Eye (2008) 22, 751–760

www.nature.com/eye

REVIEW

Antioxidant supplements to prevent or slow down the progression of AMD: a systematic review and meta-analysis

J Evans

Abstract

Introduction **The aim of this review was to examine the evidence as to whether antioxidant vitamin or mineral supplements prevent the development of AMD or slow down its progression.**

Methods **Randomised trials comparing antioxidant vitamin and/or mineral supplement to control were identified by systematic electronic searches (updated August 2007) and contact with investigators. Data were pooled after investigating clinical and statistical heterogeneity.**

Results **There was no evidence that antioxidant (vitamin E or β-carotene) supplementation prevented AMD. A total of 23 099 people were randomised in three trials with treatment duration of 4–12 years; pooled risk ratio = 1.03 (95% CI, 0.74–1.43). There was evidence that antioxidant (β-carotene, vitamin C, and vitamin E) and zinc supplementation slowed down the progression to advanced AMD and visual acuity loss in people with signs of the disease (adjusted odds ratio = 0.68, 95% CI, 0.53–0.87 and 0.77, 95% CI, 0.62–0.96, respectively). The majority of people were randomised in one trial (AREDS, 3640 people randomised). There were seven other small trials (total randomised 525).**

Conclusions **Current evidence does not support the use of antioxidant vitamin supplements to prevent AMD. People with AMD, or early signs of the disease, may experience some benefit from taking supplements as used in the AREDS trial. Potential harms of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (β-carotene), heart failure in people with vascular disease or diabetes (vitamin E) and hospitalisation for genitourinary conditions (zinc).**

Eye (2008) **22,** 751–760; doi:10.1038/eye.2008.100; published online 18 April 2008

Keywords: age-related macular degeneration; antioxidant supplements; systematic review

Introduction

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.[1]

There are a number of non-experimental studies that have examined the possible association between antioxidant micronutrients, although few studies have examined supplementation specifically.[2] 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. Inconsistent results have been found in these observational studies.

Antioxidant vitamin and mineral supplements are increasingly being marketed for use in age-related eye disease, including AMD. This article summarises the results of two

International Centre for Eye Health, London School of Hygiene and Tropical Medicine (LSHTM), London, UK

Correspondence: J Evans, International Centre for Eye Health, London School of Hygiene and Tropical Medicine (LSHTM), Keppel Street, London WC1E 7HT, UK. Tel: +207 958 8316; Fax: +207 436 4230. E-mail: jennifer.evans@lshtm.ac.uk

Received: 19 September 2007
Accepted in revised form: 30 January 2008
Published online: 18 April 2008

Conflict of interest: None.

comprehensive regularly updated systematic reviews published on the Cochrane Library.[3,4] Two questions are addressed: firstly, should the general population be taking routine antioxidant and vitamin mineral supplements to prevent or delay the onset of AMD in later life? Secondly, should people with AMD be taking these supplements to slow down the progression of the disease?

Methods

This review included randomised trials comparing antioxidant vitamin and/or mineral supplementation (alone or in combination) to control. Antioxidants were defined as any vitamin or mineral, which is known to have antioxidant properties *in vivo* or, which is known to be an important component of an antioxidant enzyme present in the retina. We considered the following: vitamin C, vitamin E, carotenoids, selenium, and zinc. AMD was defined as the presence of geographic atrophy or neovascular disease. Age-related maculopathy (ARM) was used as an overall term encompassing both early age-related macular changes (large soft drusen, hyper- and/or hypo-pigmentation) and AMD.[5,6]

Two main outcome measures were considered: development and progression of ARM and AMD and loss of vision. Quality of life was considered but not reported in the included trials. Information on adverse events was collected.

Comprehensive systematic searches were done.[3,4] In brief, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in The Cochrane Library, MEDLINE, SIGLE, EMBASE, National Research Register, AMED and PubMed, reference lists of identified reports, and the Science Citation Index. We contacted investigators and experts in the field for details of unpublished studies. Searches were updated in August 2007.

Titles and abstracts of all reports of trials identified by the searches were assessed and full texts of possibly relevant trials were obtained. Trials were selected according to prespecified inclusion criteria.[3,4] Five parameters of trial quality were assessed: allocation concealment, method of allocation to treatment, documentation of exclusions, masking of outcome assessment, and completeness of follow-up.[7] Each parameter of trial quality was graded: A, low risk of bias; B, moderate risk of bias; or C, high risk of bias. Trials scoring C on allocation concealment (ie, where allocation was not concealed properly) were excluded.

Heterogeneity was assessed by examining the forest plot to see whether the effect measures for the different studies were in the same direction and of a similar order of effect and by the I^2 value.[8] An I^2 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. A random effects model was used to pool the data, unless there were three or fewer trials in which case a fixed effect model was used. The main clinical diversity was with respect to the type of supplement. This was incorporated into the analysis strategy by considering the formulations by type. The methodological quality of the studies was reported and used to interpret the results. Currently, there are not enough published studies to enable sensitivity analysis or formal assessment of publication bias; however, the forest plots were reviewed to see whether smaller studies were reporting larger effects.

Trials in this area fall into two broad categories: those evaluating a single vitamin or mineral (eg, vitamin E or zinc) and those investigating a broad spectrum formulation (eg, Ocuguard). The following comparisons were considered in this review.

(1) Broad-spectrum formulation *vs* placebo. Within this category fall all the broad-spectrum formulations, which include one or more antioxidant vitamins or minerals.
(2) Single-component formulations *vs* placebo, eg, vitamin E alone.
(3) Broad-spectrum or single component studies together. For the progression of AMD, this comparison was subject to considerably clinical, methodological, and statistical heterogeneity and is not reported here.

Results

Results are presented for the included trials. Details of the excluded studies are available in Evans and Henshaw[3] and Evans.[4]

Prevention of AMD

Table 1 shows the trials investigating the primary prevention of AMD. In the Alpha-Tocopherol and Beta-Carotene (ATBC) Study in Finland, 29 133 male smokers were randomly allocated to α-tocopherol (vitamin E) (50 mg/day), β-carotene (20 mg/day), vitamin E or β-carotene, or placebo.[9] Treatment ranged from 5 to 8 years. A random sample of 1035 men aged 65 years and above were sampled at the end of the study and fundus photographs were taken and graded for ARM and AMD. In the Physicians' Health Study in the USA, 22 071 male physicians were randomised to aspririn (325 mg every other day), β-carotene (50 mg every other day), aspirin, and β-carotene or placebo.[10] Treatment duration ranged

Table 1 Trials investigating antioxidant vitamin and mineral supplements in the prevention of AMD

Study	*Interventions*	*Duration of treatment*	*Participants*	*Ascertainment of AMD*
α-tocopherol and β-carotene study (ATBC) Finland	Vitamin E (dl-α-tocopheryl acetate) (50 mg/day equivalent approx 110 IU) β-carotene (20 mg/day) Vitamin E or β-carotene Placebo.	Range 5–8 years Median 6.1 years	29 133 male smokers aged 50–69 years in 1984. Random sample of 1035 people aged 65 and over in 1992/3 selected for maculopathy study	Photographic grading
Physicians' Health Study (PHS I) USA	Aspirin (325 mg every other day) plus β-carotene placebo β-carotene (50 mg every other day) plus aspirin placebo Aspirin and beta-carotene Placebo	Range 11.6–14.2 years Mean 12 years	22 071 male physicians aged 40–84 years in 1982. 21 142 men provided information on ARM	AMD ascertained by self-report followed by medical record review.
Vitamin E Cataract and Age-related maculopathy Trial (VECAT) Australia	Vitamin E (dl-α-tocopherol 500 IU/day) Placebo	4 years	1193 men and women aged 55–80 years (average age 66 years). 56% female. 18% had some evidence of ARM at baseline	Photographic grading

from 11.6 to 14.2 years. A total of 21 142 men provided self-reported information on AMD, which was confirmed by medical record review.[11] In the Vitamin E cataract and ARM trial, 1204 men and women aged 55–80 years were randomly allocated vitamin E (335 mg/day) or placebo and followed up for 4 years.[12] In all, 82% of the participants in this study had no evidence of ARM at enrolment which is why this trial is included in the prevention rather than progression of AMD results. Conversely, the Age-Related Eye Disease Study (AREDS) enrolled mostly people with signs of ARM and outcome data were not reported on the 1117 people without ARM at enrolment.[13] AREDS is discussed below under the progression of AMD.

All three trials were of high quality and scored 'low risk of bias' on all quality parameters. Allocation was concealed by means of coded tablets and randomly assigned; exclusions were documented and follow-up was equal between the study groups; outcome assessment was masked to study group and analysis was intention-to-treat.

In ATBC, 728 people were randomised to any antioxidant and 213 to placebo.[9] There was no association of treatment group with any sign of maculopathy. There were 216 cases of ARM in the antioxidant groups and 53 in the placebo group (risk ratio (RR) = 1.19, 95% confidence interval (CI), 0.92–1.54). The majority of these cases were early ARM. There were only 14 cases of AMD. Of these, four were geographic atrophy and 10 neovascular disease. There was only one case of geographic atrophy in the placebo group. All the other cases of late stage disease occurred in the antioxidant groups. The findings are similar when each of the antioxidant groups—vitamin E, β-carotene, vitamin E, and β-carotene—are compared with placebo.

In PHS I, there were 162 cases of ARM causing visual loss of 6/9 or worse in the β-carotene group *vs* 170 cases in the placebo group (RR = 0.96, 95% CI, 0.78–1.20).[11] Secondary end points of ARM with or without vision loss (275 *vs* 274 cases, RR = 1.01, 95% CI, 0.86–1.20) and AMD(63 *vs* 66 cases, RR = 0.97, 95% CI, 0.69–1.37) were reported.

In VECAT, there were 92/504 in the vitamin E group with ARM compared to 92/512 in the placebo group (RR = 1.02, 95% CI, 0.78–1.32).[12] The majority of these cases were early ARM. There were nine cases of late AMD, five in the treatment group and four in the placebo group.

Overall 23 099 participants were randomised in the three trials. There were 583 cases of ARM in the antioxidant groups and 419 cases of ARM in the placebo groups (Figure 1). The results of the three studies were consistent ($I^2 = 0\%$). There was little evidence of any effect of antioxidant supplementation (RR = 1.04, 95% CI, 0.92–1.18). Similarly, for AMD, the trials were consistent and indicate little evidence of any effect of supplementation (RR = 1.03, 95% CI, 0.74–1.43) (Figure 2). There were fewer AMD events (81 antioxidant, 71 placebo).

There was less evidence available comparing vitamin E alone *vs* placebo. A total of 1466 people randomised in VECAT and ATBC resulted in 167 cases of ARM in the

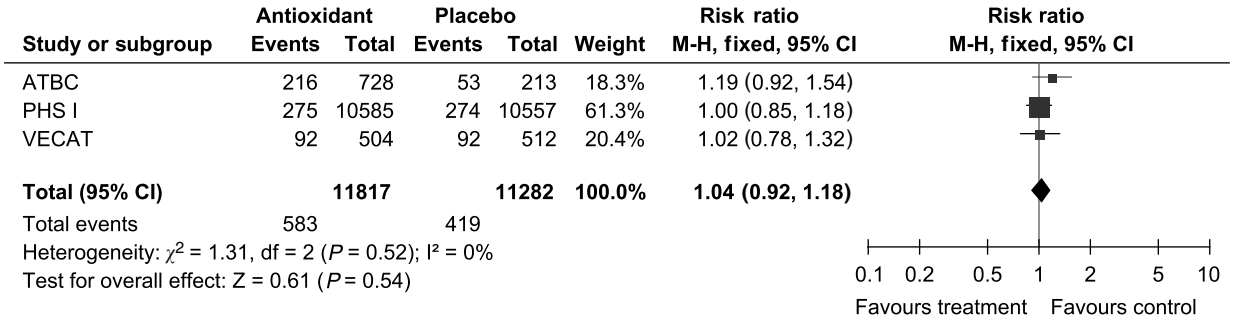

Figure 1 ARM in people given antioxidant vitamin supplements compared to people given placebo. ARM, age-related maculopathy; ATBC, vitamin E (dl-α-tocopheryl acetate 50 mg (approx 110 IU)/day) and β-carotene (20 mg/day); PHS I, β-carotene (50 mg every other day); VECAT, vitamin E (d-α tocopherol 500 IU/day).

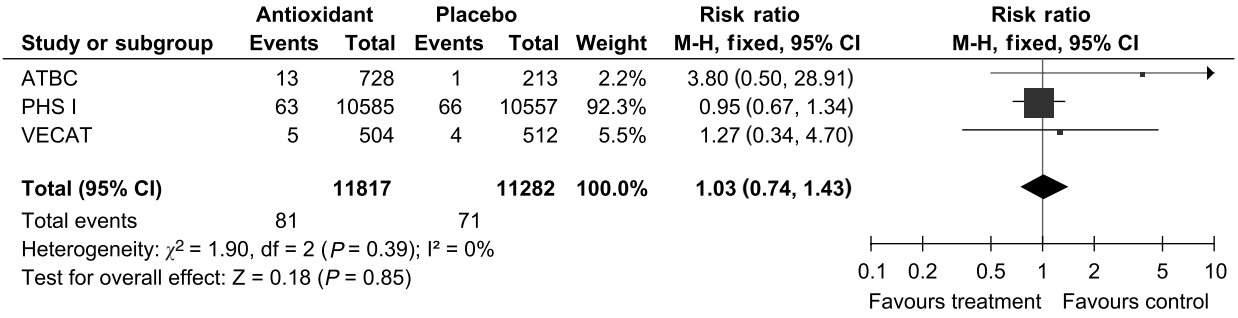

Figure 2 AMD in people given antioxidant vitamin supplements compared to people given placebo. AMD, age-related macular degeneration; ATBC, vitamin E (dl-α-tocopheryl acetate 50 mg (approx 110 IU)/day) and β-carotene (20 mg/day); PHS I, β-carotene (50 mg every other day); VECAT, vitamin E (d-α tocopherol 500 IU/day).

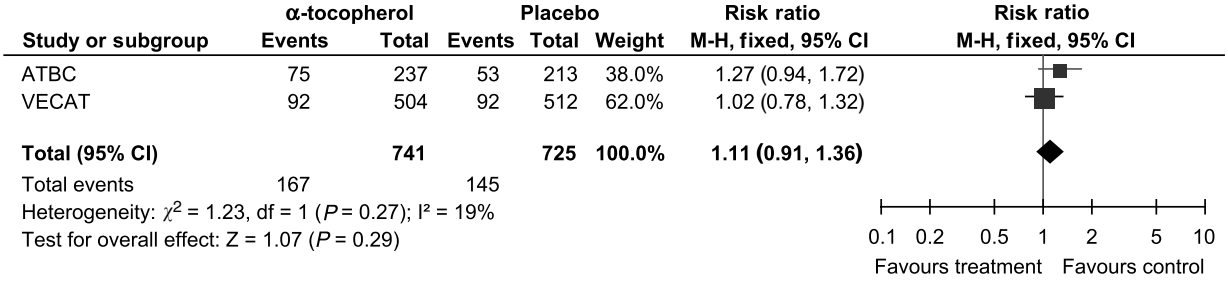

Figure 3 ARM in people given vitamin E supplements compared to people given placebo. ARM, age-related maculopathy; ATBC, vitamin E (dl-α-tocopheryl acetate 50 mg (approx 110 IU)/day); VECAT, vitamin E (d-α tocopherol 500 IU/day).

vitamin E group and 145 in the placebo group (Figure 3). The trial results were reasonably consistent, $I^2 = 19\%$. There was little evidence of any effect of supplementation with vitamin E on the incidence of ARM; RR = 1.11 (95% CI, 0.91–1.36). There were fewer cases of AMD—13 in the vitamin E groups and five in the placebo (Figure 4). All effect measures were in the direction of harm but were not consistent ($I^2 > 50\%$).

A total of 21 589 people were randomised to β-carotene or placebo in ATBC and PHS I. There were 343 cases of ARM in the β-carotene groups and 327 in the control groups (Figure 5). The results of the trials were consistent ($I^2 = 0\%$) and did not indicate any benefit of supplementation (RR = 1.03, 95% CI, 0.98–1.19). There were 65 cases of AMD in the β-carotene groups and 67 cases of AMD in the control (Figure 6). Again the results of the trials were consistent ($I^2 = 0\%$) and indicated little effect of supplementation (RR = 0.97, 95% CI, 0.69–1.36).

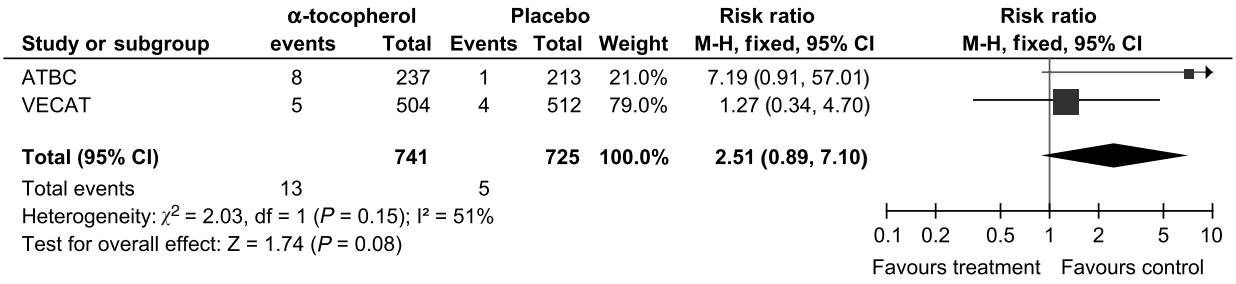

Figure 4 AMD in people given vitamin E supplements compared to people given placebo. AMD, age-related macular degeneration; ATBC, vitamin E (dl-α-tocopheryl acetate 50 mg(approx 110 IU)/day); VECAT, vitamin E (d-α tocopherol 500 IU/day).

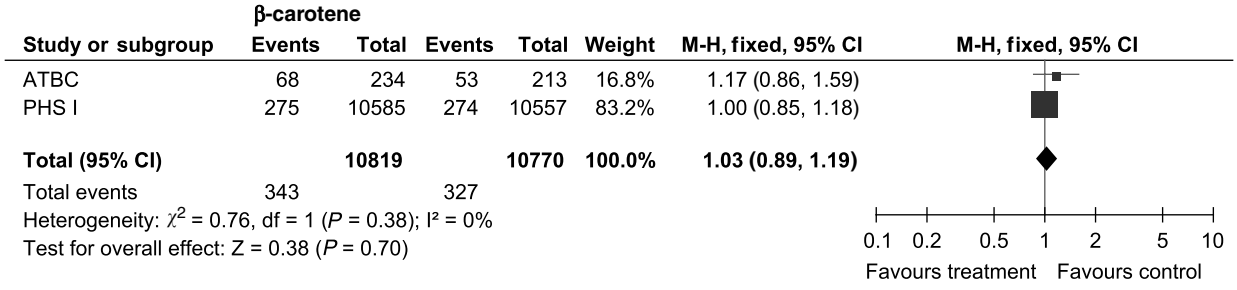

Figure 5 ARM in people given β-carotene supplements compared to people given placebo. ARM, age-related maculopathy; ATBC, β-carotene (20 mg/day); PHS I, β-carotene (50 mg every other day).

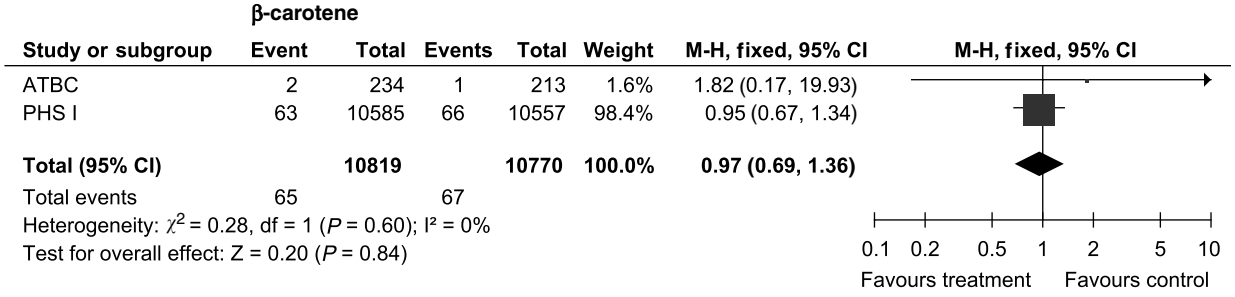

Figure 6 AMD in people given β-carotene supplements compared to people given placebo. AMD, age-related macular degeneration; ATBC, β-carotene (20 mg/day); PHS I, β-carotene (50 mg every other day).

Progression of AMD

Table 2 shows the trials investigating the effect of antioxidant supplementation on the progression of AMD.

The majority of evidence comes from one trial in the USA, AREDS, which compared four treatment groups: antioxidants (vitamin C 500 mg, vitamin E 400IU, and β-carotene 15 mg)/day, zinc (zinc oxide 80 mg and cupric oxide 2 mg), antioxidants plus zinc, and placebo.[13] A total of 3640 people were randomised. Treatment duration averaged 6.3 years. A total of 525 people have been randomised into other trials, which have evaluated a range of supplements both broad spectrum (Ocuguard,[14] Ocupower,[15] and Visaline,[16]) and single component (zinc[17,18] and lutein[15]). The smaller studies in general were of shorter duration (6–24 months) and lower quality. There have been two unpublished trials on zinc supplementation.[19,20]

In most trials, randomisation appeared to have been executed properly, ie, an unpredictable sequence of treatment allocation was concealed adequately from people recruiting participants into the trial. In AMDSG, more people in the placebo group withdrew (six) compared to the treatment group (one).[14] The description of the tablets cannot exclude the possibility that there were detectable differences between treatment and placebo that may mean that some participants in the study were unmasked. In AREDS, four people were documented as being unmasked to study group.[13] 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 in swallowing the study tablets (17.8

Table 2 Trials investigating antioxidant vitamin and mineral supplements in the progression of AMD

Study	*Interventions*	*Duration of treatment*	*Participants*	*Stage of AMD at enrolment*	*Ascertainment of AMD*
Age-related macular mdegeneration mstudy mgroup (AMDSG) USA	Ocuguard Starch placebo	18 months	71 people, average age 72 years, 66 men, five women	Early ARM	Photographic grading
Age-related eye disease study (AREDS) USA	Antioxidants (500 mg vitamin C, 400 IU vitamin E (dl-α-tocopheryl acetate), 15 mg β carotene) /day Zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide) Antioxidants and zinc Control: Placebo identical in external appearance and similar in internal appearance and taste	6 years	3640 people, average age 69 years (range 55–80). 56% women	Early ARM 29% ARM but not advanced AMD 45% Advanced AMD or reduced visual acuity due–AMD in one eye 26%	Photographic grading
Holz *et al*[a] UK	Zinc sulphate 100 mg twice daily Placebo	12–24 months	58 people aged 55–82, average age 68 years	Early ARM	Photographic grading
Kaiser *et al*[16] Switzerland	Visaline. Two tablets in the morning and at night, daily except for Saturdays and Sundays Placebo resembling active treatment prepared by sponsor	6 months	20 people aged 50 years and above, average age 72	ARM	No measures of progression
Newsome *et al*,[17] USA	Zinc sulphate 100 mg twice daily. Placebo: identical tablets with lactose and fructose.	12–24 months	151 people aged 42–89 years 61 men, 113 women	Early ARM and AMD	Photographic grading
Stur *et al*,[18] Austria	Zinc sulphate 200 mg once daily. Lemon flavoured effervescent tablet made of citric acid containing saccharine and sorbitol Placebo: as treatment but without zinc sulphate	24 months	112 people aged 50 years and above, 48 men, 64 women	Neovascular AMD in one eye and early ARM in fellow eye	Photographic grading
Veterans LAST study USA	Lutein 10 mg non-esterified lutein Ocupower Control: maltodextrin	12 months	90 people, average age 75 years, 86 men 4 women	Early ARM	

Visaline: buphenine HCl1.5 mg, β-carotene 10 mg, tocopherol acetate 10 mg, and ascorbic acid 50 mg.
Ocuguard: β-carotene 20 000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercitin (bioflavonoid) 50 mg, bilberry extract (bioflavonoid) 5 mg, rutin (bioflavonoid) 50 mg, zinc picolinate 12.5 mg, selenium 50 mcg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 mcg.
Ocupower: lutein 10 mg, vitamin A 2500 IU, β-carotene 15 000 IU, vitamin C 1500 mg, vitamin D3 400 IU, vitamin E 500 IU, vitamin B1 50 mg, B2 10 mg, B3 70 mg, B5 50 mg, B6 50 mg, B12 500 mcg, folic acid 800 mcg, biotin 300 mcg, calcium 500 mg, magnesium 300 mg, iodine 75 mcg, zinc 25 mg, copper 1 mg, manganese 2 mg, selenium 200 mcg, chromium 200 mcg, molybdenum 75 mcg, lycopene 600 mcg, bilberry extract 160 mg, 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, malic acid 325 mg, taurine 900 mg, L-glycine 100 mg, L-glutathione 10 mg, boron 2 mg.
[a]Published in abstract form only.

vs 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 percentage 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.[15] In Stur *et al*,[18] analysis of the main outcome measures (visual function and progression of disease) was not carried out on a strictly intention-to-treat basis as anyone experiencing the endpoint of late-stage AMD (neovascularisation) was withdrawn from the study. Contact with the trial investigator revealed that all of these participants ended up with visual acuity of 20/200 or less and that these participants were excluded because the investigators wished to detect functional changes caused by degeneration of the retinal pigment epithelium and the sensory retina, and not vision losses caused by choroidal neovascularisation.

AREDS was the only trial reporting progression of AMD and visual acuity loss in a dichotomous format. There was a beneficial effect of treatment on progression to AMD (odds ratio adjusted for age, sex, race, AMD category, and smoking at enrolment 0.68, 95% CI, 0.53–0.87) (Figure 7), and loss of 15 or more letters (adjusted odds ratio = 0.77, 95% CI, 0.62–0.96; Figure 8).

It was difficult to extract meaningful data on AMD progression from the smaller studies. One study reported data on the progression of AMD in a continuous format.[14] There was little evidence for any benefit of treatment (mean difference −0.06, 95% CI, −0.62 to 0.50). The number of participants in this analysis was small with 35 in the treatment group and 24 in the control group. There was some information on mean visual acuity.[14–16] A total of 69 people were randomised to treatment and 62 to placebo in pooled analyses of all three trials. Little effect of treatment on visual acuity was seen from these analyses. The pooled standardised mean difference was 0.16 (95% CI, −0.19 to 0.51). The results of these trials were consistent, $I^2 = 0$.

Four trials have reported the effect of zinc supplementation.[13,17–19] In addition, there is one unpublished study for which we have no data.[20]

Three trials provided data on progression of AMD as a dichotomous outcome[13,18,19] (Figure 9). A total of 969 people were randomised to zinc supplementation and 974 to placebo. Overall, there was a modest benefit of treatment. The pooled odds ratio was 0.73 (95% CI, 0.58–0.93). Stur *et al*[18] had quite different results to the other two trials. Over the treatment period, nine people experienced a choroidal neovascularisation (CNV) in the study eye in the zinc group compared to five people in the placebo group. However, this may have been a chance finding . The odds ratio for that trial (2.31) had wide CI and the results are, therefore, also consistent with a protective effect of treatment (95% CI, 0.58–9.26). Overall, the I^2 value was 29.0%. Holz *et al*[19] has been published in abstract form only, so we have little information about this trial.

Two trials reported dichotomous visual acuity data.[13,17] The pooled analyses include a total of 984 people randomised to zinc supplementation and 974 to placebo. There was a modest beneficial effect of treatment on visual acuity (pooled odds ratio = 0.81, 95% CI, 0.66–0.99). The trials were consistent $I^2 = 0\%$ (Figure 10).

Two trials provided data on mean visual acuity.[17,18] 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

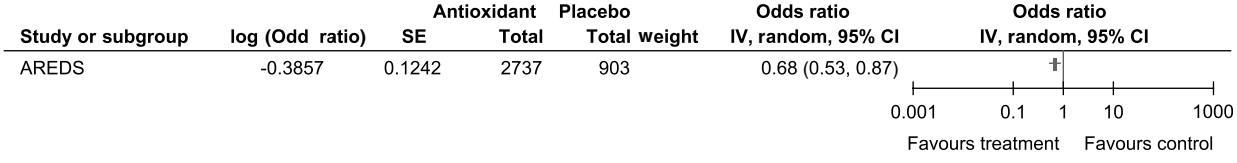

Figure 7 Progression to AMD in people with ARM given antioxidant vitamin and mineral supplements compared to placebo. ARM, age-related maculopathy; AMD, age-related macular degeneration; AREDS, vitamin C (500 mg/day), vitamin E (dl-α-tocopheryl acetate 400 IU/day), β-carotene (15 mg/day), zinc (80 mg/day).

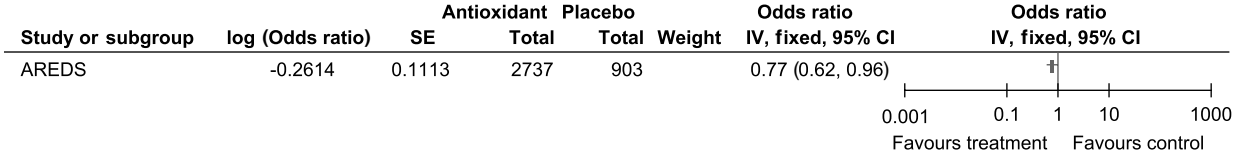

Figure 8 Loss of 15 or more letters visual acuity in people with ARM given antioxidant vitamin and mineral supplements compared to placebo. ARM, age-related maculopathy; AMD, age-related macular degeneration; AREDS, vitamin C (500 mg/day), vitamin E (dl-α-tocopheryl acetate 400 IU/day), β-carotene (15 mg/day), zinc (80 mg/day).

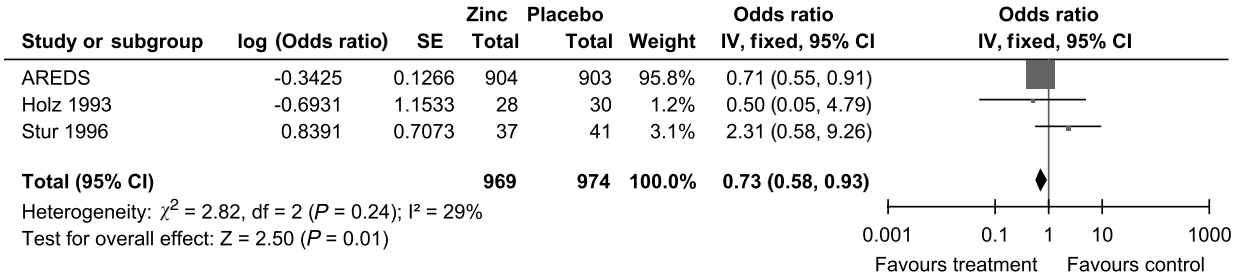

Figure 9 Progression to AMD in people with ARM given zinc supplements compared to placebo. ARM, age-related maculopathy; AMD, age-related macular degeneration; AREDS, zinc oxide (80 mg/day); Holz *et al*[19], zinc sulphate (100 mg twice daily); Stur *et al*[18], zinc sulphate (200 mg/day).

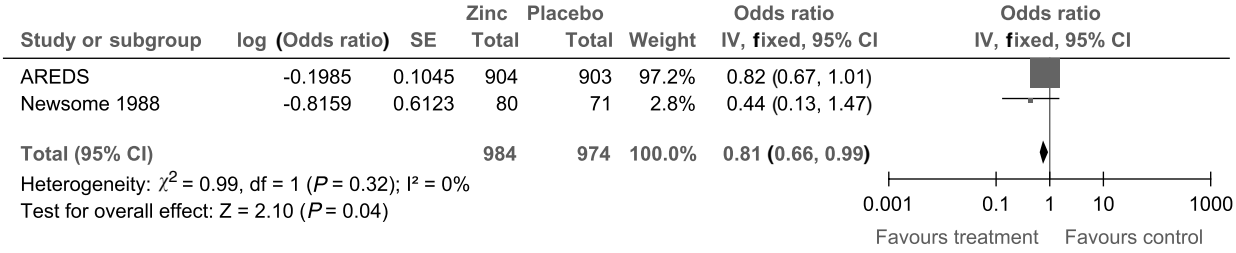

Figure 10 Loss of 15 or more letters visual acuity in people with ARM given zinc supplements compared to placebo. ARM, age-related maculopathy; AMD, age-related macular degeneration; AREDS, zinc oxide (80 mg/day); Newsome *et al*,[17] zinc sulphate (100 mg twice daily).

less consistent, $I^2 = 56.6\%$. Newsome *et al*[17] found that there was more visual acuity loss in the control group than the treatment group, although this did not reach statistical significance. Stur *et al*[18] found little difference between the two groups with respect to mean visual acuity at the end of the study. In Stur *et al*,[18] the primary outcome was incidence of CNV in all patients. During the treatment period, a CNV developed in the study eye in 14 patients (nine in the treatment group and five in the placebo group). People who experienced a CNV were not included in the analyses of visual acuity.

There has only been one trial published to date comparing supplementation with lutein *vs* placebo.[15] The trial was small with a total of 29 people randomised to lutein supplementation and 31 to placebo; the treatment duration and follow-up was 12 months. The only outcome of relevance to this review, for which data could be extracted, was mean visual acuity at the end of the study. This showed little evidence of any effect of treatment: mean difference logMAR acuity 0.04 (95% CI, −0.15–0.23). The power of the study was low.

The main reported adverse effect leading to withdrawal from the studies was gastrointestinal symptoms. Of 286 people randomised into trials of zinc sulphate supplementation compared to placebo, 5/146 zinc-treated people withdrew due to gastrointestinal symptoms compared to 2/140 controls.[17,18] No one developed copper-deficiency anaemia. In AMDSG, one person developed an 'allergic reaction,' although it was not clear whether or not this was related to the treatment.[14] AREDS considered a number of safety outcomes. They conducted over 100 comparisons of zinc *vs* no zinc and antioxidants *vs* no antioxidants. Participants in the antioxidant arms more frequently reported yellow skin (8.3 *vs* 6.0%, $P = 0.008$). Participants in the zinc arms reported more anaemia (13.2 *vs* 10.2%, $P = 0.004$), however, serum haematocrit levels were the same. People taking zinc were more likely to require hospital admission due to genitourinary complications.[21]

Discussion

Routine antioxidant vitamin supplementation with vitamin E or β-carotene probably does not protect against the development of AMD in later life. This review includes three large high quality studies that have randomised over 23 000 members of the population to antioxidant supplementation or placebo and followed-up for AMD. Duration of supplementation has ranged from 4 to 12 years. This represents a substantial amount of evidence. Most of the randomised people in these trials were men. We have no reason to suppose, however, that the effect of supplementation will be different in men and women. No trials of other antioxidant vitamins or minerals supplements to prevent AMD have been reported.

This review provides evidence that people with ARM may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation. This evidence comes from the AREDS trial and therefore only applies to the formulation used in that study (vitamins C and E, β-carotene, and zinc). This trial was 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. The other trials of broad-spectrum multivitamin preparations, eg, Ocuguard and Ocupower were too small to provide evidence either way. These trials were also of relatively short duration and lower quality. Variable methods of presenting outcome data made it difficult to pool results.

The AREDS trial provides evidence that long-term supplementation with vitamins C, E, β-carotene, and zinc, in people with ARM, 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 20–25%. However, given that treatment options for AMD are limited, and vision loss is rarely recovered, this is of interest to people with AMD. As AREDS is a large well-conducted randomised study, potential biases will have been minimised. Bias may have been introduced, if there were different systemic effects of the antioxidant and zinc supplementation (eg, yellowing of skin or difficulty in swallowing tablets), which led the participants to guess which group they were in; or alternatively, the retinal fundus photographs might have been different in some way such that the graders response was affected by treatment group. There is little evidence that this was a problem in the study.

A total of five trials investigated zinc. 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 *et al*[17] found a reduction in the risk of visual acuity loss with supplementation over 12–24 months. However, Stur *et al*[18] found no effect of treatment. Unfortunately Stur *et a*l,[18] who 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 *et al*[19] were published in abstract form and are included here.

AREDS was the only study to examine in detail the question of safety. There was some evidence that zinc supplementation at the level in the study resulted in increased hospital admissions due to genitourinary complications.[21] Similarly, the safety of some of the components of the AREDS formulation has been questioned in other studies. Two large randomised controlled trials have indicated that smokers who take β-carotene may be at increased risk of developing lung cancer.[22,23] 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.[24]

There is currently considerable interest in the potential role of lutein and zeaxanthin supplementation in AMD. This review includes only one small equivocal trial on lutein. Such supplements currently cannot be recommended. Trials are ongoing (http://www.areds2.org/, accessed 18 September 2007).

There are a number of unanswered questions in the prevention of AMD. The hypothesis that antioxidant micronutrients may protect against the disease is a reasonable one. We do not know at what stage the protective effect may be important, nor the potential interactions with genetic effects and other risk factors for the disease such as smoking. The research to date shows that we cannot extrapolate to taking vitamin supplements without good evidence of their effectiveness and safety.

Acknowledgements

Katherine Henshaw, coauthor on Cochrane Review on Prevention of AMD. The Cochrane Eyes and Vision Group editorial team prepared and executed the electronic searches for this review.

References

1 Christen WG, Glynn RJ, Hennekens CH. Antioxidants and age-related eye disease. Current and future perspectives. *Ann Epidemiol* 1996; **6**: 60–66.
2 Evans JR. Risk factors for age-related macular degeneration. *Prog Ret Eye Res* 2001; **20**: 227–253.
3 Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev* 2006, Issue 2. Art No.: CD000254. DOI:10.1002/14651858.CD000254.pub2.
4 Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev* 2008, Issue 1. Art No.: CD000253. DOI:10.1002/14651858.CD0000253.pub2.
5 The International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol* 1995; **39**: 367–374.
6 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. *Am J Ophthalmol* 2001; **132**: 668–681.
7 Higgins JPT, Green S (eds) *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5*, [updated May 2005]. In: the Cochrane Library 2005, issue 3 Chichester.

8 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
9 Teikari JM, Laatikainen L, Virtamo J, Haukka J, Rautalahti M, Liesto K *et al.* Six-year supplementation with alpha-tocopherol and beta-carotene and age-related maculopathy. *Acta Ophthalmol Scand* 1998; **76**: 224–229.
10 Hennekens CH, Eberlein K. A randomized trial of aspirin and beta-carotene among US physicians. *Prev Med* 1985; **14**: 165–168.
11 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. *Arch Ophthalmol* 2007; **125**: 333–339.
12 Taylor H, Tikellis G, Robman L, McCarty CA, McNeil JJ. Vitamin E supplementation and macular degeneration: randomised controlled trial. *BMJ* 2002; **325**: 325–311.
13 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. *Arch Ophthalmol* 2001; **119**: 1417–1436.
14 Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study-part 2: antioxidant intervention and conclusions. *J Am Optom Assoc* 1996; **67**: 30–49.
15 Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D *et al.* Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 2004; **75**: 216–230.
16 Kaiser HJ, Flammer J, Stumpfig D, Hendrickson P. Visaline in the treatment of age-related macular degeneration: a pilot study. *Ophthalmologica* 1995; **209**: 302–305.
17 Newsome DA, Swartz M, Leone NC, Elston RC, Miller E. Oral zinc in macular degeneration. *Arch Ophthalmol* 1988; **106**: 192–198.
18 Stur M, Tittl M, Reitner A, Meisinger V. Oral zinc and the second eye in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 1996; **37**: 1225–1235.
19 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). *Ger J Ophthalmol* 1993; **2**: 391.
20 Soubrane G, Arnold J. Trials on zinc supplementation and AMD. *Universitaire de Creteil, France* 2006 ref type: Personal Communication.
21 Johnson AR, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *J Urol* 2007; **177**: 639–643.
22 The Alpha Tocopherol and 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. *N Engl J Med* 1994; **330**: 1029–1035.
23 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. *N Engl J Med* 1996; **334**: 1150–1155.
24 The HOPE and HOPE-TOO trial investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005; **293**: 1338–1347.