514 people in the placebo group showed progression (OR 1.33, 0.82 to 2.16).

Lutein or zeaxanthin versus placebo

Distance visual acuity: mean

There have been two trials published to date comparing supplementation with lutein versus placebo and reporting outcomes of relevance to this review (LISA; Veterans LAST study).

Veterans LAST study 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: MD logMAR acuity 0.04 (95% CI -0.15 to 0.23). The power of the study was low.

LISA was larger with 84 participants in the lutein group and 42 participants receiving placebo. They reported a non-significant improvement in visual acuity in the lutein group over six months however currently data are not available in a form suitable for inclusion in this review; we have requested the data from the study authors.

Any multivitamin or single component antioxidant supplement versus placebo

Distance visual acuity: loss of 3 or more lines (15 or more letters)

Three trials contributed to this analysis (AREDS; Newsome 1988; VECAT). The trials were reasonably consistent (I^2 = 28%) (Analysis 3.1). Overall there was a 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.

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.

Seven trials contributed to this analysis (AMDSG; Bartlett 2007; Kaiser 1995; Newsome 1988; Newsome 2008; Stur 1996; Veterans LAST study). A total of 203 people were randomised to treatment and 187 to control. There was considerable inconsistency in trial results (I^2 = 60%) (Analysis 3.2). There was little evidence of any benefit of treatment.

Progression of AMD: dichotomous

Data on the progression of AMD were not reported or were 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 = 61%) 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 2).

Progression of AMD: continuous

Two trials reported the progression of AMD in a continuous format (AMDSG; Bartlett 2007), with 48 people randomised to treatment and 32 to control (Analysis 1.2).

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 AMD (Chi^2 test P > 0.05) but had a beneficial effect on the progression of the disease in people with advanced AMD. Twelve of 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^2 P < 0.05).

Quality of life

CARMIS reported higher NEI VFQ-25 scores in the treated compared to the non-treated group after 24 months. The mean change in overall score at 24 months follow-up was 3.6 (95% CI 0.50 to 6.81) in the treated group and -8.7 (95% CI -16.54 to -0.97) in the non-treated group.

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 (high zinc intakes can inhibit copper absorption). 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) (AREDS).

There has been one published report on a small case series describing the presence of yellow rings in the cornea of people who had been taking vitamin supplements (Eller 2012). The significance of this is unclear at present.

The main ATBC trial found an increased risk of lung cancer associated with beta-carotene supplementation (ATBC), a finding that was repeated in the large CARET trial (Omenn 1996). Beta-carotene supplementation is contraindicated in people who smoke or have been exposed to asbestos.

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

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Zinc for age-related macular degeneration

Patient or population: patients with age-related macular degeneration
Settings: community
Intervention: zinc
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Zinc				
Distance visual acuity (loss of 3 or more lines) LogMAR Follow-up: mean 6.3 years	**Moderate**		**OR 0.81** (0.66 to 0.99)	1942 (2 studies)	⊕⊕⊕◯ **moderate**[1]	
	300 per 1000	**258 per 1000** (220 to 298)				
Progression to advanced AMD Grading of fundus photographs Follow-up: mean 6.3 years	**Moderate**		**OR 0.73** (0.58 to 0.93)	1943 (3 studies)	⊕⊕⊕◯ **moderate**[2]	
	300 per 1000	**238 per 1000** (199 to 285)				

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

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

[1] Downgraded for imprecision: wide confidence intervals and upper confidence limit is close to 1.
[2] Downgraded for inconsistency: one study with OR of 2.31, overall $I^2 = 28\%$.

Vitamin E for age-related macular degeneration

Patient or population: patients with age-related macular degeneration
Settings: community
Intervention: vitamin E
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Vitamin E				
Distance visual acuity (loss of 2 or more lines) LogMAR Follow-up: 4 years	**Moderate**		**OR 1.05** (0.71 to 1.54)	1179 (1 study)	⊕⊕◯◯ **low**[1,2]	
	100 per 1000	**104 per 1000** (73 to 146)				
Progression of AMD (dichotomous) Grading of fundus photographs Follow-up: 4 years	**Moderate**		**OR 1.11** (0.81 to 1.53)	997 (1 study)	⊕⊕◯◯ **low**[1,2]	
	200 per 1000	**217 per 1000** (168 to 277)				

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

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

[1] Downgraded for inconsistency: only one study so not possible to assess consistency between studies.
[2] Downgraded for imprecision: wide confidence intervals comparable with benefit and harm.

Lutein for age-related macular degeneration

Patient or population: patients with age-related macular degeneration
Settings: community
Intervention: lutein
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lutein				
Distance visual acuity (loss of 3 or more lines)	See comments					Two relatively small trials published. Currently data on this outcome not available in a suitable format for inclusion in this review
Progression of AMD (dichotomous)	See comments					Two relatively small trials published. Currently data on this outcome not available in a suitable format for inclusion in this review

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

DISCUSSION

Summary of main results

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 11 trials are smaller (ranging from 20 to 400 participants) and have shorter duration of treatment and follow-up (six 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 age-related macular degeneration (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 (Evans 2012). 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), Visaline (Kaiser 1995) and lutein/antioxidant (Bartlett 2007) are too small to provide evidence either way or currently data are not available in a format suitable for inclusion in this review (CARMIS; LISA). Pooling results, where possible, did not provide evidence of any benefit of supplementation. However, these trials were of relatively short duration.

A total of four trials investigated zinc supplementation (AREDS; Holz 1993; Newsome 1988; Stur 1996) and one trial a novel zinc-monocysteine formulation (Newsome 2008). 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. 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. Newsome 2008 found that zinc-monocysteine had beneficial effects on visual acuity and contrast sensitivity. One unpublished trial on zinc supplementation for which data are unlikely to be available has been excluded from the review (France 1998).

Overall completeness and applicability of evidence

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. However, this is unlikely and there was little evidence that this was a problem in the study.

It is worth comment that pooling data from trials other than AREDS reveals little evidence for effectiveness of antioxidant vitamin and mineral supplements on preventing visual loss or progression of the disease. However, the other studies encompass many different formulations and in general were rather small and of short duration which may explain the lack of effect.

AREDS was the only study to examine in detail the question of safety. They found little evidence of harm but there was an increased risk of hospital admission due to genito-urinary 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 (Lonn 2005). A systematic search of the literature for systematic reviews addressing harms of vitamin supplements did not identify any further relevant evidence. One small case series raised concerns about the presence of yellow corneal rings associated with vitamin supplementation (Eller 2012).

Quality of the evidence

As the majority of the trials were placebo-controlled we mostly assessed them as being at low risk of bias. It was also often not clear the extent to which attrition bias may have played a role. There was some evidence of selective outcome reporting with respect to data on visual acuity. We identified three trials that did not report non-significant data. Another problem with visual acuity is the variety of ways in which it can be reported - dichotomous with a variety of potential cut-points, as a continuous variable reporting change or final value. It is possible that investigators have done analyses of visual acuity in a variety of ways and reported the most significant finding. However, in these trials we did not find evidence of improved visual acuity associated with treatment.

AUTHORS' CONCLUSIONS

Implications for practice

People with age-related macular degeneration (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.

There is currently considerable interest in the potential role of lutein and zeaxanthin supplementation in AMD. This review includes only two small trials on lutein, neither of which provides good evidence for the effectiveness of such supplements.

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, and long enough duration, to demonstrate effects that are meaningful for people and should also include outcomes relevant to people affected by AMD including quality of life assessment. 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. If antioxidant supplementation is protective, there may be differences in the effect depending on the stage of the disease.

Trial reporting should include enough information to assess the role of selective outcome reporting bias (ideally by providing online access to the protocol for the study) and clearer information about follow-up of participants in the study, in particular reasons for exclusion.

As antioxidant vitamin and mineral supplements have systematic effects the literature on this topic would be much improved by a systematic review of the potential harms of such products, including broader sources of evidence than just randomised controlled trials.

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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**(1):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**(1):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**(5):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**(5):716–26.

Johnson AR, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *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**(6):573–600.

Bartlett 2007 *{published data only}*

Bartlett H, Eperjesi F. A randomised controlled trial investigating the effect of nutritional supplementation on visual function in normal, and age-related macular disease affected eyes: design and methodology [ISRCTN78467674]. *Nutrition Journal* 2003;**2**:12.

* Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. *European Journal of Clinical Nutrition* 2007;**61**(9):1121–7.

CARMIS *{published data only}*

Piermarocchi S, Saviano S, Parisi V, Tedeschi M, Panozzo G, Scarpa G, et al.Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. *European Journal of Ophthalmology* 2011;**22**(2):216–25.

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**(6):302–5.

LISA *{published data only}*

Schmidl D, Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, et al.How lutein supplementation affects macular pigment optical density and visual acuity in patients with age related macular degeneration. Joint Annual Meeting of the German, Swiss, and Austrian Societies for Clinical Pharmacology and Toxicology; 2011 Oct 20-22; Zurich. British Journal of Clinical Pharmacology, 2011:Conference Publication:(var.pagings).

Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, Werkmeister RM, et al.Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2011;**52**(11):8174–8.

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**(2):192–8.

Newsome 2008 *{published data only}*

Newsome DA. A randomized, prospective, placebo-controlled clinical trial of a novel zinc-monocysteine compound in age-related macular degeneration. *Current Eye Research* 2008;**33**(7):591–8.

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 and Visual Science* 1996;**37**(7):1225–35.

VECAT *{published data only}*

* Garrett SK, 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**(3):195–208.

Garrett SK, Thomas AP, Cicuttini F, Silagy C, Taylor HR, McNeil JJ. Community-based recruitment strategies for a longitudinal interventional study: the VECAT experience. *Journal of clinical epidemiology* 2000;**53**(5):541–8.

Robman LD, Tikellis G, Garrett SK, 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**(6):410–6.

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

Tikellis G, Robman LD, Harper CA, Garrett SK, McNeil JJ, Taylor HR, et al.The VECAT study: methodology and statistical power for measurement of age-related macular features. Vitamin E, Cataract, and Age-related Maculopathy Study. *Ophthalmic epidemiology* 1999;**6**(3):181–94.

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**(5):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**(4):216–30.

Wang 2004 ***{published data only}***

Wang H, Li RX, Wang MF. 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). *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 and Metabolism* 2007;**4**: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.

Connolly 2011 ***{published data only}***

Connolly EE, Beatty S, Loughman J, Howard AN, Louw MS, Nolan JM. Supplementation with all three macular carotenoids: response, stability, and safety. *Investigative Ophthalmology and Visual Science* 2011;**52**(12):9207–17.

Cumurcu 2006 ***{published data only}***

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

France 1998 ***{unpublished data only}***

Professor Soubrane. Zinc supplementation. Universitaire de Creteil, France.

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. *Journal of Nutrition* 2006;**136**(10):2519–24.

ISRCTN35481392 ***{published data only}***

ISRCTN35481392. Macular pigment and its contribution to visual performance and comfort. www.controlled-trials.com/ISRCTN35481392 (accessed 5 April 2012).

ISRCTN57556290 ***{published data only}***

ISRCTN57556290. A multi-site trial of a novel nutritional supplement (taurine, omega-3 fatty acids, zinc, antioxidants, and lutein) and micro-current stimulation in the treatment of atrophic (dry) age-related macular degeneration. www.controlled-trials.com/ISRCTN57556290 (accessed 5 April 2012).

ISRCTN81595685 ***{published data only}***

ISRCTN81595685. Comparison of macular and serum responses after supplementation with two different macular carotenoid formulations. www.controlled-trials.com/ISRCTN81595685 (accessed 24 March 2012).

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. *Graefe's Archive for Clinical and 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 and 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.

Landrum 2012 *{published data only}*

Landrum J, Bone R, Mendez V, Valenciaga A, Babino D. Comparison of dietary supplementation with lutein diacetate and lutein: a pilot study of the effects on serum and macular pigment. *Acta Biochimica Polonica* 2012;**59**(1): 167–9.

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 and 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 and 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.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.

NCT00006202 *{published data only}*

NCT00006202. Dose ranging study of lutein supplementation in persons over age 60. clinicaltrials.gov/ct2/show/NCT00006202 (accessed 5 May 2012).

NCT00121589 *{published data only}*

NCT00121589. Lutein/zeaxanthin and omega-3 supplementation in persons over age 60. clinicaltrials.gov/ct2/show/NCT00121589 (accessed 24 March 2012).

NCT00563979 *{published data only}*

NCT00563979. Enhancement of Macular Pigment Density by Oral Lutein Supplementation (EMPOLS). clinicaltrials.gov/ct2/show/NCT00563979 (accessed 5 April 2012).

NCT00564902 *{published data only}*

NCT00564902. Randomized, double blind, lutein controlled study of zeaxanthin and visual function in atrophic age related macular degeneration patients. clinicaltrials.gov/ct2/show/NCT00564902 (accessed 24 March 2012).

NCT00718653 *{published data only}*

NCT00718653. Effects of antioxidants on human macular pigments. clinicaltrials.gov/ct2/show/NCT00718653 (accessed 24 March 2012).

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.

Nolan 2012 *{published data only}*

Nolan JM, Akkali MC, Loughman J, Howard AN, Beatty S. Macular carotenoid supplementation in subjects with atypical spatial profiles of macular pigment. *Experimental Eye Research* 2012;**101**:9–15.

Nussenblatt 2006 *{published data only}*

Nussenblatt RB, Kim J, Thompson DJ, Davis MD, Chew E, Ferris FL, et al.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 and Visual Science* 2006;**47**(4):1310–8.

PHS II *{published data only}*

Christen WG, Glynn RJ, Sesso HD, Kurth T, Macfadyen J, Bubes V, et al.Vitamins E and C and medical record-confirmed age-related macular degeneration in a randomized trial of male physicians. *Ophthalmology* 2012;**119**(8): 1642–9.

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 and Visual Science 2006;**47**(12): 5227–33.

Sasamoto 2011 *{published data only}*
Sasamoto Y, Gomi F, Sawa M, Tsujikawa M, Nishida K. Effect of 1-year lutein supplementation on macular pigment optical density and visual function. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2011;**249**(12): 1847–54.

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

Vidal 2011 *{published data only}*
Vidal K, Bucheli P, Gao QT, Moulin J, Shen LS, Blum S, et al.Effect of a milk-based wolfberry preparation on immune function and physical status of elderly. Clinical Nutrition. Gothenurg Sweden: ESPEN, 2011.

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.

Wong 2010 *{published data only}*
Wong WT, Kam W, Cunningham D, Harrington M, Hammel K, Meyerle CB, et al.Treatment of geographic atrophy by the topical administration of OT-551: results of a phase II clinical trial. *Investigative Ophthalmology and Visual Science* 2010;**51**(12):6131–9.

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

CARMA *{published data only}*
Lai Y, Grattan J, Shi Y, Young G, Muldrew A, Chakravarthy U. Functional and morphologic benefits in early detection of neovascular age-related macular degeneration using the preferential hyperacuity perimeter. *Retina* 2011;**31**(8): 1620–6.
Neelam K, Hogg RE, Stevenson MR, Johnston E, Anderson R, Beatty S, et al.Carotenoids and co-antioxidants in age-related maculopathy: design and methods. *Ophthalmic Epidemiology* 2008;**15**(6):389–401.

Dawczynski 2012 *{published data only}*
Dawczynski J, Jentsch S, Schweitzer D, Hammer M, Strobel J. [Changes of macular pigment and drusen morphology in patients with lutein supplementation] [Anderung von makulapigment und drusenmorphologie unter luteinsupplementation]. *Klinische Monatsblatter fur Augenheilkunde* 2012;**229**(1):69–71.

Falsini 2010 *{published data only}*
Falsini B, Piccardi M, Minnella A, Savastano C, Capoluonga E, Fadda A, et al.Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2010;**51**(12):6118–24.

NCT00800995 *{published data only}*
NCT00800995. Superoxide Dismutase (SOD) as antioxidant treatment of age related macular degeneration (ARMD). clinicaltrials.gov/ct2/show/NCT00800995 (accessed 5 April 2012).

References to ongoing studies

AREDS2 *{published data only}*
Hubbard LD, Danis RP, Neider MW, Thayer DW, Wabers HD, White JK, et al.Brightness, contrast, and color balance of digital versus film retinal images in the age-related eye disease study 2. *Investigative Ophthalmology and Visual Science* 2008;**49**(8):3269–82.

NCT00879671 *{published data only}*
NCT00879671. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. clinicaltrials.gov/ct2/show/NCT00879671 (accessed 30 March 2012).

NCT00893724 *{published data only}*
NCT00893724. The effect of supplemental adjuvants for intracellular nutrition and treatment on diabetic macular edema and neovascular age-related macular degeneration. clinicaltrials.gov/ct2/show/NCT00893724 (accessed 5 May 2012).

NCT01048476 *{published data only}*
NCT01048476. Effects of lutein and zeaxanthin supplementation on age-related macular degeneration. clinicaltrials.gov/ct2/show/NCT01048476 (accessed 5 April 2012).

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**(5):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**(15): 1029–35.

Bjelakovic 2012
Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD007176.pub2]

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**(6):847–52.

Bunce 2010
Bunce C, Xing W, Wormald R. Causes of blind and partial sight certifications in England and Wales: April 2007-March 2008. *Eye (London, England)* 2010;**24**(11):1692–9.

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

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Eller 2012
Eller AW, Gorovoy IR, Mayercik VA. Yellow corneal ring associated with vitamin supplementation for age-related macular degeneration. *Ophthalmology* 2012;**119**(5): 1011–6.

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 2012
Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD000253.pub3]

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 2011
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org, 2011.

Huang 2006
Huang HY, Caballero B, Chang S, Alberg AJ, Semba RD, Schneyer CR, et al.The efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults: a systematic review for a National Institutes of Health State-of-the-Science Conference. *Annals of Internal Medicine* 2006;**145**(5):372–85.

Kirkham 2010
Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al.The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365.

Klein 1991
Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology* 1991;**98**(7):1128–34.

Klein 1992
Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992;**99**(6):933–43.

Lonn 2005
Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM. Effects of long term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005;**293**(11):1338–47.

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**(18): 1189–90.

Owen 2012
Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *British Journal of Ophthalmology* 2012;**96**(5):752–6.

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al.Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

References to other published versions of this review

Evans 2006
Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD000254.pub2]

* *Indicates the major publication for the study*

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 1 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 µg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 µg 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"*Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assign-*

		ing and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Part 1 page 14 "*Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules.*" Part 1 page 14
Allocation concealment (selection bias)	Unclear risk	"*Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service*" Part 1 page 14 "*Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules.*" Part 1 page 14
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service*" Part 1 page 14 "*Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the cap-*

AMDSG (*Continued*)

		sules." Part 1 page 14
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	"*Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service*" Part 1 page 14
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service*" Part 1 page 14 "*Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules.*" Part 1 page 14
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service*" Part 1 page 14 "*Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the cap-*

AMDSG (*Continued*)

		sules." Part 1 page 14
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 patients withdrew from the study over 18 months. 4 patients died. 1 patient experienced an idiosyncratic reaction and was dropped. Attrition data were as follows: "71 patients at baseline, 67 patients at 6 m, 59 patients at 12 m, 59 patients at 18 m." Similar numbers of drop outs from groups 1 and 2
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information given

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 1 eye; ocular media clear and therefore able to obtain adequate stereoscopic fundus photographs; at least 1 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 (500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene), zinc (80 mg of zinc as zinc oxide and 2 mg 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	2 x 2 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

AREDS (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Simple randomization, stratified by clinical center and AMD category, was used to assign treatment. Participants in Categories 2, 3, and 4 were assigned with probability one quarter to each treatment group*" AREDS report number 8, randomisation "*Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant*". AREDS report number 8, randomisation
Allocation concealment (selection bias)	Low risk	"*Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant*". AREDS report number 8, randomisation
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*The 4 treatment interventions were double-masked...*" AREDS report number 8, study design. "*Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code*" AREDS report number 8, masking "*Four participants (0.1%) were reported to have been unmasked during the trial*" AREDS report number 8, data quality
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	"*The 4 treatment interventions were double-masked...*" AREDS report number 8, study design. "*Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code*" AREDS report number 8, masking "*Four participants (0.1%) were reported*

AREDS (*Continued*)

		to have been unmasked during the trial" AREDS report number 8, data quality
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Visual acuity was assessed by certified examiners using the ETDRS logMAR chart and a standardized refraction and visual acuity protocol (AREDS Manual of Operations; The EMMES Corporation, Rockville, Md)* " AREDS report number 8, study population
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*Stereoscopic fundus photographs of the macula were taken at baseline and annually beginning 2 years after randomization and graded centrally using standardized grading procedures.*" AREDS report number 8, procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups.*" AREDS report number 8, enrolment and patient characteristics "*Only 2.4% of AREDS participants were lost to follow-up (missed at least their last 2 consecutive visits). Losses to follow-up were balanced across treatment groups*" AREDS report number 8, data quality. "*Of almost 50000 possible follow-up visits, 10% were missed. The frequency of missed visits and mean follow-up time (6.3 years) did not differ by treatment group. Most participants (90%) had at least 5 years of follow-up.*" AREDS report number 8, data quality
Selective reporting (reporting bias)	Low risk	"*At the start of the study, 2 primary outcomes were defined for study eyes in the AMD trial: (1) progression to advanced AMD and (2) at least a 15-letter decrease in visual acuity score.* " AREDS report number 8, outcomes

Bartlett 2007

Methods	Method of allocation: sponsor prepared coded tablets Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: 5 (2 treatment, 3 control)
Participants	Country: UK Number of participants randomised: 30 Age: 55 to 82 years; average age 69.2 (SD 7.8)

	Sex: 53% female Inclusion criteria: (1) Provide written informed consent (2) Be available to attend one of the research centres (3) Present with no ocular pathology in at least 1 eye, or no ocular pathology other than soft or hard drusen, and areas of increased or decreased pigment associated with drusen. Fundus examination was used to determine the presence of AMD Exclusion criteria: type I and II diabetes, prescribed antiplatelet or anticoagulant medication, and concurrent use of nutritional supplements. Those with advanced AMD in 1 or both eyes were excluded
Interventions	Treatment: supplement contained: lutein esters (6 mg);retinol (750 mg); vitamin C (250 mg); vitamin E (34 mg); zinc (10 mg); copper (0.5 mg) Control: the placebo tablets contained cellulose Duration: 9 months
Outcomes	Trial report provided data on contrast sensitivity at 9 months follow-up. Protocol listed more outcomes (see below under selective reporting) and specified 9 and 18 months follow-up
Notes	Sample size calculations reported in trial report: "*A group size of nine was calculated to be sufficient to provide 80% power at the 5% significance level for CS based on an effect size of 0.3 log units, and mean and standard deviation (s.d.) values taken from a sample of 50 ARM and atrophic AMD patients of the University optometry clinic (1.3970.22 log CS).*" Bartlett 2007 Sample size calculations reported in protocol paper "*From initial data collection we have calculated the treatment group sizes required in order to have 80% power at the 5% significance level for VA, CS, MM test, and the EMS. These values suggest that a total of 63 normal, and 96 age-related macular disease participants are required.*" Bartlett 2003 http://www.controlled-trials.com/ISRCTN78467674

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The random number generator function in Microsoft Excel is being used to allocate participants to μ and λ groups. Odd numbers allocate to the μ group*" Bartlett 2003 (protocol report) page 3 "*Only one investigator (HB) was involved in the randomization process, which employed the random number generator in Microsoft Excel for Windows XP. Odd and even numbers were used to identify group.*" Bartlett 2007, page 1122

Allocation concealment (selection bias)	Low risk	"*Enrolment was carried out by HB, who, along with FE, was masked to group assignment.*" Bartlett 2007, page 1121 "*Only one investigator (HB) was involved in the randomization process, which employed the random number generator in Microsoft Excel for Windows XP. Odd and even numbers were used to identify group.*" Bartlett 2007, page 1122 "*Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation.* " Bartlett 2003 (protocol report) page 3
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*The study formulation and placebo tablets have been produced by Quest Vitamins Ltd, Aston Science Park, Birmingham, B7 4AP, and are identical in external and internal appearance, and taste. The manufacturer has allocated distinguishing symbols, μ and λ. The tablets are packaged in identical, sealed, white containers; the only difference being the symbol on the label. Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation.*" Bartlett 2003 (protocol report) page 3
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Not reported
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	"*The study formulation and placebo tablets have been produced by Quest Vitamins Ltd, Aston Science Park, Birmingham, B7 4AP, and are identical in external and internal appearance, and taste. The manufacturer has allocated distinguishing symbols, μ and λ. The tablets are packaged in identical, sealed, white containers; the only difference being the symbol on the label. Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation.*" Bartlett 2003 (protocol report) page 3 "*End of trial assessment using questionnaires indicated'masking success. Out of those participants taking the placebo tablet, 10% cor-*

		rectly guessed which tablet they were taking, and 10% incorrectly guessed. Out of those taking nutritional supplement, 13% guessed correctly which tablet they were taking, and 7% incorrectly guessed. The remaining participants did not know which group they were randomized to."
Blinding of outcome assessment (detection bias) Progression AMD	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"*Statistical analysis was carried out on a per protocol basis*."
Selective reporting (reporting bias)	High risk	Protocol report: following outcomes listed: visual acuity, contrast sensitivity, colour vision, macular mapping test, glare recovery, fundus photographs analysed by colour and edge analysis software Trial report only contrast sensitivity (CS) reported: "*Outcome measure CS was measured using a Pelli-Robson chart (Clement Clarke International, Edinburgh Way, Harlow, Essex, CM20 2TT, UK) and scored per letter.*"

CARMIS

Methods	Method of allocation: random list, unclear how delivered Masking: participant - no; provider - no; outcome - unclear Losses to follow-up: 18% in supplement group, 38% in no supplement group
Participants	Country: Italy Number of participants randomised: 145 Age: average 73 years Sex: 58 men; 87 women Inclusion criteria: AREDS category 3 features (non advanced AMD) • Visual acuity >= 20/32 (0.2 logMAR, 74 letters of ETDRS chart) • Extensive (as measured by drusen area) intermediate (63 m, 125 m) drusen • At least 1 large (125 m) drusen or geographic atrophy not involving the centre of the macula Exclusion criteria: • Visual acuity < 20/32 • Advanced AMD in 1 or both eyes • Other ocular disease with irreversible reduction in visual acuity • Lens opacity • Insufficient pupil dilation

CARMIS (*Continued*)

	• Previous laser treatment at posterior pole • Macular changes not due to AMD • Intolerant to carotenoids • Major chronic disease/life expectancy < 6 months • No informed consent • In other experimental study
Interventions	Treatment: oral daily supplementation of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg) and astaxanthin (4 mg; AZYR SIFI, Catania, Italy) Control: no dietary supplementation Duration: 24 months
Outcomes	Best-corrected visual acuity (ETDRS, logMAR), intraocular pressure, fundus examination and contrast sensitivity at baseline, 6, 12 and 24 months NEI VFQ: baseline, 12 and 24 months Multi-focal electroretinograms (ERG) at 6 and 12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*A permuted blocks allocation scheme was used to perform this random allocation*" Page 3
Allocation concealment (selection bias)	Unclear risk	"*A 24-month prospective open-label randomized study...* " Page 2 "*The study coordinator allocated study numbers sequentially, as participants were enrolled. Participants were then randomly allocated to the treatment or no treatment group. A permuted blocks allocation scheme was used to perform this random allocation. The allocation list was stored at a remote site.*" Page 2/3 "Study drug was administered by an unmasked physician who had no other role in the study." Page 2 No mention was made of allocation ratios but 103 people recruited to treatment group and 42 to no treatment group
Blinding of participants and personnel (performance bias) Visual acuity	High risk	"*A 24-month prospective open-label randomized study...* " Page 2

CARMIS (*Continued*)

Blinding of outcome assessment (detection bias) Visual acuity	High risk	"*A 24-month prospective open-label randomized study...* " Page 2 "*In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator.*" Page 2 However, as patients were not masked this could have affected the measurement of visual acuity
Incomplete outcome data (attrition bias) All outcomes	High risk	"*Nineteen people in the group T-AMD, and 16 subjects from the group NT-AMD, were excluded from final data analysis.*" Page 4. This exclusion was uneven between 2 groups: 19/103 (18.4%) and 16/42 (38.1%) and also inconsistent with the data in table III, page 6. In table III 14 people withdrew from the carotenoids group and 3 from the control group; 20 people discontinued the intervention in the carotenoids group and 17 in the control group
Selective reporting (reporting bias)	Unclear risk	Unclear. Did fundus examination but did not report progression of AMD

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 to 82, mean 68	
Interventions	Treatment: 100 mg 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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Holz 1993 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"*randomized double-blind study*"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Visual acuity	Unclear risk	"*randomized double-blind study*"
Blinding of participants and personnel (performance bias) Progression AMD	Unclear risk	"*randomized double-blind study*"
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	"*randomized double-blind study*"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*randomized double-blind study*" "*Stereo fundus photographs and fluorescein angiograms were analyzed by investigators in a masked fashion using a standardized grading scheme*"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	For visual acuity, trial report states that outcome was analysed but only reports that result was not significant

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 non serous 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 4 dioptres. Exclusion criteria: people with diabetes mellitus, endocrine problems, cardiac dysrhythmia, cardial infarction or hypotension, other ocular disorders

Kaiser 1995 (*Continued*)

Interventions	Treatment: Visaline (Novopharma Cham, Switzerland). Each tablet contains 1.5 mg 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 1 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation not described in the report but contact with investigator "*The allocation schedule was generated by the company and treatment schedule was concealed from people enrolling patients.*"
Allocation concealment (selection bias)	Low risk	Allocation concealment not described in the report but contact with investigator "*The allocation schedule was generated by the company and treatment schedule was concealed from people enrolling patients*."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Study was placebo-controlled. Placebo not described in the report but investigator reported that "*The placebo was also prepared by the company and tablets resembled the active treatment.*"
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Study was placebo-controlled. Placebo not described in the report but investigator reported that "*The placebo was also prepared by the company and tablets resembled the active treatment.*"
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Study was placebo-controlled. Placebo not described in the report but investigator reported that "*The placebo was also prepared by the company and tablets resembled the active treatment.*"

Kaiser 1995 (*Continued*)

Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Study was placebo-controlled. Placebo not described in the report but investigator reported that "*The placebo was also prepared by the company and tablets resembled the active treatment.*"
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 patients enrolled and 20 followed up
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

LISA

Methods	Method of allocation: 2:1 intervention: control Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up:	
Participants	Country: Austria Number of participants randomised: 126 Age: over 50; average age 72 Sex: 50 male, 66 female Inclusion criteria: people in categories 2, 3, or 4, according to the AREDS grading scheme, aged 50 to 90 years with clear nonlenticular ocular media and visual acuity > 0. 4. Exclusion criteria: primary retinal pigment epithelium atrophy 125 m, moderate or severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, participation in a clinical trial in the 3 weeks preceding the study, ocular surgery within the last 6 months, and a history of treatment with photosensitizing drugs	
Interventions	Treatment: Lutein (Lutamax DUO; Pharmaselect, Vienna, Austria) . The dosage in months 1 to 3 was 20 mg once daily and in months 4 to 6 was 10 mg once daily Control: placebo Duration: 6 months	
Outcomes	Only one eye per person was included in the trial; if both eyes were eligible, one eye was selected randomly Macular pigment optical density Distance visual acuity (ETDRS chart) and fundus photographs taken	
Notes	clinicaltrials.gov/ct2/show/NCT00879671	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

LISA (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"*The randomization of lutein (Lutamax DUO; Pharmaselect, Vienna, Austria) versus placebo was 2:1, resulting in a total of 84 patients in the lutein group and 42 patients in the placebo group*" Page 8175 Allocation sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment. However states 'double masked'
Blinding of participants and personnel (performance bias) Visual acuity	Unclear risk	"*All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting*." Page 8175 No description of placebo. Potential for unmasking as to intervention received No specific information provided as to the blinding of outcome assessors (grading of fundus images, assessment of MPOD or visual function)
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	"*All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting*." Page 8175 No description of placebo. Potential for unmasking as to intervention received No specific information provided as to the blinding of outcome assessors (grading of fundus images, assessment of MPOD or visual function)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/84 (11.9%) people in the lutein group were lost to follow-up. In two people, the withdrawal was due to serious adverse events. One participant had a myocardial infarction, and the other subject developed CNV in the study eye 6/42 (14.3%) people in the placebo group were lost to follow-up. One person developed CNV, which was again classified as a serious adverse event In patients who were lost to follow-up the last observation was carried forward

LISA (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available.

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 1 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 100 mg 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Subjects were randomly assigned [...] using a computer-generated table of random numbers.*" page 193
Allocation concealment (selection bias)	Low risk	"*Subjects were randomly assigned to receive either zinc or placebo [...]. The individual who recorded the zinc-treated or placebo group assignment maintained personal control over the randomization sheet and participated in no other phases of the study. This individual also handed the study tablets to subjects. All other personnel were masked to the study.*" page 193

Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*All other personnel were masked to the study.* " page 193 "*Zinc sulfate was prepared as white tablets containing 100 mg of United States Pharmacopeia-graded material. Identical-appearing tablets containing lactose and fructose served as the placebo. All tablets were bottled in identical containers.*" page 193
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	"All other personnel were masked to the study." page 193 "Zinc sulfate was prepared as white tablets containing 100 mg of United States Pharmacopeia-graded material. Identical-appearing tablets containing lactose and fructose served as the placebo. All tablets were bottled in identical containers." page 193
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*All visual acuities were determined by one of two masked observers throughout the study*" page 192
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*Two independent observers masked as to patient identity,...*" page 193
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*A total of 90 subjects [...] were randomized to zinc and 84 subjects [...] to placebo. [.....]. A total of ten subjects were lost to follow-up from the zinc-treated group and 13 subjects from the placebo group. [...] This figure represents dropout rates of 11.1% and 15.4% from the zinc-treated and placebo groups, respectively*" page 193 Reasons for loss to follow-up zinc/placebo (page 194 table 1) • Stopped taking pills 5/6 • Started taking zinc 1/2 • Gastrointestinal symptoms 1/0 • Died 2/1 • Poor compliance 0/1 • Developed diabetes mellitus 0/1 • Unavailable 1/2
Selective reporting (reporting bias)	High risk	"*Other ocular functions assessed included ocular vision and photostress recover tests (These observations are being analysed and will be reported later)*" page 193

Newsome 2008

Methods	Method of allocation: random allocation using a 50% likelihood scheme Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: 6, 3 in each group of 40 participants
Participants	Country: USA Number of participants randomised: 80 Age: average age 73.7 years Sex: 59/74 female Inclusion criteria: • Presence of macular drusen with or without pigment changes Exclusion criteria: • Choroidal neovascular activity • Any condition preventing view of the fundus • Other conditions affecting eye: diabetes, eye surgery (except cataract). Chronic open angle glaucoma with stable intraocular pressures and visual fields was allowed. Both ZMC and placebo groups enrolled 40 participants, with best-corrected visual acuity 20/25 to 20/70, macular drusen, and pigment changes
Interventions	Treatment: zinc-monocysteine 25 mg twice a day for 6 months Control: placebo Duration: 6 months
Outcomes	Masked personnel determined baseline, 3- and 6-month best-corrected visual acuity, contrast sensitivity and light flash recovery time
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*A total of 80 subjects (40 per group) volunteered for the study and were randomized using a 50% likelihood scheme.*" Page 593
Allocation concealment (selection bias)	Low risk	"*An unmasked co-ordinator gave subjects, upon enrollment, study materials in numbered containers using the randomization scheme. This individual performed no data collection.*" Page 593
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*Study materials were in tinted pharmaceutical capsules that provided an indistinguishable appearance between ZMC and the plant cellulose placebo.*" Page 593
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	

Newsome 2008 (*Continued*)

Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Functional assessment....by masked trained examiners...*" Page 593 "*Masked examiners determined contrast sensitivity....*" Page 593
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Thirty-seven [out of 40] in each group competed all visits...*" Page 593 Reasons for drop-out: 2 of placebo group died from pre-existing medical conditions; the rest of the dropouts (n = 4) were due to gastrointestinal-related complaints
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

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 1 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
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*This was a double-masked, randomized, placebo-controlled study conducted at a single center. The randomization between zinc and placebo was performed in a ratio 1:1*" Page 1228 No details provided of method of sequence generation, however since coding provided by sponsor this is unlikely to be a source of bias
Allocation concealment (selection bias)	Low risk	"*Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria) . All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers.* " Page 1227, 1228
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria) . All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers.* " Page 1227, 1228

Blinding of participants and personnel (performance bias) Progression AMD	Low risk	"*Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria) . All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers.* " Page 1227, 1228
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria) . All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers.* " Page 1227, 1228
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria) . All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers.* " Page 1227, 1228
Incomplete outcome data (attrition bias) All outcomes	High risk	"*One hundred twelve patients were enrolled between March 1, 1990 and June 30, 1992. Six patients (four in the treatment group, two in the placebo group) could not tolerate the medication because of gastrointestinal side effects and had to be withdrawn from the study. Fourteen patients did not return for the sched-*

		uled follow-up visits or decided to withdraw from the study because of personal reasons. The withdrawal of these 14 patients was not connected to any side effects of the study medication. The rest of the recruited patients (92 patients) returned for all required visits." *Page 1229* "*During the treatment period, a CNV developed in the study eye in 14 patients (nine in the treatment group, five in the placebo group) . Ten of these patients underwent laser treatment and were withdrawn from the study.*" Page 1229
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

VECAT

Methods	Method of allocation: coded bottles Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: not known
Participants	Country: Australia Number of participants randomised: 1204 Age: 55 to 80, mean 66 Sex: 56% female Inclusion criteria: lens and retina of at least 1 eye available for documentation Exclusion criteria: previous cataract surgery or advanced cataract in both eyes; steroid or anticoagulation use; serious disease; regular use or sensitivity to vitamin E
Interventions	Vitamin E 500 IU per day: natural vitamin E in soybean oil medium Control: placebo identical in sight, taste and smell Duration: 4 years
Outcomes	2 m logMAR visual acuity; clinical examination; colour stereoscopic fundus photographs graded using International Grading Scheme
Notes	Worse eye used as the study eye

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Participants were then randomly allocated to treatment group. This random allocation was performed by using a "permuted blocks" allocation scheme.*" Page 2 of online article

VECAT (*Continued*)

Allocation concealment (selection bias)	Low risk	"*Study numbers were allocated sequentially by the study coordinator as participants were enrolled in the study*." Page 2 of online article "*Bulk medications were dispensed into labelled jars by a person not involved in the study. Vitamin E and placebo were dispensed on different days to avoid confusion. Identical containers were used. The jars were packed in numerical order and then dispensed by study personnel*." Page 2 of online article
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo*." Page 2 of online article
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	"*Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo*." Page 2 of online article
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo*." Page 2 of online article
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation, although all knew that participants would be randomly assigned to receive either vitamin E or placebo*." Page 2 of online article "*At the end of the study we reassessed the initial and final photographs for any change with a "side by side" comparison in a masked and randomised fashion*." Page 2 of online article

VECAT (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	78/595 (13%) participants in vitamin E group and 72/598 (12%) of placebo group withdrawn over the course of the study. Reasons for withdrawal reported (table 3 and figure 3). Page 4 of online article.
Selective reporting (reporting bias)	High risk	For visual acuity, trial report states that outcome was analysed but only reports that result was not significant

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 groups (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, photosensitising drugs, taken lutein supplements within the previous 6 months
Interventions	Treatment: Group 1 L: lutein 10 mg 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, beta-carotene, 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

Veterans LAST study (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*... were randomly assigned to one of three capsule groups by consecutive random card-3-choice, allocation sequence*" Page 217
Allocation concealment (selection bias)	Low risk	"*Nutraceutical Sciences Institute prepared the lutein capsules, the L/A capsules, and the P capsules and also maintained and concealed the blinding and four-digit allocation codes.* " Page 218 "*All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study*" Page 218
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	"*All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study*" Page 218 "*Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food.*" Page 218
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	"*All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study*" Page 218 "*Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food.*" Page 218
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	"*All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study*" Page 218 "*Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food.*" Page 218
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"*All personnel at the DVA Medical Cetnter were unaware of the masked allocation codes during the 12-month clinical study*" Page

Veterans LAST study (*Continued*)

		218 "*Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food.*" Page 218
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up 14/90: page 217 Lutein 10 mg group n = 29 • 1 person lost to follow-up • 1 person died • 2 other withdrawals Lutein 10 mg and antioxidant group n = 30 • 2 persons lost to follow-up • 4 other withdrawals Placebo group n = 31 • 1 persons lost to follow-up • 1 person died • 1 other withdrawals Members of placebo group removed from analysis due to the fact that they had taken lutein
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

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 80 mg daily, vitamin C, vitamin E Control: placebo Duration 24 to 32 months	
Outcomes	Outcomes: visual acuity, early and late AMD	
Notes	Limited information available on this trial. AMD patients were stratified into early and late-stage disease	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Wang 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) Visual acuity	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Progression AMD	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) Progression AMD	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Visual acuity was measured but not reported, possibly because of non-significant results

AMD: age-related macular degeneration
ARM: Age-related maculopathy
ERG: electroretinogram
ETDRS: Early Treatment Diabetic Retinopathy Study
RPE: retinal pigment epithelium
MPOD: macular pigment optical density
NEI: National Eye Institute
VFQ: Visual function questionnaire
RDA: recommended dietary allowance
SD: standard deviation
ZMC: zinc-monocysteine

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
Connolly 2011	No AMD outcomes
Cumurcu 2006	Not a RCT
France 1998	Study is probably eligible for inclusion but is unpublished and data are not available
Franciose 2006	Bioavailability study
Goodrow 2006	Bioavailability study
ISRCTN35481392	Participants had no ocular pathology http://www.controlled-trials.com/ISRCTN35481392/ISRCTN35481392
ISRCTN57556290	No comparator group http://www.biomedcentral.com/1471-2415/7/3
ISRCTN81595685	Comparison of two active formulations
Kamburoglu 2006	Not a RCT, not antioxidant
Khachik 2006	Bioavailability study
Kopsell 2006	Bioavailability study
Landrum 2012	Pilot study of effects of lutein supplementation on serum and macular pigment
Lim 2006	Not antioxidant
LUNA study	Bioavailability study
LUXEA	MPOD only measured; no clinical outcomes

(*Continued*)

Moeller 2006	Not RCT
NCT00006202	Dose ranging study for lutein supplementation. No control group
NCT00121589	Phase I study only. Looking at changes in plasma levels and macular pigment density only
NCT00563979	Active comparator (omega-3)
NCT00564902	Active comparator (lutein)
NCT00718653	Effect on macular pigments only, not on AMD
Nolan 2006	Not a RCT
Nolan 2007	Not a RCT
Nolan 2012	Effect on macular pigments in healthy people only, not on AMD
Nussenblatt 2006	Not AMD
Owsley 2006	Not antioxidant
PHS II	RCT in healthy population group. Will be included in Cochrane Review on prevention of AMD with antioxidant supplements
Rosenthal 2006	Small dose ranging study. Data on vision only collected for nine months and not possible to extract from report
Sasamoto 2011	Not a RCT
Vannas 1958	Allocation concealment inadequate
Vidal 2011	RCT in healthy population group. Will be included in Cochrane review on prevention of AMD with antioxidant supplements
Wang 2007	Bioavailability study
Wenzel 2006	Bioavailability study
Wong 2010	Phase II open-label study in 10 participants only
Zhao 2006	Bioavailability study

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

Characteristics of studies awaiting assessment *[ordered by study ID]*

CARMA

Methods	Parallel group randomised controlled trial
Participants	Men and women aged 50+ with either early AMD features of sufficient severity in at least one eye or any level of AMD in one eye and advanced AMD (neovascular AMD or central geographic atrophy) in the fellow eye n = 433
Interventions	Lutein (6mg), zeaxanthin (0.3mg) and co-antioxidants ((vitamin E: 7.5 mg; vitamin C: 75 mg; zinc: 10 mg; copper: 0.2 mg) Placebo (cellulose microcrystalline, lactose and magnesium stearate) and is indistinguishable from the intervention preparation in size, colour, smell and taste
Outcomes	Primary outcome measure: distance visual acuity Secondary outcome measures: • retinal visual acuity • morphological progression of AMD (grading of stereoscopic colour fundus photographs) • macular pigment levels and serum levels of antioxidants.
Notes	http://www.controlled-trials.com/ISRCTN94557601/CARMA

Dawczynski 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Falsini 2010

Methods	Method of allocation: unclear, report suggests cross-over trial Masking: participant - unclear; provider - unclear; outcome - unclear although study described as double-masked Losses to follow-up: unclear
Participants	Country: Italy Number of participants randomised: 25 Age: 54 to 84, mean 65 12 men and 13 women
Interventions	Treatment: daily dose of oral saffron (20 mg) Control: placebo Duration: 90 days, then crossed over and followed for a further 90 days

Falsini 2010 (*Continued*)

Outcomes	Primary outcome measures: • fERG amplitude and phase • fERG function slope and threshold Secondary outcome measures: visual acuity
Notes	http://clinicaltrials.gov/show/NCT00951288

NCT00800995

Methods	Allocation: randomised Control: placebo control Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-masked (participant, caregiver, investigator, outcomes assessor) Primary purpose: prevention
Participants	n = 46
Interventions	Oral administration of Superoxide Dismutase (SOD) in its galenic form, Glisodine, versus placebo
Outcomes	Primary outcome measures: difference on AREDS score, month 24 to month 0
Notes	http://clinicaltrials.gov/show/NCT00800995

fERG: focal electroretinogram

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

AREDS2

Trial name or title	Age-Related Eye Disease Study 2 (AREDS2)
Methods	Multi-centre parallel group randomised controlled trial, follow-up five years, masked assessment of outcome
Participants	4200 participants aged 50 to 85 years enrolled on the basis of the AREDS Simplified Severity Scale for defining risk categories for development of advanced age-related macular degeneration
Interventions	10 mg lutein and 2 mg zeaxanthin (1 tablet) 350 mg docosahexaenoic acid (DHA) and 650 mg eicosapentaenoic acid (EPA) (2 soft-gel capsules) Factorial design, 3 arms (no arm with placebo for both)
Outcomes	Primary outcome measures: • progression to advanced AMD in people at moderate to high risk for progression

AREDS2 (*Continued*)

	Secondary outcome measures: • progression to moderate vision loss • adverse events • progression of lens opacity or incidence of cataract surgery • effect of study supplements on cognitive function • effect of DHA/EPA on cardiovascular morbidity and mortality
Starting date	2006 End date: December 2012
Contact information	See clinicaltrials.gov website for details
Notes	http://clinicaltrials.gov/show/NCT00345176

NCT00879671

Trial name or title	Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration
Methods	Parallel group randomised controlled trial, masked assessment of outcome
Participants	126 men and women aged 50 to 90 years with non-exudative AMD enrolled on the basis of AREDS criteria
Interventions	Dietary supplement: Lutamax (lutein) 20 mg for 3 months, then lutein 10 mg Placebo
Outcomes	Primary outcome measures: • macular pigment optical density as measured with optical reflectometry Secondary outcome measures: • visual acuity using ETDRS charts • central visual field defects assessed with scanning laser scotometry • changes in fundus appearance as documented with fundus photos • determination of an increased systemic antioxidative state in plasma and low-density lipoprotein and plasma lutein concentrations
Starting date	November 2006 End date: December 2011
Contact information	See clinicaltrials.gov website for details
Notes	http://clinicaltrials.gov/show/NCT00879671

NCT00893724

Trial name or title	Supplemental Adjuvants for Intracellular Nutrition and Treatment (SAINTS)
Methods	Parallel group randomised controlled trial, follow-up one year, masked assessment of outcome
Participants	60 men and women with a clinical diagnosis of neovascular AMD
Interventions	Dietary supplement (sustained release) Dietary supplement with minocycline (50mg) Placebo Dietary supplement contains: • inosine • tocopherols (200 IU) • tocotrienol (10 mg) • coq10 (50 mg) • niacinamide (750 mg) • vitamin C (1000 mg) • n-acetyl cysteine (600 mg)
Outcomes	Primary outcome measures: • degree of regression (optical coherence tomography) • duration of regression (optical coherence tomography) • visual change (ETDRS) Secondary outcome measures: • effect on HbA1C • effect on blood pressure • effect on serum uric acid
Starting date	June 2009 End date: September 2011
Contact information	See clinicaltrials.gov website for details
Notes	http://clinicaltrials.gov/show/NCT00893724

NCT01048476

Trial name or title	Effects of Lutein and Zeaxanthin Supplementation on Age-related Macular Degeneration
Methods	Parallel group randomised controlled trial, follow-up one year, masked assessment of outcome
Participants	120 men and women aged 50 to 90 years with nonexudative AMD (AREDS categories 2,3, and 4)
Interventions	Dietary supplement: 20 mg lutein; daily supplementation 1 year Dietary supplement: 10 mg lutein; daily supplementation 1 year Dietary supplement: placebo; daily supplementation 1 year

NCT01048476 (*Continued*)

Outcomes	Primary outcome measures: • macular pigment optical density and visual function, such as visual acuity, multifocal electroretinograms, contrast sensitivity and glare sensitivity in AMD and healthy participants Secondary outcome measures: • serum lutein concentrations and the safety and efficacy of lutein in reducing the risk of the development of advanced AMD
Starting date	September 2009
Contact information	See clinicaltrials.gov website for details
Notes	http://clinicaltrials.gov/show/NCT01048476

AMD: age-related macular degeneration
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
ETDRS: Early Treatment Diabetic Retinopathy Study

DATA AND ANALYSES

Comparison 1. Multivitamin antioxidant vitamin or mineral supplement versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity: mean	4	161	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.14, 0.49]
1.1 Mean visual acuity at end of study	2	79	Std. Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.45, 0.45]
1.2 Change in visual acuity	2	82	Std. Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.10, 0.79]
2 Progression of AMD			Other data	No numeric data

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	1942	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)	0.0 [0.0, 0.0]
2.2 Change in visual acuity	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Progression of 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

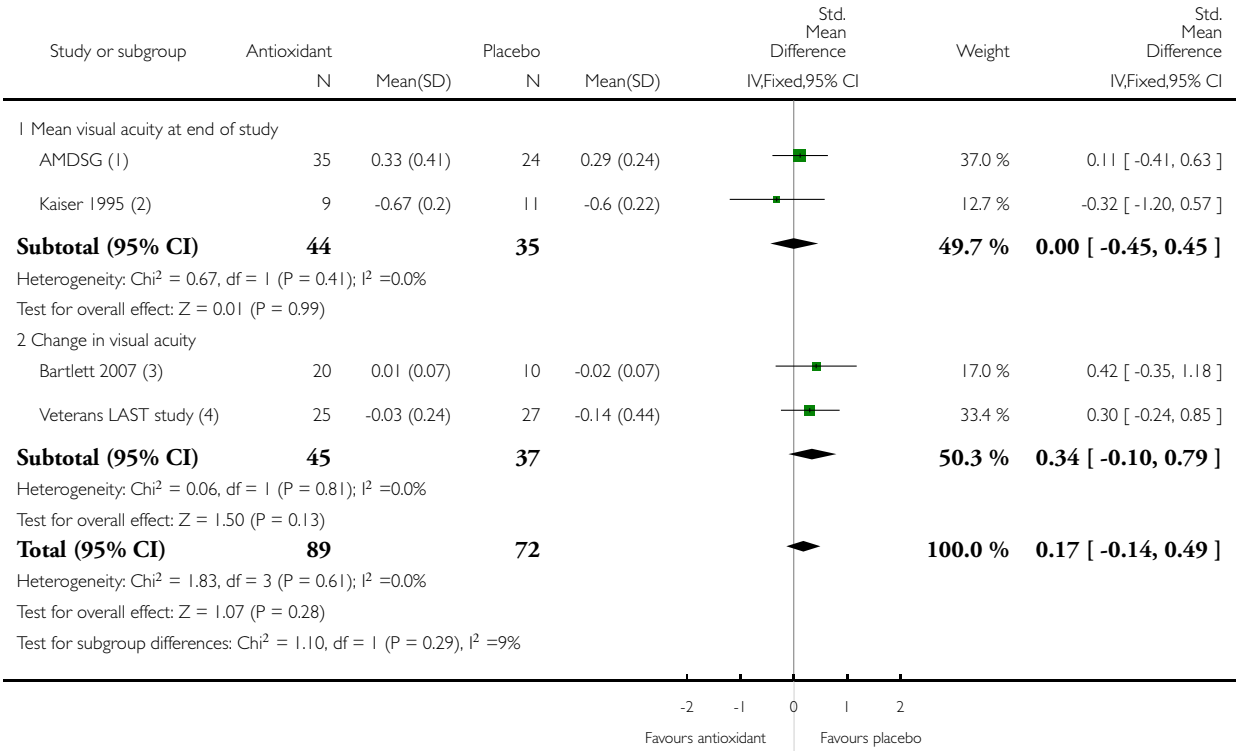
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity: loss of 3 or more lines	3	4970	Odds Ratio (Fixed, 95% CI)	0.81 [0.67, 0.98]
2 Distance visual acuity: mean	7		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Mean visual acuity at end of study	4		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Change in visual acuity	3		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Progression AMD: dichotomous	4		Odds Ratio (Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Multivitamin antioxidant vitamin or mineral 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 antioxidant vitamin or mineral supplement versus placebo

Outcome: 1 Distance visual acuity: mean



(1) Right eye: LogMAR score (converted from Snellen decimal acuity) at 18 months

(2) Study eye: Snellen acuity (expressed as decimal) at six months,

(3) Study eye: Change in logMAR score (EDTRS chart) over 9 months

(4) Right eye: Change in logMAR score (converted from Snellen decimal acuity) over 12 months

Analysis 1.2. Comparison 1 Multivitamin antioxidant vitamin or mineral supplement versus placebo, Outcome 2 Progression of AMD.

Progression of AMD

Study	Outcome	Antioxidant group	Placebo group	Comment
AMDSG	Right eye: Mean (SD) grade at end of study (18 months follow-up)	3.08 (1.22)	3.31 (1.08)	Chesapeake Bay Waterman Study grading system (scale with four categories). Higher grades reflect more severe disease

Bartlett 2007	Study eye: Mean (SD) change in grade (over 9 months)	0.1 (0.3)	0.3 (0.1)	AREDS AMD classification system (scale with four categories). Higher grades reflect more severe disease

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 N	Placebo N	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
AREDS (1)	897	894	-0.19845 (0.104457)		97.2 %	0.82 [0.67, 1.01]
Newsome 1988 (2)	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: Chi^2 = 0.99, df = 1 (P = 0.32); I^2 =0.0%

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

Test for subgroup differences: Not applicable

(1) By person (event in at least one eye): ETDRS chart over an average of 6.3 years

(2) Study eye: ETDRS chart over 24 months

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 N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 Mean visual acuity at end of study						
Stur 1996 (1)	37	0.05 (0.12)	41	0.03 (0.14)		0.15 [-0.29, 0.60]
2 Change in visual acuity						
Newsome 1988 (2)	40	4.1 (6.2)	37	7.1 (10.95)		-0.34 [-0.79, 0.11]

(1) Study eye: LogMAR score (Bailey-Lovie chart) at 24 months

(2) Study eye: Change in number of correct letters (EDTRS chart) 19 to 24 months

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

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

Comparison: 2 Zinc versus placebo

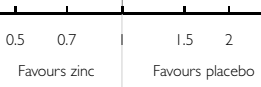
Outcome: 3 Progression of AMD: dichotomous

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 (1)	904	903	-0.3425 (0.1266)		95.8 %	0.71 [0.55, 0.91]
Holz 1993 (2)	28	30	-0.6931 (1.1533)		1.2 %	0.50 [0.05, 4.79]
Stur 1996 (3)	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: Chi^2 = 2.82, df = 2 (P = 0.24); I^2 =29%

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

Test for subgroup differences: Not applicable



(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up

(2) By person: "new exudative or dry macular lesions" over 12 to 24 months

(3) Study eye: incidence of exudative AMD over 24 months

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 (1)	2737	903	-0.2614 (0.1113)		75.4 %	0.77 [0.62, 0.96]
Newsome 1988 (2)	80	71	-0.8159 (0.6123)		2.5 %	0.44 [0.13, 1.47]
VECAT (3)	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: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%

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

Test for subgroup differences: Not applicable

(1) By person (event in at least one eye): ETDRS chart over an average of 6.3 years

(2) Study eye: ETDRS chart over 24 months

(3) Worse eye: Loss of 2 or more lines, Bailey-Lovie chart over four years

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	Std. Mean Difference IV,Random,95% CI
1 Mean visual acuity at end of study						
AMDSG (1)	35	0.33 (0.41)	24	0.29 (0.24)		0.11 [-0.41, 0.63]
Kaiser 1995 (2)	9	-0.67 (0.2)	11	-0.6 (0.22)		-0.32 [-1.20, 0.57]
Newsome 2008 (3)	37	-43.43 (4.77)	37	-39.24 (5.6)		-0.80 [-1.27, -0.32]
Stur 1996 (4)	37	0.046 (0.12)	41	0.03 (0.14)		0.14 [-0.30, 0.59]
2 Change in visual acuity						
Bartlett 2007 (5)	20	0.01 (0.07)	10	-0.02 (0.07)		0.42 [-0.35, 1.18]
Newsome 1988 (6)	40	4.1 (6.2)	37	7.1 (10.95)		-0.34 [-0.79, 0.11]
Veterans LAST study (7)	25	-0.03 (0.24)	27	-0.14 (0.44)		0.30 [-0.24, 0.85]

(1) Right eye: LogMAR score (converted from Snellen decimal acuity) at 18 months

(2) Study eye: Snellen acuity (expressed as decimal) at 6 months

(3) Right eye: Number of letters correctly identified (EDTRS chart) at 6 months

(4) Study eye: LogMAR acuity (Bailey Lovie chart) at 24 months

(5) Study eye: Change in logMAR score (EDTRS chart) over 9 months

(6) Study eye: Number of letters lost (EDTRS chart) over 24 months

(7) Right eye: Change in logMAR score (converted from Snellen decimal acuity) over 12 months

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 (1)	2737	903	-0.3857 (0.1242)		0.68 [0.53, 0.87]
Holz 1993 (2)	28	30	-0.6931 (1.1533)		0.50 [0.05, 4.79]
Stur 1996 (3)	37	41	0.8391 (0.7073)		2.31 [0.58, 9.26]
VECAT (4)	587	592	0.1033 (0.1696)		1.11 [0.80, 1.55]

(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up

(2) By person: "new exudative or dry macular lesions" over 12 to 24 months

(3) Study eye: incidence of exudative AMD over 24 months

(4) Worse eye: development of early AMD over four years

ADDITIONAL TABLES

Table 1. Outcome reporting matrix

	√ reported	Loss of 3 or more lines visual acuity	Visual acuity continuous scale	Progression of disease: dichotomous	Progression of disease: continuous	Comment
1	AMDSG	F	✓	F	✓	
2	AREDS	✓	F	✓	F	
3	Bartlett 2007	F	✓	F	✓	
4	CARMIS	F	C	H	H	
5	Holz 1993	A	A	✓	H	Abstract only
6	Kaiser 1995	F	✓	A	A	
7	LISA	F	✓	E	F	
8	Newsome 1998	✓	✓	✓	F	

Table 1. Outcome reporting matrix (*Continued*)

9	Newsome 2008	F	✓	H	H	
10	Stur 1996	F	✓	✓	H	
11	VECAT	A	A	✓	H	
12	Veterans LAST study	F	✓	F	✓	
13	Wang 2004	E	E	✓	H	Limited translation only

See Appendix 10 for full ORBIT classification.

A: Trial report states that outcome was analysed but only reports that result was not significant (typically stating P > 0.05) (high risk of bias).

C: Trial report states that outcome was analysed but insufficient data were presented for the trial to be included in meta-analysis or to be considered to be fully tabulated (low risk of bias).

E: Clear that outcome was measured but not necessarily analysed. Judgement says likely to have been analysed but not reported because of non-significant results (high risk of bias).

F: Clear that outcome was measured but not necessarily analysed. Judgement says unlikely to have been analysed but not reported because of non-significant results (low risk of bias).

H: Not mentioned but clinical judgement says unlikely to have been measured at all (low risk of bias).

Table 2. Supplementary information on trials

Study	Type of AMD	Treatment (dose/day)	Treatment duration	Follow-up	Data on eyes or people?	Visual acuity	Progression AMD	Notes
AMDSG	Early AMD	Ocuguard: 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)	18 months	18 months	Right and left eyes reported separately	Measured using Snellen chart but reported in logMAR: units	Based on Chesapeake Bay grading but using indirect ophthalmoscopy: expressed as an average grade	

Table 2. Supplementary information on trials (*Continued*)

		5 mg Rutin (bioflavonoid 50 mg Zinc picolinate 12.5 mg Selenium 50 µg Taurine 100 mg N-acetyl cysteine 100 mg l-glutathione 5 mg Vitamin B_2 25 mg Chromium 100 µg)						
AREDS	AMD and VA 20/32 or better in 1 eye 956/3640 had AMD	Antioxidants: Vitamin C 500 mg Vitamin E 400 IU Beta-carotene 15 mg) Zinc (zinc oxide 80 mg) Cupric oxide 2 mg Factorial design Antioxidants x zinc	Average duration 6.3 years	Average follow-up 6.3 years, 2.4% lost to follow-up	Person, outcome "in at least one eye"	Loss of 3 or more lines VA (equivalent to doubling visual angle) measured using ETDRS chart	Progression to advanced AMD: photocoagulation or other treatment for CNV; GA involving centre of the macula, RPE detachment, haemorrhage under the retina, subretinal fibrosis. Colour fundus photography	
Bartlett 2007	Soft or hard drusen, and areas of increased or decreased pigment asso-	Lutein esters 6 mg Retinol 750 mg Vitamin C 250 mg Vitamin E	9 months	9 months	Trial eye selected (initial visit only) If both eyes were eligible for in-	Change in logMAR acuity measured using ETDRS chart	Fundus photographs graded using AREDS classification system (4 cate-	

Table 2. Supplementary information on trials (*Continued*)

	ciated with these drusen	34 mg Zinc 10 mg Copper 0.5 mg			clusion, the right eye was used		gories) . Mean (SD) grade was reported	
CARMIS	AMD in at least 1 eye having extensive (as measured by drusen area) intermediate (>= 63 mm, < 125 mm) drusen; and at least one large (>= 125 mm) drusen or geographic atrophy not involving the centre of the macula	Vitamin C 180 mg Vitamin E 30 mg Zinc 22.5 mg Copper 1 mg Lutein 10 mg Zeaxanthin 1 mg Astaxanthin 4 mg	24 months	24 months	The eye with the best VA was selected. When both eyes had the same VA, the right eye was chosen for final analysis	Letters and lines reported as continuous variable (ETDRS chart)	Not reported	
Holz 1993	People with drusen	Zinc sulfate 200 mg	Not stated but assume same as follow-up duration	12 to 24	Unclear but assumed to be people	Not reported	"Incidence of new exudative or dry macula lesions"	
Kaiser 1995	"Nonserous AMD"	Visaline: Buphenine HCL 1.5 mg Beta-carotene 10 mg Tocopherol acetate 10 mg Vitamin C 50 mg	6	6	Study eye identified	Decimal acuity measured using a Snellen chart	Not reported	
LISA	AREDS categories 2, 3	Lutein 20 mg a day	6	6	Study eye identified. If	Reported in graph form,	Not reported	

Table 2. Supplementary information on trials (*Continued*)

	or 4	for 3 months and then lutein 10 mg a day for 3 months			both eyes were eligible, one eye was selected randomly	not possible to extract data. Measured using ETDRS chart		
Newsome 1988	Drusen and/or pigmentary change, VA 20/80 or better	Zinc sulfate 200 mg	12 to 24	12 to 24	Reported by eye and also data from 2 eyes averaged	Number of letters lost on EDTRS chart	Difficult to extract data on this. Reported number with increased pigment, drusen and atrophy for 2 observers. In general found results favouring the zinc-treated group	
Newsome 2008	Presence of macular drusen with or without pigment changes	Zinc-monocysteine 25 mg	6 months	6 months	Right and left eyes reported separately	Number of letters read on EDTRS chart	Not reported	
Stur 1996	Neovascular AMD in 1 eye, VA better than 20/40 in other eye	Zinc sulfate 200 mg	24	24	"Study eye" which was fellow eye, other eye had neovascular AMD	Mean logMAR score measured using Bailey-Lovie chart 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 "did not show any treatment benefit"

Table 2. Supplementary information on trials (*Continued*)

VECAT	Early AMD (18%) Late AMD (0.5%) Rest presumably had no signs of AMD	Vitamin E 500 IU	48	48	"Worse eye"	Loss of more than 9 letters (2 or more lines) on (Bailey-Lovie chart	Investigators defined 6 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 10 mg Ocupower: Natural beta-carotene (Betatenem) 15,000 IU Vitamin C 1500 mg (as calcium ascorbate-Ester CB) Vitamin D3 400 IU Vitamin E 500 IU (d-alpha tocopherol succinate) Vitamin B1 50 mg Vitamin B2 10 mg Vitamin B3 70 mg Vitamin B5 50 mg Vitamin B6 50 mg Vitamin B12 500 µg Folic acid	12 months	12 months	Right and left eyes reported separately	Change in logMAR score. Measured using Snellen chart but reported in logMAR: units	Data not reported	

Table 2. Supplementary information on trials (*Continued*)

		800 µg Biotin 300 µg Calcium 500 mg Magnesium 300 mg Iodine 75 µg Zinc 25 mg (as zinc L-methionine-L-OptiZ-incB) Copper 1 mg Manganese 2 mg Selenium 200 µg Chromium 200 µg Molybdenum 75 µg Lycopene 600 µg Bilberry extract 160 mg (standardised to 25% anthocyanosides) Alpha lipoic acid 150 mg N-acetyl cysteine 200 mg Quercetin 100 mg Rutin 100 mg Citrus bioflavonoids 250 mg Plant enzymes 50 mg Black pepper extract 5 mg (BioperineB)						

Table 2. Supplementary information on trials (*Continued*)

		Malic acid 325 mg Taurine 900 mg L-glycine 100 mg L-glutathione 10 mg Boron 2 mg						

AMD: age-related macular degeneration
CNV: choroidal neovascularisation
ETDRS: Early Treatment Diabetic Retinopathy Study
GA: geographic atrophy
RPE: retinal pigment epithelium
VA: visual acuity

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Degeneration
#2 MeSH descriptor Retinal Degeneration
#3 MeSH descriptor Retinal Neovascularization
#4 MeSH descriptor Choroidal Neovascularization
#5 MeSH descriptor Macula Lutea
#6 macula* near lutea*
#7 ((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 (OvidSP) search strategy

1. randomized controlled trial.pt.
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. (macula$ adj2 lutea).tw.
19. ((macul$ or retina$ or choroid$) adj4 degener$).tw.
20. ((macul$ or retina$ or choroid$) adj4 neovasc$).tw.
21. (AMD or ARMD or CNV).tw.
22. maculopath$.tw.
23. or/13-22
24. exp vitamins/
25. exp vitamin A/
26. vitamin A.tw.
27. retinol$.tw.
28. exp beta carotene/
29. (caroten$ or betacaroten$).tw.
30. exp ascorbic acid/

31. ascorbic acid$.tw.
32. vitamin C.tw.
33. exp Vitamin E/
34. exp alpha tocopherol/
35. alpha?tocopherol$.tw.
36. alpha tocopherol$.tw.
37. vitamin E.tw.
38. exp Vitamin B12/
39. vitamin B12.tw.
40. cobalamin$.tw.
41. exp antioxidants/
42. ((antioxidant$ or anti) adj1 oxidant$).tw.
43. exp carotenoids/
44. carotenoid$.tw.
45. exp zinc/
46. zinc$.tw.
47. exp riboflavin/
48. riboflavin$.tw.
49. exp selenium/
50. selenium$.tw.
51. exp lutein/
52. lutein$.tw.
53. exp xanthophylls/
54. xanthophyll.tw.
55. zeaxanthin$.tw.
56. or/24-55
57. 23 and 56
58. 12 and 57

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

Appendix 3. EMBASE (OvidSP) search strategy

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

21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula degeneration/
34. exp retina degeneration/
35. exp retina neovascularization/
36. exp subretinal neovascularization/
37. (AMD or ARMD or CNV).tw.
38. ((macul$ or retina$ or choroid$) adj4 degener$).tw.
39. ((macul$ or retina$ or choroid$) adj4 neovasc$).tw.
40. exp retina macula lutea/
41. (macula$ adj2 lutea$).tw.
42. maculopath$.tw.
43. or/33-42
44. exp vitamins/
45. exp Retinol/
46. vitamin A.tw.
47. retinol$.tw.
48. exp beta carotene/
49. (caroten$ or betacaroten$).tw.
50. exp ascorbic acid/
51. ascorbic acid$.tw.
52. vitamin C.tw.
53. exp alpha tocopherol/
54. alpha?tocopherol$.tw.
55. alpha tocopherol$.tw.
56. vitamin E.tw.
57. vitamin B12.tw.
58. exp cyanocobalamin/
59. cobalamin$.tw.
60. exp antioxidants/
61. ((antioxidant$ or anti) adj1 oxidant$).tw.
62. exp carotenoid/
63. exp zinc/
64. zinc$.tw.
65. exp riboflavin/
66. riboflavin$.tw.
67. exp selenium/
68. selenium$.tw.
69. exp zeaxanthin/
70. zeaxanthin$.tw.
71. lutein$.tw.
72. xanthophyll.tw.
73. or/44-72

74. 43 and 73
75. 32 and 74

Appendix 4. AMED (OvidSP) search strategy

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

Appendix 5. OpenGrey search strategy

macular degeneration AND antioxidant

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

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

Appendix 7. ClinicalTrials.gov search strategy

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

Appendix 8. ICTRP search strategy

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

Appendix 9. MEDLINE (OvidSP) adverse effects search strategy

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

Appendix 10. ORBIT classification

The Outcome Reporting Bias In Trials (ORBIT) study classification system for missing or incomplete outcome reporting in reports of randomised trials

Description		Level of reporting	Risk of bias*
Clear that the outcome was measured and analysed			
A	Trial report states that outcome was analysed but only reports that result was not significant (typically stating P > 0.05)	Partial	High risk
B	Trial report states that outcome was analysed but only reports that result was significant (typically stating P < 0.05)	Partial	No risk
C	Trial report states that outcome was analysed but insufficient data were presented for the trial to be included in meta-analysis or to be considered to be fully tabulated	Partial	Low risk
D	Trial report states that outcome was analysed but no results reported	None	High risk
Clear that the outcome was measured			
E	Clear that outcome was measured but not necessarily analysed. Judgement says likely to have been analysed but not reported because of non-significant results	None	High risk
F	Clear that outcome was measured but not necessarily analysed. Judgement says unlikely to have been analysed but not reported because of non-significant results	None	Low risk
Unclear whether the outcome was measured			
G	Not mentioned but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results	None	High risk

(*Continued*)

H	Not mentioned but clinical judgement says unlikely to have been measured at all	None	Low risk
Clear that the outcome was not measured			
I	Clear that outcome was not measured	NA	No risk

Appendix 11. Results of searches for previous versions of this review

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, we made no further attempt 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 1998a). 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 Wang 2004 and have been incorporated into the review. The searches were updated in January 2006 and August 2007 but no new trials were identified.

WHAT'S NEW

Last assessed as up-to-date: 20 August 2012.

Date	Event	Description
11 July 2012	New search has been performed	Issue 9, 2012: John Lawrenson assisted with this review update
11 July 2012	New citation required but conclusions have not changed	Issue 9, 2012: Update searches were conducted and 3 new trials have been added to the review

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 1, 1998

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

CONTRIBUTIONS OF AUTHORS

JE wrote the protocol and completed the first published version of this review.

JGL checked all the data in the originally published review.

For this update (2012) both authors searched for new studies, did 'Risk of bias' assessment and extracted data. JE cut and pasted data into RevMan and updated the text. JGL checked the data and provided comments on the text.

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.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol was published in 1996. Since then there have been several improvements in review methods including:

- Risk of bias assessment;
- Summary of findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Aged; Humans