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Evans JR, Lawrenson JG

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[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 (2017, Issue 2), MEDLINE Ovid (1946 to March 2017), Embase Ovid (1947 to March 2017), AMED (1985 to March 2017), OpenGrey (System for Information on Grey Literature in Europe, the ISRCTN registry (www.isrctn.com/editAdvancedSearch), 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 29 March 2017.

Selection criteria

We included randomised controlled trials (RCTs) that compared antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention, in people with AMD.

Data collection and analysis

Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5; the other author checked the data entry. We graded the certainty of the evidence using GRADE.

Main results

We included 19 studies conducted in USA, Europe, China, and Australia. We judged the trials that contributed data to the review to be at low or unclear risk of bias.

Nine studies compared multivitamins with placebo (7 studies) or no treatment (2 studies) in people with early and moderate AMD. The duration of supplementation and follow-up ranged from nine months to six years; one trial followed up beyond two years. Most evidence

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came from the Age-Related Eye Disease Study (AREDS) in the USA. People taking antioxidant vitamins were less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 2445 participants; 3 RCTs; moderate-certainty evidence). In people with very early signs of AMD, who are at low risk of progression, this would mean that there would be approximately 4 fewer cases of progression to late AMD for every 1000 people taking vitamins (1 fewer to 6 fewer cases). In people at high risk of progression (i.e. people with moderate AMD) this would correspond to approximately 8 fewer cases of progression for every 100 people taking vitamins (3 fewer to 13 fewer). In one study of 1206 people, there was a lower risk of progression for both neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; moderate-certainty evidence) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; moderate-certainty evidence) and a lower risk of losing 3 or more lines of visual acuity (OR 0.77, 95% CI 0.62 to 0.96; 1791 participants; moderate-certainty evidence). Low-certainty evidence from one study of 110 people suggested higher quality of life scores (National Eye Institute Visual Function Questionnaire) in treated compared with the non-treated people after 24 months (mean difference (MD) 12.30, 95% CI 4.24 to 20.36).

Six studies compared lutein (with or without zeaxanthin) with placebo. The duration of supplementation and follow-up ranged from six months to five years. Most evidence came from the AREDS2 study in the USA. People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94, 95% CI 0.87 to 1.01; 6891 eyes; low-certainty evidence), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 6891 eyes; low-certainty evidence), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15 or more letters was seen in the lutein and control groups (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; low-certainty evidence). Quality of life (measured with Visual Function Questionnaire) was similar between groups in one study of 108 participants (MD 1.48, 95% -5.53 to 8.49, moderate-certainty evidence).

One study, conducted in Australia, compared vitamin E with placebo. This study randomised 1204 people to vitamin E or placebo, and followed up for four years. Participants were enrolled from the general population; 19% had AMD. The number of late AMD events was low (N = 7) and the estimate of effect was uncertain (RR 1.36, 95% CI 0.31 to 6.05, very low-certainty evidence). There were no data on neovascular AMD or geographic atrophy.There was no evidence of any effect of treatment on visual loss (RR 1.04, 95% CI 0.74 to 1.47, low-certainty evidence). There were no data on quality of life.

Five studies compared zinc with placebo. The duration of supplementation and follow-up ranged from six months to seven years. People taking zinc supplements may be less likely to progress to late AMD (OR 0.83, 95% CI 0.70 to 0.98; 3790 participants; 3 RCTs; low-certainty evidence), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 2442 participants; 1 RCT; moderate-certainty evidence), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 2442 participants; 1 RCT; moderate-certainty evidence), or visual loss (OR 0.87, 95% CI 0.75 to 1.00; 3791 participants; 2 RCTs; moderate-certainty evidence). There were no data reported on quality of life.

Very low-certainty evidence was available on adverse effects because the included studies were underpowered and adverse effects inconsistently reported.

Authors' conclusions

People with AMD may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation. This finding was largely drawn from one large trial, conducted in a relatively well-nourished American population. We do not know the generalisability of these findings to other populations. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed. Supplements containing lutein and zeaxanthin are heavily marketed for people with age-related macular degeneration but our review shows they may have little or no effect on the progression of AMD.

PLAIN LANGUAGE SUMMARY

Antioxidant vitamin and mineral supplements to slow down the progression of age-related macular degeneration (AMD)

What is the aim of this review?
The aim of this Cochrane Review was to find out whether taking antioxidant vitamin and mineral supplements slows down the progression of AMD and prevents visual loss. Cochrane researchers collected and analysed all relevant studies to answer this question and found 19 studies.

Key messages
Taking an antioxidant multivitamin supplement may slow down the progression of AMD. Most benefit will be seen in people who have a higher chance of progression. Although vitamin supplements are generally regarded as safe, the studies included in this review did not provide good evidence as to safety as they were generally too small.

What was studied in the review?
AMD is a condition of the central area (macula) of the back of the eye (retina). The macula degenerates with age. In some people, this deterioration happens more quickly, and is associated with a particular appearance at the back of the eye. In its earliest stage (early AMD), yellow spots (drusen) can be seen under the retina by an eye health professional on examining the eye. The affected person will probably be unaware that they a problem. As AMD progresses, it can lead to the loss of the cells in the back of the eye, which are needed for vision. This is known as geographic atrophy. Sometimes, new (harmful) blood vessels grow in the macula. These new blood vessels may bleed

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and cause scarring. This is known as neovascular or wet AMD. Any damage to the macula can affect vision, particularly central vision. Neovascular AMD and geographic atrophy are known as late AMD.

It is possible that antioxidant vitamins may help to protect the macula against this deterioration and loss of vision. Vitamin C, E, beta-carotene, lutein, zeaxanthin, and zinc are examples of antioxidant vitamins commonly found in vitamin supplements.

The Cochrane researchers only looked at the effects of these supplements in people with AMD. There is another Cochrane Review on the effects of these supplements in people who do not already have AMD.

What are the main results of the review?
The Cochrane researchers found 19 relevant studies. Ten studies were from Europe, six from USA, two from China, and one from Australia. These studies compared multivitamin supplements, zinc, vitamin E and lutein and zeaxanthin with placebo.

•Taking antioxidant vitamins plus zinc probably slows down the progression to late AMD and vision loss (moderate-certainty evidence). This may result in a small improvement in quality of life (low-certainty evidence).
•Taking lutein alone (or combined with zeaxanthin) may have little or no effect on progression to late AMD and vision loss (low-certainty evidence).
•Taking vitamin E alone may have little or no effect on the progression to late AMD and vision loss (low-certainty evidence).

Although vitamin supplements are generally regarded as safe, the studies included in this review did not provide good evidence as to safety as they were generally too small and adverse effects were reported inconsistently.

How up-to-date is this review?
The Cochrane researchers searched for studies that had been published up to 29th March 2017.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Multivitamin versus placebo

Antioxidant multivitamin and mineral supplement versus placebo or no treatment

Patient or population: people with AMD
Setting: community
Intervention: antioxidant multivitamin and mineral supplement*
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Multivitamin antioxidant vitamin or mineral supplement				
Progression to late AMD (neovascular AMD, geographic atrophy or both)	Low		OR 0.72 (0.58 to 0.90)	2445 (3 RCTs)	⊕⊕⊕⊖ MODERATE[1]	Average follow-up in study contributing most of the events was 6 years
	15 per 1000	11 per 1000 (9 to 14)				
	High					
	430 per 1000	352 per 1000 (304 to 404)				
Progression to neovascular AMD	Low		OR 0.62 (0.47 to 0.82)	1206 (1 RCT)	⊕⊕⊕⊖ MODERATE[1]	Average follow-up 6 years. Estimate of effect from study population including AMD category 3 & 4 only
	10 per 1000	6 per 1000 (5 to 8)				
	High					
	300 per 1000	210 per 1000 (168 to 260)				
Progression to geographic atrophy	Low		OR 0.75 (0.51 to 1.10)	1206 (1 RCT)	⊕⊕⊕⊖ MODERATE[1]	Average follow-up 6 years. Estimate of effect from study population including AMD category 3 & 4 only
	10 per 1000	8 per 1000 (5 to 11)				
	High					

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	300 per 1000	243 per 1000 (179 to 320)				
Progression to visual loss (loss of 3 or more lines on logMAR chart)	Low		OR 0.77 (0.62 to 0.96)	1791 (1 RCT)	⊕⊕⊕⊖ MODERATE[1]	Average follow-up 6 years
	15 per 1000	12 per 1000 (9 to 14)				
	High					
	430 per 1000	367 per 1000 (319 to 420)				
Quality of life assessed with: change in National Eye Institute Visual Function Questionnaire (NEI-VFQ) score (higher scores better)	The mean change in NEI-VFQ score in the control group was -8.7	The mean NEI-VFQ quality of life score in the intervention group was 12.3 higher (4.24 higher to 20.36 higher)	-	110 (1 RCT)	⊕⊕⊖⊖ LOW [2,3]	Follow-up 24 months
Adverse effects	Data from AREDS suggested no serious adverse effects associated with multivitamin use (hazard ratio for mortality 0.87, 95% CI 0.60 to 1.25) but participants in the antioxidant arms more frequently reported yellow skin (8.3% versus 6.0%, P = 0.008)..				⊕⊖⊖⊖ VERY LOW [4]	-
Resource use and costs	-	-	-	-	-	Not reported

* Most of the evidence in this table is drawn from the AREDS study which studied antioxidants (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg daily) plus zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide (daily)

****The risk in the intervention group** (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). The assumed risk in the comparison group is estimated using data from AREDS: low risk = AREDS category 2; high risk = AREDS category 4.

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for imprecision because upper confidence interval crosses line of minimum important difference (0.8 to 1.25)
[2] Downgraded one level for risk of bias because study was not placebo-controlled and at high risk of performance and detection bias
[3] Downgraded one level for imprecision because confidence intervals included clinically insignificant effect

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4 Downgraded for one level for imprecision (as included studies were underpowered to look at adverse effects), one level for risk of bias (adverse effects were inconsistently reported) and one level for inconsistency (inconsistent results reported).

Summary of findings 2. Lutein or zeaxanthin versus placebo

Lutein and/or zeaxanthin versus placebo

Patient or population: people with AMD
Setting: community
Intervention: lutein and zeaxanthin*
Comparison: placebo

Outcomes	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Lutein and zeaxanthin				
Progression to late AMD (neovascular AMD, geographic atrophy, or both)	Low		RR 0.94 (0.87 to 1.01)	6891 eyes (1 RCT)	⊕⊕⊝⊝ LOW [1, 2]	Average follow-up 5 years
	15 per 1000	14 per 1000 (13 to 15)				
	High					
	430 per 1000	404 per 1000 (374 to 434)				
Progression to neovascular AMD	Low		RR 0.92 (0.84 to 1.02)	6891 eyes (1 RCT)	⊕⊕⊝⊝ LOW [1, 2]	Average follow-up 5 years
	10 per 1000	9 per 1000 (8 to 10)				
	High					
	300 per 1000	276 per 1000 (252 to 306)				
Progression to geographic atrophy	Low		RR 0.92 (0.80 to 1.05)	6891 eyes (1 study)	⊕⊕⊝⊝ LOW [1, 2]	Average follow-up 5 years
	10 per 1000	9 per 1000 (8 to 11)				
	High					

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	300 per 1000	276 per 1000 (240 to 315)				
Progression to visual loss (loss of 3 or more lines on logMAR chart)	Low		RR 0.98 (0.91 to 1.05)	6656 eyes (1 RCT)	⊕⊕⊝⊝ LOW [1, 2]	Average follow-up 5 years
	15 per 1000	15 per 1000 (14 to 16)				
	High					
	430 per 1000	421 per 1000 (391 to 452)				
Quality of life assessed with Visual Function Questionnaire (VFQ) (higher scores better)	The mean VFQ quality of life score in the control group was 77.3	The mean VFQ quality of life score in the intervention group was 1.48 higher (5.53 lower to 8.49 higher)	-	108 (1 RCT)	⊕⊕⊕⊝ MODERATE [2]	Follow-up 12 months.
Adverse effects	Data from AREDS2 suggested no serious adverse effects associated with lutein and zeaxanthin use (hazard ratio for mortality was 1.06 (95% CI 0.87 to 1.31).				⊕⊝⊝⊝ VERY LOW [3]	-
Resource use and costs	-	-	-	-	-	Not reported

* Most of the evidence in this table is drawn from the AREDS2 study in which participants too a daily dose of lutein 10mg and zeaxanthin 2mg or placebo. All participants in the study took AREDS formula (vitamin C, E, zinc with/without beta-carotene).

The risk in the intervention group (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). The assumed risk in the comparison group is estimated using data from AREDS: low risk = AREDS category 2; high risk = AREDS category 4.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for indirectness, as everyone in trial took AREDS formula, which may have affected the estimate of effect
[2] Downgraded one level for imprecision, as confidence intervals crossed line of minimum important difference.
[3] Downgraded for one level for imprecision (as included studies were underpowered to look at adverse effects), one level for risk of bias (adverse effects were inconsistently reported) and one level for inconsistency (inconsistent results reported).

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Summary of findings 3. Vitamin E versus placebo

Vitamin E versus placebo

Patient or population: people with AMD
Setting: community
Intervention: vitamin E*
Comparison: placebo

Outcomes	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Multivitamin antioxidant vitamin or mineral supplement				
Progression to late AMD (neovascular AMD, geographic atrophy or both)	Low		RR 1.36 (0.31 to 6.05;	998 (1 RCT)	⊕⊕⊝⊝ VERY LOW[1,2]	Average follow-up 4 years
	15 per 1000	20 per 1000 (5 to 91)				
	High					
	430 per 1000	585 per 1000 (133 to 1000)				
Progression to neovascular AMD	Not reported					
Progression to geographic atrophy	Not reported					
Progression to visual loss (loss of 3 or more lines on logMAR chart)	Low		RR 1.04 (0.74 to 1.47)	1179 (1 RCT)	⊕⊕⊝⊝ LOW[1,2]	Average follow-up 4 years
	15 per 1000	16 per 1000 (11 to 22)				
	High					
	430 per 1000	447 per 1000 (318 to 632)				
Quality of life	Not reported					

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Adverse effects	No serious adverse effects were seen. Similar numbers of people in the vitamin E and placebo groups withdrew due to adverse effects (four versus seven), reported any adverse effect (91 versus 83), or ocular adverse effect (105 versus 90).				⊕⊝⊝⊝ VERY LOW [3]	-
Resource use and costs	-	-	-	-	-	Not reported

*Vitamin E 500 IU per day: natural vitamin E in soybean oil medium

****The risk in the intervention group** (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). The assumed risk in the comparison group is estimated using data from AREDS: low risk = AREDS category 2; high risk = AREDS category 4.

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded two levels for imprecision as only 7 events.
[2] Downgraded one level for indirectness as over 80% of the participants in this trial had no signs of AMD at baseline.
[3] Downgraded three levels for imprecision as study was underpowered to look at rare adverse effects.

Summary of findings 4. Zinc versus placebo

Zinc versus placebo

Patient or population: people with AMD
Setting: community
Intervention: zinc*
Comparison: placebo

Outcomes	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Zinc				
Progression to late AMD (neovascular AMD, geographic atrophy or both)	Low		OR 0.83 (0.70 to 0.98)	3790 (3 RCTs)	⊕⊕⊝⊝ LOW [1, 2]	Average follow-up in study contributing most of the events was 6 years
	15 per 1000	12 per 1000 (11 to 15)				

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	High					
	430 per 1000	385 per 1000 (346 to 425)				
Progression to neovascular AMD	Low		OR 0.76 (0.62 to 0.93)	2442 (1 RCT)	⊕⊕⊕⊖ MODERATE[2]	Average follow-up 6 years
	10 per 1000	8 per 1000 (6 to 9)				
	High					
	300 per 1000	246 per 1000 (210 to 285)				
Progression to geographic atrophy	Low		OR 0.84 (0.64 to 1.10)	2442 (1 RCT)	⊕⊕⊕⊖ MODERATE[2]	Average follow-up 6 years
	10 per 1000	8 per 1000 (6 to 11)				
	High					
	300 per 1000	265 per 1000 (215 to 320)				
Progression to visual loss (loss of 3 or more lines on log-MAR chart)	Low		OR 0.87 (0.75 to 1.00)	3791 (2 RCTs)	⊕⊕⊕⊖ MODERATE[2]	Average follow-up in study contributing most of the events was 6 years
	15 per 1000	13 per 1000 (11 to 15)				
	High					
	430 per 1000	396 per 1000 (361 to 430)				
Quality of life	Not reported					
Adverse effects	In some studies, gastrointestinal symptoms was reported as a reason for withdrawal. Of 286 people randomised into trials of zinc sulfate supplementation compared with placebo (not including AREDS), 5/146 zinc-treated people withdrew due to gastrointestinal symptoms compared with 2/140 controls. No-one developed copper-deficiency anaemia (high zinc intakes can inhibit copper absorption). In AREDS participants in the zinc arms reported more anaemia (13.2% versus 10.2%, P = 0.004), however, serum haematocrit levels were the same. In AREDS zinc was associated with higher risk of genitourinary problems in men, but no difference seen between high- and low-dose zinc groups in AREDS2				⊕⊖⊖⊖ VERY LOW [3]	-

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Resource use and costs	-	-	-	-	-	Not reported

* Most of the evidence in this table is drawn from the AREDS study which studied a daily dose of zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide.

****The risk in the intervention group** (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). The assumed risk in the comparison group is estimated using data from AREDS: low risk = AREDS category 2; high risk = AREDS category 4.

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for inconsistency because study effects ranged from 0.50 to 2.31, although $I^2 = 14\%$
[2] Downgraded one level for imprecision because confidence interval crossed line of minimum important difference.
3 Downgraded for one level for imprecision (as included studies were underpowered to look at adverse effects), one level for risk of bias (adverse effects were inconsistently reported) and one level for inconsistency (inconsistent results reported).

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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.

In general, the early stages of the disease are 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). The estimated prevalence of late AMD is 1.4% (95% Credible Interval (CrI), 1.0% to 2.0%) at 70 years of age, 5.6% (95% CrI, 3.9% to 7.7%) at age 80, and 20% (95% CrI, 14% to 27%) at age 90 (Rudnicka 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 that is known to have antioxidant properties in vivo, or that 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 on the progression of AMD in people with 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 with placebo or no intervention. Antioxidants were defined as any vitamin or mineral that was known to have antioxidant properties in vivo, or that was 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.

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 multivitamin formulation (for example, Ocuguard). The following comparisons were considered in this review.

1. Multivitamin formulation versus placebo. All the formulations which include two or more antioxidant vitamins or minerals fall into this category.
2. Single-component formulations versus placebo. Currently, only vitamin E, zinc and lutein have been studied as single formulations, however, in principle any of the antioxidant vitamins or minerals could be assessed as individual components.

Types of outcome measures

We modified our protocol for the current update (2017) to include outcomes specified by the UK NICE macular degeneration guideline panel (NICE 2016); see Differences between protocol and review.

We considered the following outcomes:

- Progression to late AMD (neovascular AMD, geographic atrophy, or both);
- Progression to neovascular AMD;
- Progression to geographic atrophy;
- Progression to visual loss (loss of 3 or more lines on logMAR chart)*;

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- Quality of life;
- Resource use and costs.

*As visual acuity is also commonly reported as a 'mean score' we also include mean visual acuity as a continuous outcome.

Follow-up:

We considered the maximum follow-up identified in the studies at any point in time.

Adverse effects

We considered any adverse effects reported by the included studies.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 29 March 2017.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 29 March 2017) (Appendix 1);
- MEDLINE Ovid (1946 to 29 March 2017) (Appendix 2);
- Embase Ovid (1980 to 29 March 2017) (Appendix 3);
- AMED (Allied and Complementary Medicine Database) (1985 to 29 March 2017) (Appendix 4);
- OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/; searched 29 March 2017) (Appendix 5);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 29 March 2017) (Appendix 6);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 29 March 2017) (Appendix 7);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp; searched 29 March 2017) (Appendix 8).

For the 2012 and 2017 updates, we specifically looked for adverse effects, using a simple search aimed to identify systematic reviews of adverse effects of vitamin supplements, see 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 cited 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 independently assessed the titles and abstracts of all reports of trials identified by the electronic searches. 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

We extracted data using a standardised form, developed by Cochrane Eyes and Vision. For the initial review, we sent these data for verification to the trial investigators of all studies included in the review. In the 2012 and current updates, data were independently extracted by both authors, compared, disagreements resolved by discussion, and data cut and pasted into Review Manager (Review Manager 5 2014) by one author and checked by the other. In the current update, citations were screened and duplicate data extracted using web-based review management software (Covidence).

Assessment of risk of bias in included studies

We assessed risk of bias using Cochrane'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

We used the risk ratio (RR) for dichotomous outcomes where possible. As one of the main large trials reported odds ratios (OR) and their confidence intervals only (derived from repeated measures logistic regression), we used the OR as the measure of effect for analyses that included this trial (AREDS 2001).

For continuous outcomes, we used the mean difference (MD) where possible, and the standardised mean difference (SMD) when visual acuity was measured on different scales. In this case, 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 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.

As the intervention is applied to the individual, the unit of randomisation is the individual person. As people have two eyes, it is possible for there to be a unit of analysis issue if eyes are reported, rather than results for the person. For each included trial we documented whether the unit of analysis was the same as the unit of randomisation and noted any implications for the analysis. For studies reporting right and left eyes separately, we extracted data for the right eye.

Dealing with missing data

The data included in the review represent an 'available case analysis'. The majority of the data in the current review came from two large trials with high (over 95%) follow-up.

Two studies specifically excluded people who experienced a neovascular event (one component of late-stage AMD) from the

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analyses (CARMA 2013; Stur 1996). The published reports 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 was the type of supplement. This was 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.

Data synthesis

We planned to pool data using a random-effects model (because it was likely that the effects of antioxidant vitamin and mineral supplementation may vary in different population groups) but with the proviso that if there were three or fewer trials we would use the fixed-effects model. In the event most of our analyses fell into the latter category and so we largely used a fixed-effects 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. Characteristics that may be important are the type and severity of AMD. Subgroup analyses on type or severity of AMD may be considered in future.

Sensitivity analysis

A sensitivity analysis was not planned.

Summary of findings tables

We prepared separate 'Summary of findings' tables for the different types of vitamin supplement.

We assessed the certainty of the evidence (GRADE) for each outcome using customised software (GRADEpro 2014). JE did the initial assessment, which was checked by JL. We considered risk of bias, inconsistency, indirectness, imprecision, and publication bias when judging the certainty of the evidence (Schünemann 2011).

The 'Summary of findings' tables include an estimate of the risk of each outcome in the general population. We used data from AREDS to estimate the risk in the control group in low risk (AREDS category 2) and high risk (AREDS category 4) populations.

RESULTS

Description of studies

Results of the search

Summary of searches for previous versions of this review

Date review published	Date searches up to date	Newly included trials	Total number of trials included in the review	Total number of excluded trials	Trials awaiting assessment	Ongoing trials
November 1997	August 1997	AMDSG 1996; Newsome 1988; Stur 1996	3	1	Holz 1993 (included February 2002)	AREDS 2001; VECAT 2002
November 1998	October 1998	Kaiser 1995	4	1	France 1998 (unpublished but included in current update)	-
February 2002	November 2001	AREDS 2001; Holz 1993; VECAT 2002	7	1	-	-
February 2006	January 2006	Veterans LAST study 2004	8	1	Wang 2004 (included November 2007)	-
November 2007	August 2007	Wang 2004	9	25	-	-

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October 2012	August 2012	Bartlett 2007; CARMIS 2011; LISA 2011; Newsome 2008	13	41	CARMA 2013 (included current update) LUTEGA 2013 and Falsini 2010 (both excluded current update)	AREDS2 2013 and NCT91948476 (Ma 2012) (both included current update): NCT00879671 (this is the same trial as LISA 2011 included in October 2012) NCT00893724 (excluded current update)
June 2017 (current update)	March 2017	AREDS2 2013; Berrow 2013; CARMA 2013; CLEAR 2013; France 1998*; Ma 2012	19	55	-	NCT01694680; NCT02625376

* This is an unpublished trial for which we are unlikely to be able to obtain the data. We originally excluded this, but following more recent guidelines (see MECIR standard C12; methods.cochrane.org/mecir), we are including this study in the current review.

Searches for current update (2017)

Update searches run in March 2017 yielded a further 872 records (Figure 1). After 157 duplicate were removed, the Cochrane Information Specialist (CIS; formerly the Trial Search Co-ordinator) screened the remaining 715 records and removed 562 references that were not relevant to the scope of the review. We screened the remaining 153 references and obtained 38 full-text reports for further assessment. We identified 18 reports of six new studies for further details; see Characteristics of included studies. France 1998, which had previously been excluded, has now been reassessed and added to the review as an included study. We excluded 18 reports of 15 studies and identified two new ongoing studies; see Characteristics of excluded studies. In the previous version of this review, there were five reports of studies awaiting classification. For this update, we assessed these reports; two have now been included and three were excluded. The previous ongoing studies were reassessed and those studies that had been completed were either included or excluded in this update.

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Figure 1. Study flow diagram.

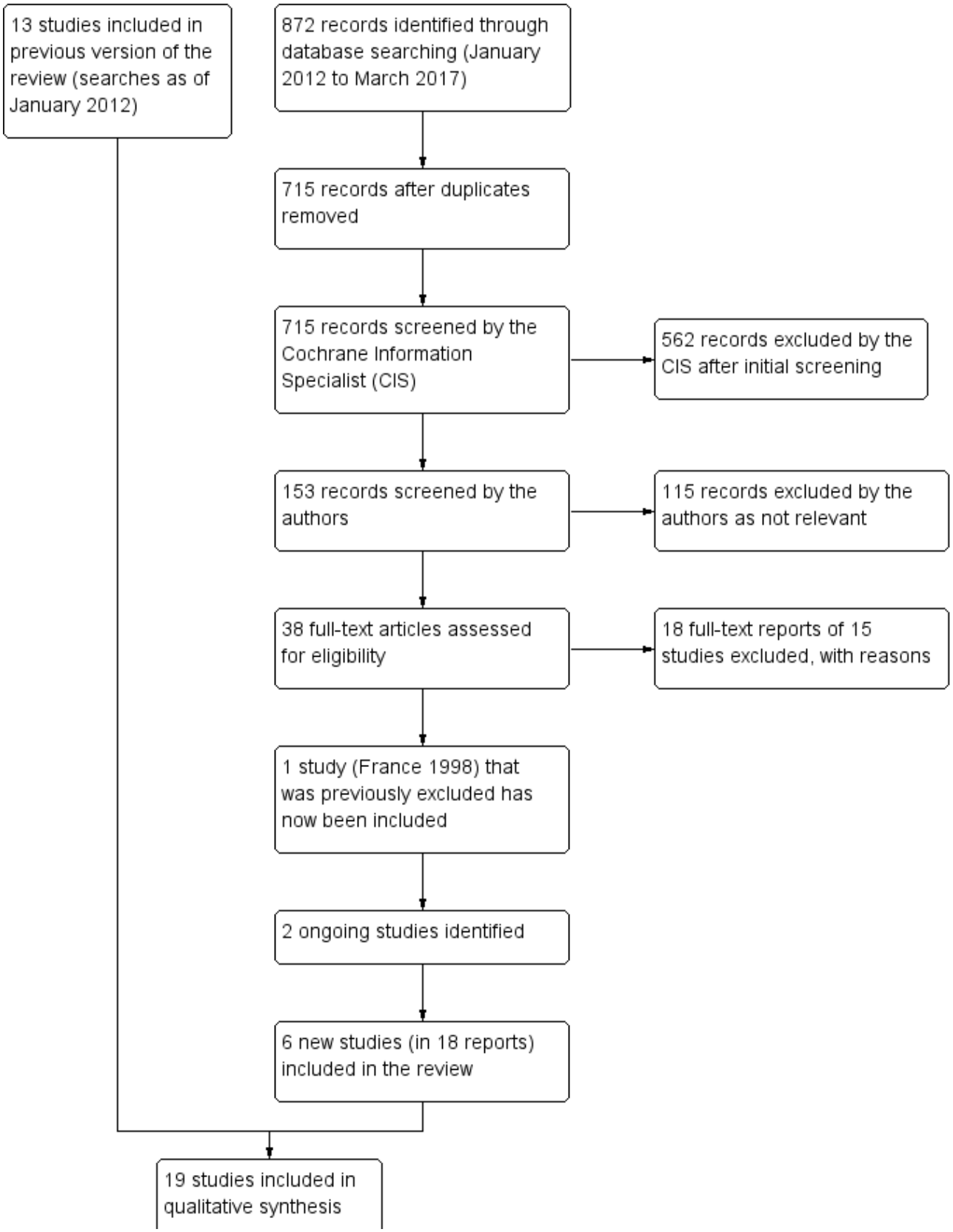

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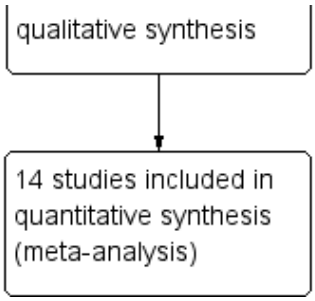
Figure 1. (Continued)



Included studies

Below is a summary of the 19 trials included in this review. See Characteristics of included studies for detailed information on individual trials.

Multivitamin supplements

Seven studies compared multivitamin supplements with placebo (AMDSG 1996; AREDS 2001; Bartlett 2007; CARMA 2013; Kaiser 1995; Veterans LAST study 2004; Wang 2004), and two studies compared multivitamin supplements with no treatment (Berrow 2013; CARMIS 2011). Table 1 summarises the daily dose of key antioxidant vitamin and mineral supplements considered. These studies were conducted in USA (AMDSG 1996; AREDS 2001; Veterans LAST study 2004), Europe (Bartlett 2007; CARMA 2013; Kaiser 1995), and China (Wang 2004).

AMDSG 1996, Bartlett 2007, Berrow 2013, CARMIS 2011, and Veterans LAST study 2004 only enrolled people with early AMD. Wang 2004 recruited people with both early and late-stage disease. In AREDS 2001, participants had a range of disease, from mild or borderline features to late AMD. CARMA 2013 enrolled people with either late AMD in one eye and any AMD in the other, or people with AMD features of "sufficient severity" in both eyes, i.e. either more than 20 drusen, or a combination of drusen and pigmentary abnormalities. Kaiser 1995 recruited people with "non-serous" AMD.

People taking part in the trials were identified by referral from local ophthalmologists (Kaiser 1995), from people attending Department of Veterans Medical Centers (AMDSG 1996; Veterans LAST study 2004), from retinal specialty clinics and general population volunteers (AREDS 2001), from an eye outpatient clinic (Berrow 2013; Wang 2004), and from regional tertiary referral centres (CARMA 2013). Bartlett 2007 recruited participants by sending letters to "local optometrists, ophthalmologists, and a specialist centre for rehabilitation of people with sight loss"; participants were then seen at the University research centre. In CARMIS 2011, it was not clear how they identified participants.

The number of participants enrolled ranged from 14 (Berrow 2013), to 3640 (AREDS 2001). Apart from AREDS 2001, all these trials recruited fewer than 500 people; the median number randomised was 90. The average age of participants ranged from 66 to 75 years; the median percentage of women was 55%, two trials recruited mainly men (AMDSG 1996; Veterans LAST study 2004).

The duration of supplementation and follow-up ranged from nine months (Bartlett 2007), to six years (AREDS 2001). Only one trial followed up beyond two years (AREDS 2001).

Lutein and zeaxanthin supplements

Five studies compared lutein supplements with placebo (AREDS2 2013; CLEAR 2013; LISA 2011; Ma 2012; Veterans LAST study 2004). In AREDS2 2013, all participants also took the AREDS formula (Table 1).

The daily dose of lutein used in all these studies was 10 mg; two studies considered additional doses of 20 mg (LISA 2011; Ma 2012). Two studies combined lutein with zeaxanthin, either a dose of 2 mg (AREDS2 2013), or 10 mg (Ma 2012). These studies were conducted in USA (AREDS2 2013; Veterans LAST study 2004), Europe (CLEAR 2013; LISA 2011), and China (Ma 2012).

CLEAR 2013, Ma 2012, and Veterans LAST study 2004 only considered people with early macular degeneration. AREDS2 2013 enrolled people "at risk for progression to advanced AMD, with bilateral large drusen, or large drusen in one eye and advanced AMD in the fellow eye". LISA 2011 recruited individuals in categories 2, 3, and 4 according to AREDS criteria (similar to the participants in AREDS 2001).

People taking part in the trials were identified from people attending Department of Veterans Medical Centers (Veterans LAST study 2004), from "clinical centers" (AREDS2 2013), and "local communities" (Ma 2012). In CLEAR 2013, "An advertising campaign was conducted within the universities and in local newspapers". In LISA 2011, it was not clear how they identified participants.

The number of participants enrolled ranged from 84 (CLEAR 2013), to 4203 (AREDS2 2013). Apart from AREDS2 2013, all of these trials recruited fewer than 150 people; the median number randomised was 110. The average age of participants ranged from 69 to 75 years; the median percentage of women was 57%; one trial recruited mainly men (Veterans LAST study 2004).

The duration of supplementation and follow-up ranged from six months (LISA 2011), to five years (AREDS2 2013). The majority of trials followed up to 12 months, only one trial followed up to two years (Ma 2012).

Vitamin E

One study, conducted in Australia, compared vitamin E with placebo (VECAT 2002). This study randomised 1204 people to vitamin E 400 IU daily or placebo, and followed up for four years. Participants were enrolled from the general population and only 19% had AMD, mainly early AMD. Average age was 66 years, and 56% were women.

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Zinc

Six studies compared zinc with placebo (AREDS 2001; France 1998; Holz 1993; Newsome 1988; Newsome 2008; Stur 1996).

In France 1998, 170 people with neovascular AMD in one eye and drusen in the other were randomised to receive zinc 30 mg or placebo. This study was unpublished and we have no further information.

Three studies considered zinc sulfate 200 mg daily (Holz 1993; Newsome 2008; Stur 1996), one study investigated zinc oxide 80 mg daily (AREDS 2001), and one study used zinc monocysteine 50 mg daily (Newsome 2008).

Holz 1993 and Newsome 2008 only enrolled people with early macular degeneration; in AREDS 2001, participants had a range of disease, from mild or borderline features to late AMD; Newsome 1988 recruited people with both early and late-stage disease; Stur 1996 only enrolled people with late-stage disease in one eye.

The number of participants enrolled ranged from 58 (Holz 1993), to 3640 (AREDS 2001). Apart from AREDS2 2013, all of these trials recruited fewer than 500 people; the median number randomised was 141. The average age of people participating in the trials ranged from 65 to 74 years; median percentage of women was 57%.

People taking part in the trials were identified by referral from local ophthalmologists (Newsome 1988), eye outpatient clinics (Stur 1996), and from retinal specialty clinics and general population volunteers (AREDS 2001). In Holz 1993 and Newsome 2008, it was not clear how they identified participants.

The duration of supplementation and follow-up in these trials ranged from six months to seven years.

Excluded studies

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

Risk of bias in included studies

Figure 2 and Figure 3 summarise the 'Risk of bias' assessment. Overall, we considered the trials to be 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, except Berrow 2013 and CARMIS 2011, had a placebo control. Three trials were not well reported (Holz 1993; LISA 2011; Wang 2004), and one trial was unpublished (France 1998).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

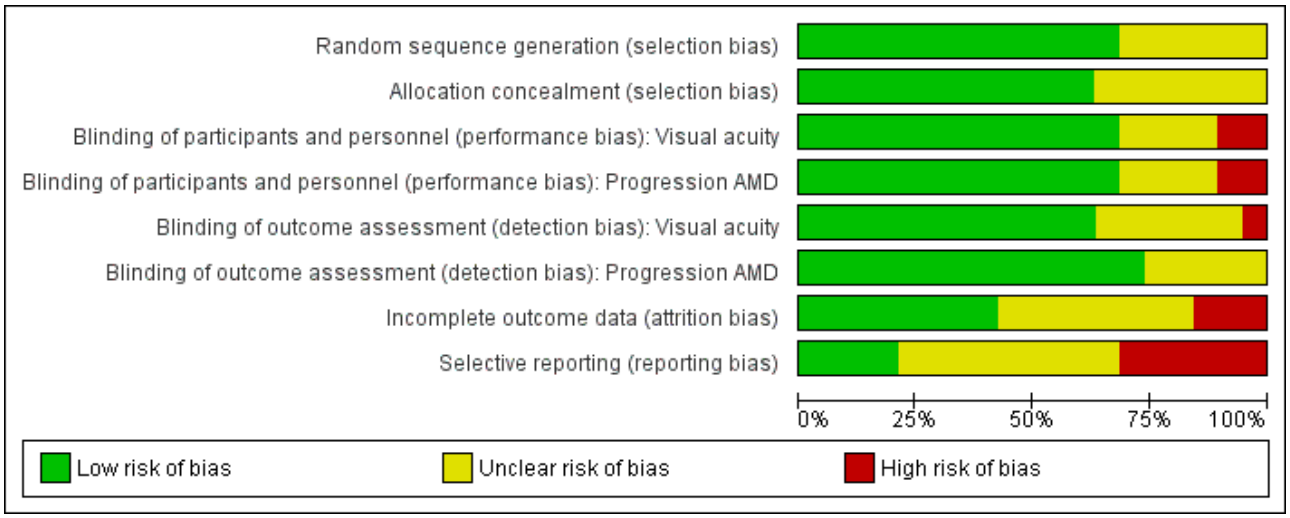

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Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

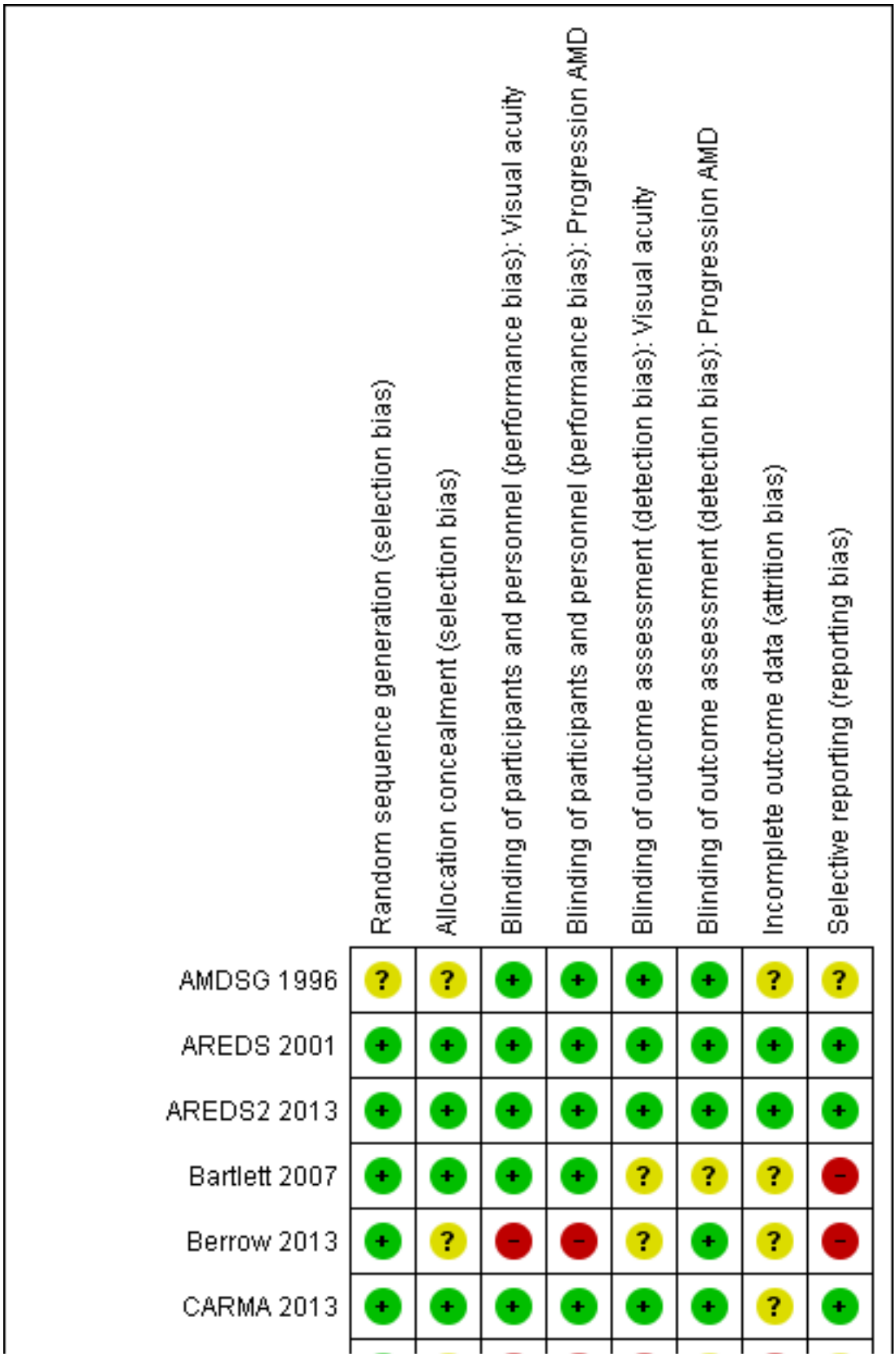

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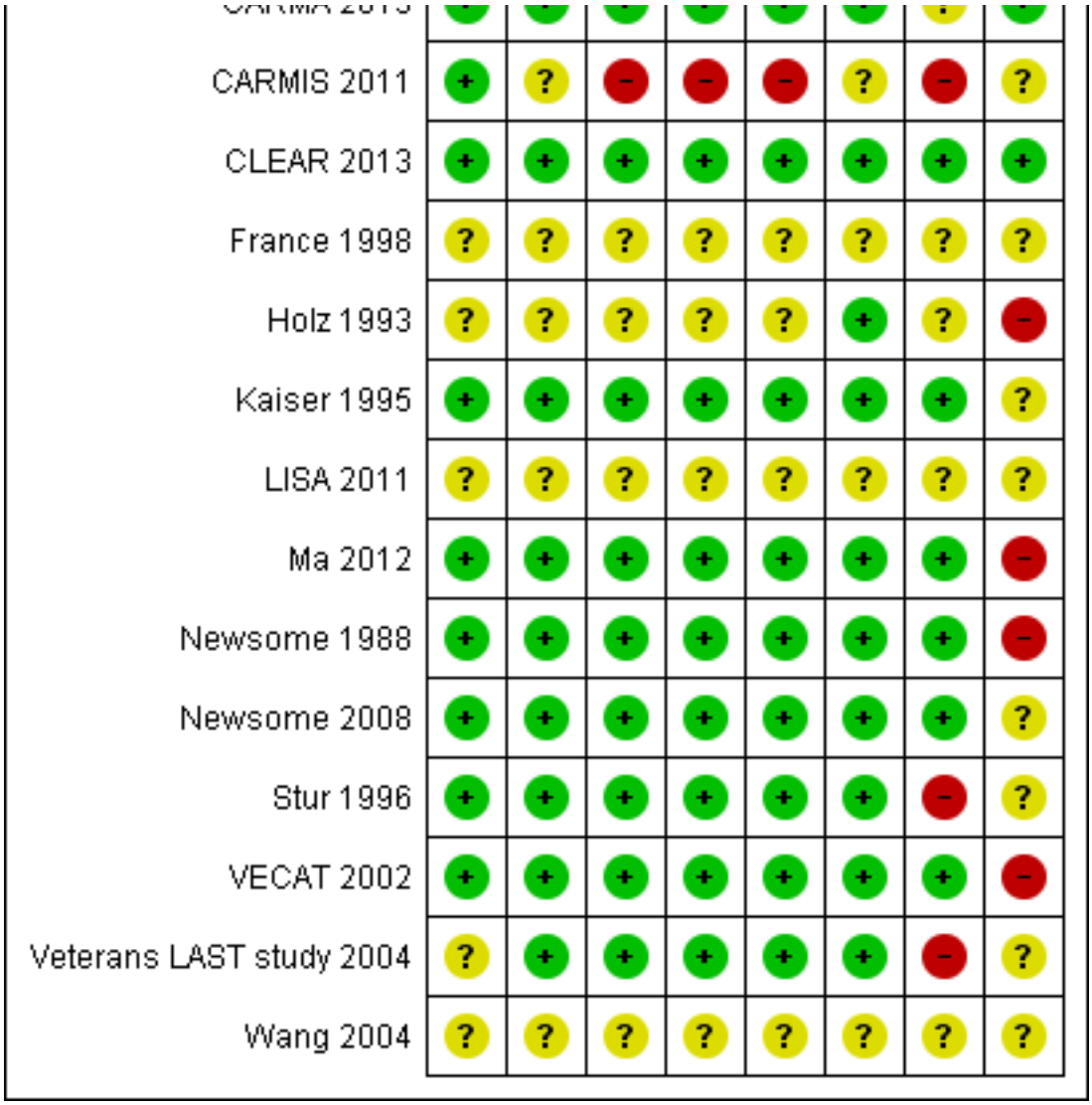
Figure 3. (Continued)



Allocation

In most trials randomisation appeared to have been executed properly, that is, an unpredictable sequence of treatment allocation was adequately concealed from people recruiting participants into the trial. As Holz 1993 had only been published in abstract form to date, the details of randomisation were not clear.

Blinding

Two trials had a 'no treatment' control group so were considered to be at high risk for performance and detection bias (Berrow 2013; CARMIS 2011).

In general, there was not a lot of information to judge the success of the masking. In AREDS 2001, 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 participants were asked to guess their treatment assignment at the end of the study. 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 2004, 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. Three studies were considered to be at high risk of attrition bias.

In CARMIS 2011, 19% of the treated group and 38% of the untreated group were excluded from the final analysis.

In Veterans LAST study 2004, members of the placebo group were removed from analysis, due to the fact that they had taken lutein.

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 end

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point 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 (6/60) 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. Similarly, CARMA 2013 excluded people with CNV from analyses of visual acuity.

Selective reporting

There was some evidence of selective reporting in six studies, but this was generally difficult to assess, and we could not be confident that selective reporting did not occur in other included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Multivitamin versus placebo; **Summary of findings 2** Lutein or zeaxanthin versus placebo; **Summary of findings 3** Vitamin E versus placebo; **Summary of findings 4** Zinc versus placebo

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

Multivitamin and mineral supplement versus placebo

See Summary of findings for the main comparison.

Nine studies investigated multivitamin supplements (Table 1).

Only three trials reported data on our primary outcome of progression to late AMD (AREDS 2001; CARMA 2013; CARMIS 2011), and only one of these trials reported data separately on neovascular AMD and geographic atrophy (AREDS 2001). Mean visual acuity was more commonly reported, but there was considerable variability in the measurement and reporting of this outcome. AMDSG 1996 and Veterans LAST study 2004 measured visual acuity using a Snellen chart and converted the score into logMAR units. AREDS 2001, CARMIS 2011 and Bartlett 2007 used the logMAR visual acuity chart developed as part of the Early Treatment of Diabetic Retinopathy Study (ETDRS 1980). No useable data could be extracted for Berrow 2013, Kaiser 1995 and Wang 2004.

Only one trial reported on quality of life (CARMIS 2011) using the Italian version of the National Eye Institute Visual function questionnaire (NEI-VFQ).

There were several different strategies for dealing with eyes. Some studies reported AMD for the person which means that the unit of analysis was the person and they were counted as having AMD if it was present in one or both eyes (AREDS 2001). Some studies reported findings on right eyes and left eyes separately (AMDSG 1996; Veterans LAST study 2004), selected a trial eye (Bartlett 2007; Kaiser 1995; Wang 2004) or averaged the data for the two eyes in participants where both eyes were included (CARMA 2013).

Data from AREDS 2001 were reported as adjusted odds ratios only. The odds ratios were calculated using repeated-measures logistic regression and were adjusted for baseline co-variates age, sex, race, AMD category and smoking status.

People taking antioxidant vitamins were probably less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 2445 participants; 3 studies; moderate-certainty evidence; Analysis 1.1), neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; 1206 participants; 1 study; moderate-certainty evidence; Analysis 1.2) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; 1206 participants; 1 study; moderate-certainty evidence; Analysis 1.3), and probably less likely to lose 3 or more lines of visual acuity (OR 0.77, 95% CI 0.62 to 0.96; 1791 participants; 1 study; moderate-certainty evidence; Analysis 1.4).

Trials reporting mean visual acuity in continuous format were smaller and had shorter treatment and follow-up durations (AMDSG 1996; Bartlett 2007; CARMA 2013; CARMIS 2011; Veterans LAST study 2004). No effect of treatment on visual acuity was seen from these analyses. The pooled mean difference (MD) was 0.02 logMAR, 95% CI -0.03 to 0.07; participants = 595; studies = 5; I^2 = 38%) (Analysis 1.5).

CARMIS 2011 reported higher quality of life (NEI VFQ-25) scores in the treated compared with 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 (mean difference (MD) 12.30, 95% CI 4.24 to 20.36; 110 participants; 1 study; low-certainty evidence).

Table 3 summarises information available on adverse effects.

Very low-certainty evidence was available on adverse effects from these Included studies. They were underpowered to look at adverse effects and these were inconsistently reported. Data from AREDS 2001 suggested no important effect on mortality associated with multivitamin use (hazard ratio for mortality 0.87, 95% CI 0.60 to 1.25). In AREDS 2001 participants in the antioxidant arms more frequently reported yellow skin (8.3% versus 6.0%, P = 0.008).

None of the trials reported resource use and costs.

Lutein and/or zeaxanthin versus placebo

See Summary of findings 2.

Five studies compared lutein supplements (10 or 20 mg) with placebo and followed up for six months to five years (AREDS2 2013; CLEAR 2013; LISA 2011; Ma 2012; Veterans LAST study 2004). In AREDS2 2013, all participants also took the AREDS formula (Table 1).

Only one trial reported data on progression to late AMD, neovascular AMD, and geographic atrophy (AREDS2 2013). CLEAR 2013, LISA 2011, and Ma 2012 reported mean logMAR visual acuity measured on an ETDRS chart. Veterans LAST study 2004 measured visual acuity using a Snellen chart and converted the score into logMAR units. LISA 2011 did not report any data in a form that could be used in this review.

Only one trial reported on quality of life, using the Chinese version of the NEI-VFQ (Ma 2012).

There were several different strategies for dealing with eyes. AREDS2 2013 reported by eye. The study reports hazard ratios adjusted for one or two eyes per person. We have extracted data on eyes only. The confidence intervals for effect estimates from this study, as reported in this review, are therefore narrower than they should be as they do not take into account within-person correlation. As all confidence intervals around effect estimates from

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this study include 1 (no effect), this lack of adjustment does not make any difference to the conclusions of the review. Some studies reported findings on right eyes and left eyes separately (Veterans LAST study 2004) or selected a trial eye (CLEAR 2013; LISA 2011). In some studies there was not enough information to tell (Ma 2012).

People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (risk ratio (RR) 0.94, 95% CI 0.87 to 1.01; 6891 eyes; 1 study; low-certainty evidence; Analysis 2.1), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 6891 eyes; 1 study; low-certainty evidence; Analysis 2.2), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 6891 eyes; 1 study; low-certainty evidence; Analysis 2.3). Similar risk of progression to visual loss of 15 or more letters was seen in lutein and control group (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; 1 study; low-certainty evidence; Analysis 2.4).

Three studies reported mean logMAR visual acuity; there was no evidence of any difference between treatment and control groups (MD 0.00 logMAR, 95% CI -0.05 to 0.05; 231 participants; $I^2 = 0\%$).

Ma 2012 observed similar changes in quality of life scores between supplement and placebo groups (MD 1.48 score, 95% CI -5.53 to 8.49; 108 participants; 1 study; low-certainty evidence).

Table 3 summarises information available on adverse effects.

Very low-certainty evidence was available on adverse effects from these Included studies. They were underpowered to look at adverse effects and these were inconsistently reported. Data from AREDS2 2013 suggested no serious adverse effects associated with lutein and zeaxanthin use. Hazard ratio for mortality comparing lutein/zeaxanthin to no lutein/zeaxanthin was 1.06 (95% CI 0.87 to 1.31).

None of the trials reported resource use and costs.

Vitamin E versus placebo

See Summary of findings 3.

There was only one trial investigating vitamin E alone (VECAT 2002). This trial randomised 587 participants to vitamin E supplementation and 592 to placebo, and followed them up for an average of four years. Over 80% of the participants in this trial had no signs of AMD. One eye per person was included in the trial.

The number of late AMD events was low (4/494 in vitamin E and 3/504 in placebo group) and therefore, the estimate of effect was very uncertain (RR 1.36, 0.31 to 6.05). We judged this to be very low-certainty evidence as there were only 7 events (downgraded two levels for imprecision) and only 19% of the study population had AMD (downgraded one level for indirectness). There were no data on neovascular AMD or geographic atrophy.

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 (RR 1.04, 95% CI 0.74 to 1.47). We downgraded for imprecision and indirectness giving low-certainty evidence.

No serious adverse effects were seen. Similar numbers of people in the vitamin E and placebo groups withdrew due to adverse effects (four versus seven), reported any adverse effect (91 versus 83), or ocular adverse effect (105 versus 90).

There were no data on quality of life or resource use and costs.

Zinc versus placebo

See Summary of findings 4.

Four trials investigated the effect of zinc supplementation (AREDS 2001; 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 further trial investigated zinc-monocysteine (Newsome 2008).

Three trials reported data on our primary outcome of progression to late AMD (AREDS 2001; Holz 1993; Stur 1996); only one of these trials reported data separately for neovascular AMD and geographic atrophy (AREDS 2001). Two studies reported mean visual acuity (Newsome 1988; Stur 1996).

There were several different strategies for dealing with eyes. Some studies reported AMD for the person which means that the unit of analysis was the person and they were counted as having AMD if it was present in one or both eyes (AREDS 2001). Some studies reported findings on right eyes and left eyes separately (Newsome 2008), selected a trial eye (Stur 1996) or averaged the data for the two eyes in participants where both eyes were included (CARMA 2013; Newsome 1988). In some studies there was not enough information to tell how eyes had been dealt with (France 1998; Holz 1993).

Data from AREDS 2001 were reported as adjusted odds ratios only. The odds ratios were calculated using repeated-measures logistic regression and were adjusted for baseline co-variates age, sex, race, AMD category and smoking status.

People taking zinc supplements may be less likely to progress to late AMD (OR 0.83, 95% CI 0.70 to 0.98; 3790 participants; 3 studies; low-certainty evidence; Analysis 4.1), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 2442 participants; 1 study; moderate-certainty evidence; Analysis 4.2), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 2442 participants; 1 study; moderate-certainty evidence; Analysis 4.3), and visual loss (OR 0.87, 95% CI 0.75 to 1.00; 3791 participants; 2 studies; moderate-certainty evidence; Analysis 4.4).

Only one trial has investigated zinc-monocysteine (Newsome 2008). At six months, people taking zinc-monocysteine read more letters (distance visual acuity). In people treated with zinc-monocysteine, the mean (SD) number of letters read correctly on an EDTRS charts with best correction was 39 (0.672) at baseline and 43 (0.784) at six months in their right eyes. In people taking placebo, the values were 40 (0.649) at baseline and 39 (0.921) in their right eyes. Differences between the groups were statistically significant. Similar findings were seen for the left eye.

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

Table 3 summarises information available on adverse effects.

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Very low-certainty evidence was available on adverse effects from these Included studies. They were underpowered to look at adverse effects and these were inconsistently reported.

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 with placebo (excluding AREDS 2001), 5/146 zinc-treated people withdrew due to gastrointestinal symptoms compared with 2/140 controls. No one developed copper-deficiency anaemia (high zinc intakes can inhibit copper absorption). In AREDS 2001 participants in the zinc arms reported more anaemia (13.2% versus 10.2%, P = 0.004), however, serum haematocrit levels were the same. 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). In AREDS2 2013 reported gastrointestinal disorders and hospitalizations for genitourinary diseases were similar comparing high-dose and low-dose zinc.

There were no data reported on quality of life and resource use and costs.

DISCUSSION

Summary of main results

The trials contributing to this review fall into two categories. There are three large trials with reasonably long treatment duration and follow-up of four to six years (AREDS 2001; AREDS2 2013; VECAT 2002). The other 16 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 provided reasonably clear answers to different questions. The AREDS 2001 trial provided evidence that long-term supplementation with vitamins C, E, beta-carotene, and zinc, in people with AMD, reduced the risk of progression of the disease and loss of visual acuity. The overall benefit was 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 may be of interest to people with AMD. In people with very early signs of AMD, who are at low risk of progression, this would mean that there would be approximately 4 fewer cases of progression to late AMD for every 1000 people taking vitamins (1 fewer to 6 fewer cases). In people at high risk of progression (i.e. people with moderate AMD) this would correspond to approximately 8 fewer cases of progression for every 100 people taking vitamins (3 fewer to 13 fewer).

AREDS2 2013 compared lutein or zeaxanthin with placebo. There was a modest or no risk reduction in AMD progression that was not statistically significant, but as all participants took the AREDS formula, there was no proper control group. Secondary analyses from the trial suggested that there may be some benefit in replacing beta-carotene with lutein, but these analyses were only exploratory (AREDS 2014). Other trials of lutein or zeaxanthin were small, of short duration, and did not report relevant outcomes. Limited data on mean visual acuity and quality of life did not suggest any important effects of these supplements on outcomes important to patients.

The VECAT 2002 study suggested that the general population should not take vitamin E with a view to preventing the incidence or progression of AMD (Evans 2017). However, the study was underpowered to answer the question about whether people with signs of AMD, such as those participating in the AREDS 2001 study, should take vitamin E. Currently, VECAT 2002 is the only published trial on vitamin E supplementation and AMD.

The other trials of multivitamin preparations, Ocuguard (AMDSG 1996), Ocupower (Veterans LAST study 2004), Visaline (Kaiser 1995), and lutein or antioxidant (Bartlett 2007), were either too small to provide evidence either way, or the data were not available in a format suitable to include in this review (CARMIS 2011; LISA 2011). 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 published trials investigated zinc supplementation (AREDS 2001; Holz 1993; Newsome 1988; Stur 1996), and one trial examined a novel zinc-monocysteine formulation (Newsome 2008). The AREDS 2001 study indicated that the beneficial effect of zinc supplementation was of a similar order to that of vitamin supplementation. The other trials provided 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 participants 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 were included here. Newsome 2008 found that zinc-monocysteine had beneficial effects on visual acuity and contrast sensitivity.

Overall completeness and applicability of evidence

The main evidence that antioxidant vitamin and mineral supplementation was of benefit came from the AREDS 2001 trial. As AREDS 2001 was a large, well-conducted randomised study, potential biases would have been minimised. The only area where bias may have been introduced was 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 2001 revealed little evidence for effectiveness of antioxidant vitamin and mineral supplements on preventing visual loss or progression of the disease. However, the other studies encompassed many different formulations and in general, were rather small and of short duration, which may explain the lack of effect.

AREDS 2001 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 genitourinary complications in people taking the zinc supplements. The safety of some of the components of the AREDS formulation have been questioned in other studies. Two large randomised controlled trials

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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. 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 that investigated antioxidant supplements for preventing all cause mortality, included 78 trials with 296,707 participants, and 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).

Quality of the evidence

As the majority of the trials were placebo-controlled, we mostly assessed them as being at low risk of bias. In particular, the two trials that contributed most of the data to this review were judged at low risk of bias (AREDS 2001; AREDS2 2013). There was some variable reporting of the smaller trials; the extent to which attrition bias may have played a role was not always clear. 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 was the variety of ways in which it could be reported – dichotomous with a variety of potential cut-points, as a continuous variable reporting change or final value. It was possible that investigators had 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.

The main reasons for downgrading the evidence were imprecision and indirectness. In particular, as all participants in AREDS2 2013 took multivitamin supplements, the results may not have represented a true reflection of the effect of lutein supplementation.

Potential biases in the review process

This review follows the guidance for the preparation of Cochrane reviews. We have made various changes to the protocol over the years (see Differences between protocol and review) but these have been guided by improvements in Cochrane methods, the structure of the data, or collaboration with NICE, rather than being data driven.

Agreements and disagreements with other studies or reviews

There have been a number of reviews published on this topic in the last 3 years (Andreatta 2014; Angelo 2015; Broadhead 2015; Buschini 2015; Carneiro 2017; Chew 2014; Downie 2014; Grover 2014; Hanus 2016; Liu 2015; Manikandan 2016; Prasad 2014; Sacconi 2017; Schmidl 2015; Zampatti 2014). In general, these reviews have been a narrative assessment of observational studies and RCT evidence, focusing mainly on the results of AREDS and AREDS2. On the basis of AREDS, these reviews generally conclude that supplementation may benefit people with AMD. This is the same conclusion as the current review. In general, more emphasis has been placed by these other studies on the secondary analyses of the AREDS2 study of lutein and zeaxanthin as a replacement for beta-carotene in the AREDS formula.

There has been one systematic review of lutein and zeaxanthin supplementation published (Liu 2015) which pooled data for 8 studies. All of these studies were identified by the current review but one has been excluded because lutein/zeaxanthin were combined with omega-3 fatty acids (LUTEGA 2013). In the current review, we only included studies that were lutein/zeaxanthin alone i.e. not combined with other antioxidant vitamins (CARMA 2013; CARMIS 2011). The data for the remaining studies were similar, but not identical, comparing Liu 2015 and the current review. The overall estimates of effect for visual acuity were similar with a pooled mean difference of -0.04 logMAR (95% CI -0.06 to -0.03) in Liu 2015 and -0.00 logMAR (95% CI -0.05 to 0.05) in the current review. Liu 2015 used the Jadad scale to assess quality of the included studies but this assessment was ignored in the conclusions. Similarly, no attempt was made to assess the overall certainty of the evidence. Although Liu 2015 concluded that lutein/zeaxanthin improve visual performance, we would probably have concluded, with the same data, that there was low-certainty evidence that lutein/zeaxanthin make little important difference to visual acuity as a mean difference of 2 letters (0.04 logMAR) is probably not clinically significant. Liu 2015 also included contrast sensitivity as an outcome and concluded that lutein/zeaxanthin showed "remarkable benefit". We did not consider contrast sensitivity.

The authors of AREDS2 2013 concluded in the main trial report that "Addition of lutein + zeaxanthin [...] to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD." This is similar to the findings of this review, where we conclude that supplements containing lutein and zeaxanthin may have little or no effect on the progression of AMD. The authors of AREDS2 2013 go onto suggest that "...because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation." Subsequent exploratory analyses of trial data from AREDS2 2013 suggested a benefit of lutein/zeaxanthin versus beta-carotene in this trial population, all of whom were taking supplements. For this reason, the authors of AREDS2 2013 recommend replacing beta-carotene with lutein. See for example https://nei.nih.gov/areds2/PatientFAQ. We have not considered these secondary analyses of AREDS2 2013 in this review. They were exploratory analyses and the subgroups considered were not pre-planned in this review.

AUTHORS' CONCLUSIONS

Implications for practice

People with AMD may experience modest delay in progression of the disease with antioxidant vitamin and mineral supplementation. This finding was 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. Our review shows little effect, if any, of supplements containing lutein and zeaxanthin on the progression of AMD but the evidence was low-certainty.

Antioxidant vitamin and mineral supplements are readily available for purchase without prescription in many countries. The decision to take these supplements is at the discretion of the person with AMD. The following benefits and harms need to be considered.

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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. However, it may be difficult to consume, as part of a normal diet, the levels of antioxidants and zinc described in the trials included in this review.

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; and 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 systemic 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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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

AMDSG 1996

Methods	Parallel group RCT 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 people randomised: 71 (eyes unknown) Number (%) of people followed up: 59 (83%) (eyes unknown) Average age (range): 72 years (unknown) Percentage women: 7% Ethnic group: unknown Baseline visual acuity: unknown Comorbidities affecting the eye: unknown Percentage current smokers: unknown

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AMDSG 1996 *(Continued)*

	Inclusion criteria: • people with a monocular 1 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: • longer than 1 year use of vitamins • ex-prisoners of war • chronic alcoholics with tobacco or nutritional amblyopia • gastrointestinal absorption disorders
Interventions	Intervention: • 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 (daily) * unknown number people randomised (eyes unknown) * 39 (unknown %) people followed up (eyes unknown) Comparator: • placebo, starch * unknown number people randomised (eyes unknown) * 32 (unknown %) people followed up (eyes unknown) Duration: 18 months Similarity between intervention and comparator: treatment and placebo may not have been identical
Outcomes	Primary: not specified Secondary: not specified Outcomes reported in the paper: • 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 Follow-up: 18 months Eyes: Reported right and left eyes separately
Notes	Source of funding: 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 Declaration of interest: unknown Date study conducted: unknown Trial registration number: unknown
Risk of bias	

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AMDSG 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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, labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote: "Group one and group two patients were randomised 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."
Allocation concealment (selection bias)	Unclear risk	Quote: "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, labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote: "Group one and group two patients were randomised 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."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "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, labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote: "Group one and group two patients were randomised 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."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "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, labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "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, labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote: "Group one and group two patients were randomised 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."

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AMDSG 1996 *(Continued)*

Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "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, labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service" Quote: "Group one and group two patients were randomised 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."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 participants withdrew from the study over 18 months. 4 participants died. 1 participant 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 dropouts from groups 1 and 2 but the numbers were not clearly described.
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information given - no access to study protocol and trial was not registered.

AREDS 2001

Methods	Parallel group RCT 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. 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 people randomised: 3640 (eyes unknown) Number (%) of people followed up: 2.4% lost to follow up Average age (range): 69 years (55 to 80) Percentage women: 56% Ethnic group: 96% white Baseline visual acuity: unknown Comorbidities affecting the eye: unknown Percentage current smokers: 8% 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:

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AREDS 2001 *(Continued)*

	• illness or disorders that would make long-term follow-up or compliance with study protocol unlikely or difficult

Interventions	Intervention:
	• antioxidants vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg (daily)
	• zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide (daily)
	  * 2737 people randomised (eyes unknown) (945 antioxidants only, 904 zinc only, 888 antioxidants plus zinc)
	  * 2.4% lost to follow-up but numbers by group not reported. Quote: "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups."
	Comparator:
	• placebo
	  * 903 people randomised (eyes unknown)
	  * 2.4% lost to follow-up but numbers by group not reported. Quote: "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups."
	Duration: average follow-up 6.3 years
	Similarity between intervention and comparator: Quote: "Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste."

Outcomes	Primary: • progression to advanced AMD (assessed using stereoscopic fundus colour photograph) • 15 letter or more decrease in visual acuity score (EDTRS logMAR chart) Secondary: • safety outcomes included: reported adverse events; serum levels of haemoglobin; hospitalisations and mortality. Follow-up: annual follow-up for at least 5 years Eyes: outcome was "in at least one eye" i.e. reported by person
Notes	Source of funding: Quote: "Supported by contracts from the National Eye Institute, National Institutes of Health, with additional support from Bausch and Lomb Pharmaceuticals." Declaration of interest: Quote: "The AREDS investigators have no commercial or proprietary interest in the supplements used in this study." Date study conducted: 1992 to 2001 Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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" Quote: "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".

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AREDS 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "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".
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "The 4 treatment interventions were double-masked..." "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" Quote: "Four participants (0.1%) were reported to have been unmasked during the trial"
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "The 4 treatment interventions were double-masked..." Quote: "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" Quote: "Four participants (0.1%) were reported to have been unmasked during the trial"
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "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)"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "Stereoscopic fundus photographs of the macula were taken at baseline and annually, beginning 2 years after randomization, and graded centrally using standardized grading procedures."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." Quote: "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" Quote: "Of almost 50,000 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."
Selective reporting (reporting bias)	Low risk	Quote: "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."

AREDS2 2013

Methods	Parallel group RCT Method of allocation: coded tablets Masking: participant - yes; provider - yes; outcome - yes Loss to follow-up: Quote: "Of the 4203 randomised participants, 141 (3%) were lost to follow-up and 368 (9%) died during the course of the study. Distributions were similar across the 4 treatment groups." Quote: "Participants lost to follow-up or who died during the course of the study were censored at the time of last contact." See follow-up data below - 99% of participants were included in the analysis.

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AREDS2 2013 *(Continued)*

Participants	Country: USA Number of people randomised: 4203 (6916 eyes) Number (%) of people followed up: 4176 (99%) using LOCF (6891 eyes) Average age (range): 74 years (68 to 79) Percentage women: 56% Ethnic group: 97% white Baseline visual acuity: average 78 letters on EDTRS chart Comorbidities affecting the eye: 25% bilateral pseudophakic, 13% with diabetes Percentage current smokers: 7% Inclusion criteria: • high risk of progression to advanced AMD with either bilateral large drusen or non-foveal geographic atrophy (no advanced AMD) or large drusen or non-foveal geographic atrophy in one eye and advanced AMD in the fellow eye (AREDS Simple Scale Score of 2, 3 or 4) • age 50 to 85 years • took at least 75% of study medication during the run-in phase • able and willing to consent to both the qualification and the randomisation/follow-up phases of the study • likely, willing, and able to undergo yearly examinations for at least five years • agreed to stop current use of supplements containing lutein, zeaxanthin, omega-3 LCPUFAs (specifically DHA+EPA), vitamin C, vitamin E, beta-carotene, zinc or copper, other than those supplied by AREDS2 • fundus photographs of adequate quality as assessed with a standardized protocol by the Reading Center (University of Wisconsin Fundus Photograph Reading Center) • randomised within three months following the qualification visit Exclusion criteria: • the presence of ocular disease in either eye that may have confounded evaluation of the retina • previous retinal or other ocular surgical procedures (other than cataract extraction) that may have complicated assessment of the progression of AMD • a chronic requirement for any systemic or ocular medication administered for other diseases and known to be toxic to the retina or optic nerve • previous daily supplementation with 2 mg or more of lutein, or 500 mg or more of omega-3 LCPUFAs, or both, for a period of 1 year or more prior to the date of randomization. (A participant was eligible for the study if he or she agreed to stop taking these supplements during the study run-in period) • intraocular pressure of 26 mm Hg or higher, or some reason to believe that the participant might have glaucoma • cataract surgery within 3 months or capsulotomy within 6 weeks prior to the qualification visit • history of lung cancer • any systemic disease with a poor five-year survival prognosis • haemochromatosis • Wilson's disease • recent diagnosis of oxalate kidney stones • any condition that would make adherence or follow-up difficult or unlikely • current participation in other studies that might affect adherence to the AREDS2 follow-up schedule • use of systemic anti-angiogenic therapy for treatment of choroidal neovascularization or cancer
Interventions	Intervention:

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AREDS2 2013 *(Continued)*

- lutein 10 mg and zeaxanthin 2 mg (1 tablet/day)
  * 2123 people randomised (3468 eyes)
  * 2107 (99%) people followed up (3451 eyes)

Comparator:

- placebo (1 tablet/day)
  * 2080 people randomised (3448 eyes)
  * 2069 (99%) people followed up (3440 eyes)

Almost all participants in both intervention and comparator groups took AREDS supplement and multivitamin with the study medication.

Duration: 5 years (median)

Similarity between intervention and comparator: The placebo was composed from free flowing corn starch-coated matrix of beadlets formed into a tablet of identical shape, size, and coating/internal colour (using the same quantity of colorings agents) as that containing lutein + zeaxanthin.

Other study arm: There was another study arm looking at docosahexaenoic acid (DHA) 350 mg and eicosapentaenoic acid (EPA) 650 mg (2 soft-gel capsules/day); it was not included in this review

Outcomes

Primary:

• progression to advanced AMD in people at moderate to high risk for progression
Secondary:
• 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

Follow-up: annual follow-up for 5 years

Eyes: Quote: "The unit of analysis for ophthalmic outcomes was by eye. The primary efficacy outcome, time to progression to advanced AMD, was assessed using a Cox proportional hazards model incorporating the method of Wei et al for obtaining robust variance estimates that allows for dependence among multiple event times (1 or 2 study eyes)."

Notes

Source of funding: Quote: "This study is supported by the intramural program funds and contracts from the National Eye Institute/National Institutes of Health (NEI/NIH), Department of Health and Human Services, Bethesda, MD. Contract No. HHS-N-260-2005-00007-C. ADB Contract No. N01-EY-5-0007. Funds were generously contributed to these contracts by the following NIH institutes: Office of Dietary Supplements (ODS), National Center for Complementary and Alternative Medicine (NCCAM), National Institute on Aging (NIA), National Heart, Lung and Blood Institute (NHLBI), and National Institute of Neurological Disorders and Stroke (NINDS)"

Declaration of interest: Quote: "A complete list of all AREDS2 investigator financial disclosures, which were collected for regulatory purposes, pursuant to US FDA regulations in 21 CFR Part 54, can be found at www.areds2.org. The member(s) of the writing committee have made the following disclosure(s): Frederick L. Ferris III; Bausch & Lomb (P) and the remainder had no conflicts of interest."

Date study conducted: September 2006 to October 2012 (from clinicaltrials.gov entry)

Trial registration number: NCT00345176

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random block design was implemented using the AREDS2 Advantage Electronic Data Capture system (AdvantageEDC SM) by the AREDS2 Co-

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AREDS2 2013 *(Continued)*

		ordinating Center (The EMMES Corporation, Rockville, Maryland) and stratified by clinical center and AMD status (large drusen both eyes or large drusen in one eye and advanced AMD in the fellow eye) to assure approximate balance across centers over time."
Allocation concealment (selection bias)	Low risk	Judgement comment: Central co-ordinating centre organised the random allocation and placebo controlled study.
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Judgement comment: Placebo controlled trial. Personnel measuring visual acuity unaware of allocation. Quote: "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and color."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Judgement comment: Placebo controlled trial. Fundus images graded by masked graders. Quote: "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and color."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Judgement comment: Placebo controlled trial. Personnel measuring visual acuity unaware of allocation. Quote: "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and color."
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Judgement comment: Placebo controlled trial. Fundus images graded by masked graders. Quote: "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and color."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 4203 randomised participants, 141 (3%) were lost to follow-up and 368 (9%) died during the course of the study. Distributions were similar across the 4 treatment groups."
Selective reporting (reporting bias)	Low risk	Judgement comment: AMD outcomes pre-specified in clinical trials registry and in published protocol paper were reported.

Bartlett 2007

Methods	Parallel group RCT 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 people randomised: 30 (30 eyes) Number (%) of people followed up: 25 (83%) (25 eyes) Average age (range): 69 years (55 to 82) Percentage women: 53% Ethnic group: 100% white

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Bartlett 2007 *(Continued)*

Baseline visual acuity: average visual acuity in intervention group was 0.20 logMAR and in control group was 0.08 logMAR

Comorbidities affecting the eye: unknown

Percentage current smokers: unknown

Inclusion criteria:

- provide written informed consent
- be available to attend one of the research centres
- 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
- concurrent use of nutritional supplements
- advanced AMD in 1 or both eyes

Interventions	Intervention:
	• lutein esters 6 mg, retinol 750 mg, vitamin C 250 mg, vitamin E 34 mg, zinc 10 mg, copper 0.5 mg (daily)
	  * 17 people randomised (17 eyes)
	  * 15 (88%) people followed up (15 eyes)
	
	Comparator:
	• placebo tablets containing cellulose (daily)
	  * 13 people randomised (13 eyes)
	  * 10 (77%) people followed up (10 eyes)
	
	Duration: 9 months
	
	Similarity between intervention and comparator: Quote: "The study formulation and placebo tablets were produced by Quest Vitamins Ltd, and were identical in external and internal appearance, and taste."

Outcomes	Primary: unknown Secondary: unknown Outcome measures specified on trial registration entry: • Distance and near visual acuity (VA) measured using Bailey-Lovie logMAR charts • Contrast sensitivity (CS) measured using a Pelli-Robson chart (Clement Clarke International, Harlow Essex, UK) • Colour vision measured using the PV-16 quantitative colour vision test • Macular Mapping (MM) test • Eger Macular Stressometer (EMS) used to assess glare recovery • Fundus photographs of the macular will be assessed using colour and edge analysis software Trial publication provided data on contrast sensitivity at 9-month follow-up. Protocol listed more outcomes (see below under selective reporting) and specified 9 and 18 months follow-up. Follow-up: 9 months (reported) and 18 months (not reported)

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Bartlett 2007 *(Continued)*

	Eyes: Trial eye selected (initial visit only). If both eyes were eligible for inclusion, the right eye was used
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 (SD) values taken from a sample of 50 ARM and atrophic AMD patients of the University optometry clinic (1.3970.22 log CS)." 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." Source of funding: Quote: "The project was sponsored by the UK College of Optometrists. Intervention and placebo tablets were provided by Quest Vitamins Ltd UK." Declaration of interest: unknown Date study conducted: March 2003 and December 2004 Trial registration number: ISRCTN78467674 (registered retrospectively)

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." "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."
Allocation concealment (selection bias)	Low risk	"Enrolment was carried out by HB, who, along with FE, was masked to group assignment." "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." "Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation."
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."
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

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Bartlett 2007 *(Continued)*

		and participants do not know which symbol represents the placebo tablets, and which represents the active formulation." "End of trial assessment using questionnaires indicated` masking success. Out of those participants taking the placebo tablet, 10% correctly 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 randomised 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 reported contrast sensitivity (CS): Quote: "Outcome measure CS was measured using a Pelli-Robson chart (Clement Clarke International, Edinburgh Way, Harlow, Essex, CM20 2TT, UK) and scored per letter."

Berrow 2013

Methods	Parallel group RCT Method of allocation: unclear Masking: participant - no; provider - no; outcome - yes Loss to follow-up: unclear, either no loss to follow-up or 2/16 (12.5%) loss to follow-up
Participants	Country: UK Number of people randomised: 14 (14 eyes) Number (%) of people followed up: 14 (100%) (14 eyes) Average age (range): 68 years (56 to 83) Percentage women: unknown Ethnic group: Caucasian Baseline visual acuity: unknown Comorbidities affecting the eye: unknown Percentage current smokers: unknown but average 7 pack-years in antioxidant group and 13.5 pack-years in the placebo group Inclusion criteria: • best-corrected distance VA of 0.2 LogMAR or better (for good mfERG central fixation) • clear optical media, as determined by a clear view of the fundus

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Berrow 2013 *(Continued)*

- no signs of other retinal or optic nerve disease other than ARM (as determined by fundal photography and questionnaire) in the study eye
- good general health (as determined by health questionnaire)
- no prescribed medication that could affect the retina (as determined by health questionnaire)

Exclusion criteria:

- moderate-to-dense lens opacities
- intraocular lens
- corneal opacities
- glaucoma or ocular hypertension
- previous history of intraocular inflammation
- previous history of retinal detachment
- retinal disease (other than ARM)
- previous retinal laser
- diabetes
- systemic hypertension
- history of ocular trauma
- neurological disease
- age-related macular degeneration (AMD) in the study eye
- drugs causing retinal toxicity
- previous ocular surgery
- epilepsy

Interventions	Intervention:
	• Ocuvite Duo (Bausch and Lomb) vitamin C 150 mg, cupric oxide 400 µg, vitamin E 15 mg, zinc oxide 20 mg, lutein 12 mg, zeaxanthin 0.6 mg, EPA 240 mg, DHA 840 mg
	  * 8 people randomised (8 eyes)
	  * 8 (100%) people followed up (8 eyes)
	Comparator:
	• no treatment
	  * 6 people randomised (6 eyes)
	  * 6 (100%) people followed up (6 eyes)
	Duration: 40 weeks
	Similarity between intervention and comparator: different because no placebo group

Outcomes	from clinical trial registry entry Primary: • multifocal electroretinogram amplitudes and latencies, assessed every 20 weeks for a period of 80 weeks Secondary: • macular pigment optical density, assessed every 20 weeks for a period of 80 weeks No numeric data on outcomes reported. Quote: "All participants undertook VA and CS assessment at all three visits. There were no significant changes between the treated and non-treated groups over 40 weeks for these measures." Follow-up: 40 weeks and 60 weeks Eyes: Quote: "Only one eye from each participant was studied.[...] The eye with the best-corrected distance VA was determined at the participant's first visit and this eye was assessed for subsequent visits.

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Berrow 2013 *(Continued)*

	If one eye had ARM, this eye was used. If both eyes had ARM, the eye with the best-corrected distance VA was used to ensure good mfERG fixation."
Notes	Source of funding: Quote: "The authors would like to thank Bausch and Lomb, Kingston-Upon-Thames, Surrey, UK for funding the research position and supplying the Ocuvite Duo nutritional supplement." Declaration of interest: Quote: "The authors declare no competing financial interests" Date study conducted: January 2009 to December 2011 Trial registration number: ISRCTN17842302 (retrospectively registered)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A total of fourteen participants with ARM were randomly allocated, using Microsoft Excel random number generator, to either receive a lutein-based oral supplement (treated group) or no supplement (non-treated group) at visit one."
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not clearly reported.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: No placebo - control group did not receive any intervention.
Blinding of participants and personnel (performance bias) Progression AMD	High risk	Judgement comment: No placebo - control group did not receive any intervention.
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	Judgement comment: No placebo - control group did not receive any intervention but study was described as "single masked", so outcome assessors were not aware of group assignment up to 40 weeks, when unmasking occurred. However, measurement of visual acuity may be influenced by participants knowledge of intervention.
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Judgement comment: No placebo - control group did not receive any intervention but study was described as "single masked", so outcome assessors were not aware of group assignment up to 40 weeks, when unmasking occurred.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A total of fourteen participants with ARM were randomly allocated, using Microsoft Excel random number generator, to either receive a lutein-based oral supplement (treated group) or no supplement (non-treated group) at visit one. These were from an original cohort of sixteen participants, two of which withdrew without giving reason. Only one eye from each" Judgement comment: Unclear to which group the 2 participants who withdrew had been randomly allocated.
Selective reporting (reporting bias)	High risk	Judgement comment: Trial was registered retrospectively, so not possible to check this. Follow-up at 80 weeks was not reported.

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CARMA 2013

Methods	Parallel group RCT Method of allocation: labelled containers Masking: participant - yes; provider - yes; outcome - yes Loss to follow-up: high attrition after 12 months - 9% follow-up at 3 years
Participants	Country: Ireland Number of people randomised: 433 (614 eyes) Number (%) of people followed up: at 12 months, 493 eyes (80%); at 24 months, 260 eyes (42%); and at 36 months, 58 eyes (9%) Average age (range): 74 years (unknown) Percentage women: 57% Ethnic group: unknown Baseline visual acuity: average 80 letters on logMAR chart Comorbidities affecting the eye: unknown Percentage current smokers: 14% Inclusion criteria: • 50 years and older • any severity of early AMD in one eye and late AMD (neovascular AMD or central geographic atrophy) in the fellow eye. The study eye was the eye free of late-stage AMD. • features of early AMD in at least 1 eye when both eyes were free of late-stage AMD.The minimum severity level was 20 soft distinct or indistinct drusen in the central macular field; if there were fewer than 20 drusen, focal hyperpigmentation was required to be present. Both eyes could be study eyes. • visual acuity of 0.3 logMAR units or better (70 letters or better on the ETDRS chart equivalent to Snellen 20/40) in the eye selected to be study eye Exclusion criteria: • not explicitly stated

Interventions	Intervention:
	
	• Ocuvite (Bausch and Lomb, Berlin, Germany) lutein 12 mg, zeaxanthin 0.6 mg, vitamin E 15 mg, vitamin C 150 mg, zinc oxide 20 mg, copper 0.4 mg (daily dose) one tablet twice daily
	  * 216 people randomised (304 eyes)
	  * unknown number (unknown %) people followed up (243 eyes) at 12 months
	
	Comparator:
	
	• Placebo (cellulose microcrystalline, lactose and magnesium stearate) (twice daily)
	  * 217 people randomised (310 eyes)
	  * unknown number (unknown %) people followed up (250 eyes) at 12 months
	
	Duration: Total study duration 3 years but high attrition after 12 months
	
	Similarity between intervention and comparator: Quote: "The placebo consisted of cellulose, lactose, and magnesium stearate and was manufactured to be indistinguishable from the active preparation in size, color, smell, and taste."

Outcomes	Primary:

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CARMA 2013 *(Continued)*

	• distance visual acuity Secondary: • retinal visual acuity • morphological progression of AMD (grading of stereoscopic colour fundus photographs) • macular pigment levels and serum levels of antioxidants Follow-up: every 6 months for 3 years, but high attrition after 12 months Eyes: mixture of one or two eyes per person (see above for details). Quote "Data will be aggregated to one result per participant—the sole result will stand for group 1 participants,and the mean of the two results will be applied to group 2 participants. " Analysis were then weighted by number of eyes.
Notes	Source of funding: Quote: "Supported by a grant from Bausch and Lomb, Dr. Mann Pharma, Berlin, Germany. The data set was managed and analyzed by the independent statistician (MRS) and his team. The senior corresponding author (UC) had full access to the data outputs. The funders had no access to the data, were not involved in the data analysis, and had no role in the construction of the manuscript, except in the approval of the final draft." Declaration of interest: Quote: "The author(s) have no proprietary or commercial interest in any materials discussed in this article." Date study conducted: June 2004 to April 2008 Trial registration number: ISRCTN94557601 (retrospectively registered)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each participant enrolled in the CARMA Study is allocated a unique number, which determines treatment allocation according to the computerized randomization database." Quote: "A block randomization design was used with stratification by center and by group status, and separate block randomised lists were provided to each site."
Allocation concealment (selection bias)	Low risk	Quote: "Each participant enrolled in the CARMA Study is allocated a unique number, which determines treatment allocation according to the computerized randomization database." and "This unique number exists on the identification label of each study preparation box. The masked study-preparation boxes are kept in the hospital pharmacy, and released in a sequential manner by the pharmacist on randomization of each participant, beginning with the first in the numerical series assigned to each clinical center. The participants are advised to take 1 tablet twice daily with a meal.The CARMA Study is strictly a double-masked clinical trial in that neither the CARMA participants nor the study staff, including the study investigator, are aware of the nature of study preparation allocated to the participants. To ensure masking, the study-preparation boxes are labelled with pre-assigned numbers at the site of manufacturing, and then shipped to both clinical centers for distribution. A single pharmacist involved with manufacturing of the study preparation holds the key to randomization of the CARMA supplements."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other." and "Participants and study staff were masked to treatment assignments"

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CARMA 2013 *(Continued)*

Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other." and "Participants and study staff were masked to treatment assignments"
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other." and "Participants and study staff were masked to treatment assignments"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Judgement comment: Fundus images graded by masked graders and all study personnel masked to intervention allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: High attrition and people with CNV and geographic atrophy excluded from analyses of visual acuity.
Selective reporting (reporting bias)	Low risk	Judgement comment: Negative primary outcome eventually published (in Ophthalmology) as letter, separately from the publication of the positive results in the secondary analysis, which appeared as a full paper in the same journal.

CARMIS 2011

Methods	Parallel group RCT 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 people randomised: 145 (145 eyes) Number (%) of people followed up: 84 (58%) (84 eyes) Average age (range): 73 years (unknown) Percentage women: 59% Ethnic group: unknown Baseline visual acuity: average 82 letters (ETDRS chart) Comorbidities affecting the eye: 30% of intervention group had had cataract surgery but none of the control group Percentage current smokers: 17% Inclusion criteria: • age 55 to 80 • diagnosis of nonexudative (dry) age-related macular degeneration (AMD) in at least one 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 center of the macula • best-corrected visual acuity in the trial eye ≥ 20/32 (0.2 logarithm of the minimum angle of resolution [logMAR]), 74 letters of Early Treatment Diabetic Retinopathy Study [ETDRS] chart) • able to understand and comply with the requirements of the trial

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CARMIS 2011 *(Continued)*

- no condition limiting view of the fundus (e.g. vitreous haemorrhage, cataracts, epiretinal membrane)
- available for a minimum trial duration of approximately 6 months
- agree to take only the nutritional supplement that is provided during this study

Exclusion criteria:

- ocular disease that causes irreversible reduction of visual acuity (amblyopia, uncontrolled glaucoma, anterior ischaemic optic neuropathy, clinically significant macular edema)
- lens opacity and score 4+ (Lens Opacity Classification System II)
- insufficient pupil dilation
- previous laser treatment of the posterior pole for any other reason
- macular changes not attributable to AMD
- carotenoids intolerance
- major chronic disease
- life expectation lower than 6 months
- withdrawal of informed consent
- enrolment in another clinical study with experimental product within the last 4 weeks or during the current study

Interventions	Intervention:
	• 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) (daily)
	  * 103 people randomised (103 eyes)
	  * 84 (82%) people followed up (84 eyes)
	Comparator:
	• no dietary supplementation
	  * 42 people randomised (42 eyes)
	  * 26 (62%) people followed up (26 eyes)
	Duration: 24 months
	Similarity between intervention and comparator: different, no placebo group

Outcomes	Reported in methods section of paper: Primary: • change in BCVA (the number of letters read on the logMAR chart) Secondary: • changes in macular function by CS using a Pelli-Robson chart (Clement Clarke International, Harlow Essex, UK) scored per lines • changes in visual function via the Italian-validated version of the 25-item NEI VFQ Reported in results section: • multi-focal electroretinograms (ERG) at 6 and 12 months Follow-up: 6, 12, and 24 months Eyes: One eye per person. Quote: "When patients fulfilled the inclusion criteria (Tab. I), the eye with the best VA was selected. When both eyes had the same VA, the right eye was chosen for final analysis."
Notes	Source of funding: unknown Declaration of interest: Quote: "The authors report no proprietary interest or financial support."

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CARMIS 2011 *(Continued)*

Date study conducted: December 2003 to September 2006

Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A permuted blocks allocation scheme was used to perform this random allocation"
Allocation concealment (selection bias)	Unclear risk	Quote: "A 24-month prospective open-label randomised study... " Quote: "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." Quote: "Study drug was administered by an unmasked physician who had no other role in the study." No mention was made of allocation ratios, but 103 people were recruited to treatment group and 42 to no treatment group
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "A 24-month prospective open-label randomised study... "
Blinding of participants and personnel (performance bias) Progression AMD	High risk	Quote: "A 24-month prospective open-label randomised study... "
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "A 24-month prospective open-label randomised study... " Quote: "In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator." However, as participants were not masked, this could have affected the measurement of visual acuity.
Blinding of outcome assessment (detection bias) Progression AMD	Unclear risk	Quote: "A 24-month prospective open-label randomised study... " Quote: "In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Nineteen people in the group T-AMD, and 16 subjects from the group NT-AMD, were excluded from final data analysis." This exclusion was uneven between the 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. Fundus examination but progression of AMD was not reported.

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CLEAR 2013

Methods	Parallel group RCT Method of allocation: coded tablets prepared by manufacturer Masking: participant - yes; provider - yes; outcome - yes Loss to follow-up: 13%
Participants	Country: The Netherlands and the UK Number of people randomised: 84 (84 eyes) Number (%) of people followed up: 73 (87%) (73 eyes) Average age (range): 71 years (unknown) Percentage women: 61% (56% in intervention group, 67% in control group) Ethnic group: unknown Baseline visual acuity: average 0.1 logMAR in intervention group, and 0.05 logMAR in control group Comorbidities affecting the eye: unknown Percentage current smokers: unknown Inclusion criteria: • 50 to 80 years • AMD grade 0 to 4 in one eye (Rotterdam grading) • best corrected visual acuity (BCVA) of logMAR 0.5 or better • minimal cataract Exclusion criteria: • any ophthalmic disorder, such as diabetic retinopathy; optic atrophy; pigmentary abnormalities considered by the investigating ophthalmologist to be less typical of AMD than of some other condition (e.g. myopia) • history of glaucoma • any dietary supplements containing lutein, zeaxanthin, or meso-zeaxanthin within 3 months of the start of the study • unable to understand the study procedures or unable to give informed consent

Interventions	Intervention:
	
	• lutein 10 mg (daily)
	  * 42 people randomised (42 eyes)
	  * 36 (86%) people followed up (36 eyes)
	
	Comparator:
	
	• placebo soya bean oil (daily)
	  * 42 people randomised (42 eyes)
	  * 37 (88%) people followed up (37 eyes)
	
	Duration: 12 months
	
	Similarity between intervention and comparator: Quote: "The [..] capsules and their packaging were completely indistinguishable"

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CLEAR 2013 *(Continued)*

Outcomes	Primary: • not described in paper but main aim was to investigate effects on MPOD and VA Secondary: • not described in paper Quote: "Other measurements conducted as part of the study were scanning laser ophthalmoscope (SLO)–based MPOD, retinal reflectometry–based MPOD, dark adaptometry, optical coherence tomography (OCT), and ocular scatter. These data will be described in separate reports." From clinical trials registry entry (but not prospectively registered): Primary Outcome Measures: Macular Pigment Optical Density (time frame: baseline, 4 months, 8 months, 12 months; designated as safety issue: No) Secondary Outcome Measures: Visual Acuity (time frame: baseline, 4 months, 8 months, 12 months; designated as safety issue: No) Follow-up: 3, 8, and 12 months Eyes: one eye per person, unclear how selected. Quote: "According to the inclusion criteria, a 'test eye' was allocated to each patient and data from only this eye were analyzed".
Notes	Source of funding: Quote: "Supported partly by BASF, the UK Medical Research Council, the Manchester Biomedical Research Centre, and the Greater Manchester Comprehensive Local Research Network." Declaration of interest: All authors reported no declaration of interest Date study conducted August 2007 to August 2009 (from clinical trials registry entry) Trial registration number: NCT01042860 (registered retrospectively)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization code was generated by the sample manufacturer. Treatment numbers were allocated in ascending order using the next available consecutive number and capsules distributed accordingly." Judgement comment: Unclear how code was generated, but we have assumed it was unpredictable.
Allocation concealment (selection bias)	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the in-

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CLEAR 2013 *(Continued)*

		tervention trial. The experimenters were unaware of which patients were assigned to which groups"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Follow-up high and similar between lutein (86%) and placebo groups (88%).
Selective reporting (reporting bias)	Low risk	Judgement comment: Outcomes in trials registry entry were reported.

France 1998

Methods	Parallel group RCT Method of allocation: unknown Masking: participant - unknown; provider - unknown; outcome - unknown Loss to follow-up: unknown
Participants	Country: France Number of people randomised: 170 (170 eyes) Number (%) of people followed up: unknown Average age (range): unknown Percengage female: unknown Ethnic group: unknown Baseline visual acuity: unknown Comorbidities affecting the eye: unknown Percentage current smokers: unknown Inclusion criteria: • neovascular AMD in one eye and drusen in the other

Interventions	Intervention:
	• zinc supplementation (30 mg/day)
	  • unknown number people randomised (eyes unknown)
	  • unknown number people followed up (eyes unknown)
	Comparator:
	• not known, but study described as "double blind"
	  • unknown number people randomised (eyes unknown)
	  • unknown number people followed up (eyes unknown)
	Duration: unknown

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France 1998 *(Continued)*

	Similarity between intervention and comparator: unknown
Outcomes	Primary: unknown Secondary: unknown Follow-up: unknown Eyes: one eye per person
Notes	Trial is unpublished. "Following an initial analysis, the study was terminated due to lack of effect, combined with high rate of intolerance to study medication." [Personal communication from investigator.] Source of funding: unknown Declaration of interest: unknown Date study conducted: unknown Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) Visual acuity	Unclear risk	No information available
Blinding of participants and personnel (performance bias) Progression AMD	Unclear risk	No information available
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	No information available
Blinding of outcome assessment (detection bias) Progression AMD	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available
Selective reporting (reporting bias)	Unclear risk	No information available

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Holz 1993

Methods	Parallel group RCT Method of allocation: not known Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: not known
Participants	Country: UK Number of people randomised: 58 (eyes not known) Number (%) of people followed up: not known Average age (range): 68 years (55 to 82) Percentage women: not known Ethnic group: not known Baseline visual acuity: not known Comorbidities affecting the eye: not known Percentage current smokers: not known

Interventions	Intervention:
	
	• zinc sulfate 200 mg (daily) 2 x 100 mg tablet
	  * 28 people randomised (eyes not known)
	  * unknown number people followed up (eyes not known)
	
	Comparator:
	
	• placebo (lactose capsule) 2 x 1 tablet daily
	  * 30 people randomised (eyes not known)
	  * unknown number people followed up (eyes not known)
	
	Duration: 12 to 24 months
	
	Similarity between intervention and comparator: not known

Outcomes	Primary: not known Secondary: not known Quote: "Parameters tested included visual acuity, peripheral and macular colour-contrast-sensitivity; pattern ERG and dark adaptation. Stereo fundus photographs and fluorescein angiograms were analyzed by investigators in a masked fashion using a standardized grading scheme" Follow-up: 12 to 24 months Eyes: unclear
Notes	Data available from abstract only: Source of funding: Gertrud-Kusen-Stiftung, Hamburg, grant # Ho92/93-01-2 Declaration of interest: not known Date study conducted: not known Trial registration number: not known

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Holz 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised double-blind study"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Visual acuity	Unclear risk	"randomised double-blind study"
Blinding of participants and personnel (performance bias) Progression AMD	Unclear risk	"randomised double-blind study"
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	"randomised double-blind study"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	"randomised 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	Parallel group RCT Method of allocation: sponsor prepared coded tablets Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: none
Participants	Country: Switzerland Number of people randomised: 20 (20 eyes) Number (%) of people followed up: 20 (20 eyes) Average age (range): 73 years (50 to unknown) Percentage women: 74% Ethnic group: not known Baseline visual acuity: not known

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Kaiser 1995 *(Continued)*

	Comorbidities affecting the eye: not known Percentage current smokers: not known 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

Interventions	Intervention:
	
	• 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.
	  * 9 people randomised (9 eyes)
	  * 9 (100%) people followed up (9 eyes)
	
	Comparator:
	
	• placebo resembling active treatment prepared by sponsor
	  * 11 people randomised (11 eyes)
	  * 11 (100%) people followed up (11 eyes)
	
	Duration: 6 months
	
	Similarity between intervention and comparator: not known

Outcomes	Primary: not specified Secondary: not specified Outcomes reported: • distance and near visual acuity • intraocular pressure • visual fields • lens opacity • retinal visual acuity • colour vision • contrast sensitivity Follow-up: 3 and 6 months Eyes: Only 1 eye per person was evaluated. In cases of bilateral AMD, the eye with better visual acuity was selected
Notes	Source of funding:not known Declaration of interest: not known Date study conducted: not known Trial registration number: not known

Risk of bias

Bias	Authors' judgement	Support for judgement

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Kaiser 1995 *(Continued)*

Random sequence generation (selection bias)	Low risk	Sequence generation not described in the report but through contact with investigator Quote: "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 through contact with investigator Quote: "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."
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 participants enrolled and 20 followed up
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

LISA 2011

Methods	Parallel group RCT Method of allocation: 2:1 intervention:control Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: unclear
Participants	Country: Austria Number of people randomised: 126 (126 eyes) Number (%) of people followed up: 116 (92%) using LOCF (116 eyes) Average age (range): 72 years (50 to 90) Percentage women: 57% Ethnic group: not known Baseline visual acuity: 83.9% (visual acuity reported as a percentage)

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LISA 2011 *(Continued)*

	Comorbidities affecting the eye: not known Percentage current smokers: not known Inclusion criteria: • people in categories 2, 3, or 4, according to the AREDS grading scheme • aged 50 to 90 years • clear nonlenticular ocular media • visual acuity > 0.4 Exclusion criteria: • primary retinal pigment epithelium atrophy >125 µm • 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 • history of treatment with photosensitising drugs

Interventions	Intervention:
	
	• 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
	  * 84 people randomised (84 eyes)
	  * unknown number people followed up (eyes unknown)
	
	Comparator:
	
	• placebo
	  * 42 people randomised (42 eyes)
	  * unknown number people followed up (eyes unknown)
	
	Duration: 6 months
	
	Similarity between intervention and comparator: unclear

Outcomes	Primary: not known Secondary: not known Outcomes reported in paper: • macular pigment optical density • mean differential light threshold • distance visual acuity (ETDRS chart) • mean arterial pressure • pulse rate • intraocular pressure From clinical trials.gov, but retrospectively registered Primary Outcome Measures: Macular pigment optical density (MPOD) as measured with optical reflectometry (time frame: 5 minutes; designated as safety issue: No) Secondary Outcome Measures: visual acuity using ETDRS charts (time frame: 15 minutes; designated as safety issue: No) Central visual field defects assessed with scanning laser scotometry (time frame: 30 minutes; designated as safety issue: No) Changes in fundus appearance as documented with fundus photos (time Frame: 5 minutes; designated as safety issue: No) Determination of an increased systemic antioxidative state in plasma and low density lipoprotein and Ppasma lutein concentrations (time frame: 5 minutes; designated as safety issue: No)

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LISA 2011 *(Continued)*

	Follow-up: 1 month, 3 months, and 6 months Eyes: Quote: "In each subject only one eye was chosen for inclusion. If both eyes were eligible, one eye was selected randomly."
Notes	Source of funding: Quote: "Supported by Pharmaselect, Vienna, Austria" Declaration of interest: All authors reported none Date study conducted: November 2006 to May 2011 (from clinicaltrials.gov) Trial registration number: NCT00879671 (registered retrospectively)

Risk of bias

Bias	Authors' judgement	Support for judgement
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." 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." 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 participants and personnel (performance bias) Progression AMD	Unclear risk	"All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting." 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." 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) Progression AMD	Unclear risk	"All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting." 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)

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LISA 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 people were not included in the analysis, but not clear to which group these people were randomised . In addition, 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 participant 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 participants who were lost to follow-up, the last observation was carried forward.
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available.

Ma 2012

Methods	Parallel group RCT Method of allocation: not described Masking: participant - yes; provider - yes; outcome - yes Loss to follow-up: unclearly reported but could be 1/108
Participants	Country: China Number of people randomised: 108 (eyes unknown) Number (%) of people followed up: 107 (99%) (eyes unknown) Average age (range): 69 (unknown) Percentage women: 58% Ethnic group: unknown Baseline visual acuity: 0.30 logMAR Comorbidities affecting the eye: 23% early cataracts Percentage current smokers: 6% Inclusion criteria: • early AMD defined as the presence of soft drusen, presence of any retinal pigmentary abnormalities in the absence of signs of late AMD, or both), according to the AREDS classification system Exclusion criteria • late AMD or other macular or choroidal disorders (e.g. macular edema, macular holes, central serous chorioretinopathy, or macular epiretinal membrane) • demonstrated the presence of significant central lens opacities precluding fundus autofluorescence • had an implanted intraocular lens • glaucoma • unstable chronic illness • history of intraocular inflammation • ocular trauma • laser treatment for retinal diseases • retina-vitreous surgery

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Ma 2012 *(Continued)*

	• photodynamic therapy • currently taking medications affecting macular function (e.g., chloroquine or oxazepam) • consumed dietary supplements containing vitamins or carotenoids within the 6 months before enrolment

Interventions	Intervention:
	• lutein 10 mg or lutein 20 mg or lutein 10 mg and zeaxanthin 10 mg (3 groups) (daily)
	  * 80 people randomised (eyes unknown)
	  * 79 (99%) people followed up (eyes unknown)
	Comparator:
	• placebo (daily)
	  * 27 people randomised (eyes unknown)
	  * 27 (100%) people followed up (eyes unknown)
	Duration: 12 months
	Similarity between intervention and comparator: unclear, placebo was not described

Outcomes	From the published paper: Primary: • macular pigment optical density Secondary: • best-corrected visual acuity • contrast sensitivity • photorecovery time • Amsler grid testing From clinical trials.gov (registered retrospectively): Primary Outcome Measures: MPOD and multifocal electroretinograms (time frame: 1 year) Secondary Outcome Measures: risk of advanced AMD. (time frame: 1 year) Follow-up: 24 weeks and 48 weeks Eyes: unclear how many eyes included in study
Notes	Source of funding: Quote: "Supported by the National Natural Science Foundation of China (grant no.: NSFC-30872113), Beijing, China." Declaration of interest: Quote: "The author(s) have no proprietary or commercial interest in any materials discussed in this article." Date study conducted: September 2009 to April 2012 Trial registration number: NCT01048476 (registered retrospectively) and NCT10528605 (registered retrospectively)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence with stratification by baseline macular pigment optical density (MPOD) was computer generated, using a permuted block design with block size of 8."

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Ma 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment." Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment." Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment." Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color."
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment." Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Only 1/108 participants apparently discontinued treatment and was excluded from the analysis. All other participants were followed up.
Selective reporting (reporting bias)	High risk	Judgement comment: Trial registered midway through recruitment. Outcome "late AMD" on trials register but not reported because: "... the present study was not powered adequately to detect a reduction in late AMD incidence". Other differences noted between publication and trials register entry - see above.

Newsome 1988

Methods	Parallel group RCT 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 people randomised: 174 (eyes unknown) Number (%) of people followed up: 151 (87%) (258 eyes) Average age (range): unknown (42 to 89 years) Percentage women: 65% Ethnic group: unknown Baseline visual acuity: unknown

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Newsome 1988 *(Continued)*

	Comorbidities affecting the eye: unknown Percentage current smokers: unknown 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 1 line • other known serious eye disease; diabetes mellitus • other known systemic or metabolic disease or congenital condition, which might interfere with results

Interventions	Intervention:
	
	• zinc sulfate 200 mg (daily) 1 x 100 mg twice daily
	  * 90 people randomised (eyes unknown)
	  * 80 (89%) people followed up (134 eyes)
	
	Comparator:
	
	• placebo
	  * 84 people randomised (eyes unknown)
	  * 71 (85%) people followed up (124 eyes)
	
	Duration: 1 to 2 years
	
	Similarity between intervention and comparator: Quote: "Identical appearing tablets containing lactose and fructose served as the placebo." Analyses were also stratified according to number of eyes per person.

Outcomes	Primary: not specified Secondary: not specified Outcomes reported in paper: • 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 Follow-up: 6, 12, 18, and 24 months Eyes: Some people had one eye enrolled in the study and some had two eyes: "To analyze the results of two eyes of the same participant, the individual eye data were averaged and that value was used."
Notes	Source of funding: Research Fund, Department of Veterinary Science, Utah State University, Logan; James L Shupe, DVM; Mary Katherine Peterson Foundation, Houston Declaration of interest: unknown Date study conducted: unknown Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement

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Newsome 1988 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned [...] using a computer-generated table of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "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."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "All other personnel were masked to the study." Quote: "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."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "All other personnel were masked to the study." Quote: "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."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "All visual acuities were determined by one of two masked observers throughout the study"
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "Two independent observers masked as to patient identity,..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"A total of 90 subjects [...] were randomised 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." Reasons for loss to follow-up zinc/placebo • 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)"

Newsome 2008

Methods	Parallel group RCT Method of allocation: random allocation using a 50% likelihood scheme Masking: participant - yes; provider - yes; outcome - yes

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Newsome 2008 *(Continued)*

	Losses to follow-up: total of 6; 3 in each group of 40 participants
Participants	Country: USA Number of people randomised: 80 (eyes unknown) Number (%) of people followed up: 74 (93%) (74 right and 72 left eyes) Average age (range): 74 years (unknown) Percentage women: 80% Ethnic group: 81% white Baseline visual acuity: unknown Comorbidities affecting the eye: unknown Percentage current smokers: unknown 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	Intervention:
	
	• zinc-monocysteine 50 mg (daily 1 x 25 mg twice daily
	  * 40 people randomised (eyes unknown)
	  * 37 (100%) people followed up (37 right and 25 left eyes)
	
	Comparator:
	
	• placebo
	  * 40 people randomised (eyes unknown)
	  * 37 (100%) people followed up (37 right and 37 left eyes)
	
	Duration: 6 months
	
	Similarity between intervention and comparator: unknown

Outcomes	Primary: • change in acuity • change in contrast sensitivity • change in photorecovery time Secondary: not specified Follow-up: 6 months Eyes: analysed right and left eyes separately
Notes	Source of funding: "This study was supported in part by the Retinal Disease Research Foundation, Inc. DN co-owns the U.S. patents on ZMC, licensed to Pipex Pharmaceuticals." Declaration of interest: unknown

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Newsome 2008 *(Continued)*

Date study conducted: unknown

Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A total of 80 subjects (40 per group) volunteered for the study and were randomised using a 50% likelihood scheme."
Allocation concealment (selection bias)	Low risk	Quote: "An unmasked co-ordinator gave subjects, upon enrolment, study materials in numbered containers using the randomization scheme. This individual performed no data collection."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "Study materials were in tinted pharmaceutical capsules that provided an indistinguishable appearance between ZMC and the plant cellulose placebo."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "Study materials were in tinted pharmaceutical capsules that provided an indistinguishable appearance between ZMC and the plant cellulose placebo."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "Functional assessment....by masked trained examiners..." Quote: "Masked examiners determined contrast sensitivity...."
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "Functional assessment....by masked trained examiners..." Quote: "Masked examiners determined contrast sensitivity...."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Thirty-seven [out of 40] in each group competed all visits..." 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	Judgement comment: Difficult to assess with the information available.

Stur 1996

Methods	Parallel group RCT 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 people randomised: 112 (112 eyes) Number (%) of people followed up: 92 (82%) (92 eyes); 78 (70%) (78 eyes) included the analyses because eyes that developed CNV were excluded

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Stur 1996 *(Continued)*

	Average age (range): 71 years (50 to unknown) Percentage women: 57% Ethnic group: unknown Baseline visual acuity: average 0.075 logMAR Comorbidities affecting the eye: unknown Percentage current smokers: 21% 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 that 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	Intervention:
	
	• zinc sulfate 200 mg (daily) 1 tablet
	  * 56 people randomised (56 eyes)
	  * unknown number (%) people followed up but 37 (37 eyes) included in the analyses, excluding eyes that developed CNV
	
	Comparator:
	
	• placebo 1 tablet
	  * people randomised (eyes unknown)
	  * unknown number (%) people followed up but 41 (41 eyes) included in the analyses, excluding eyes that developed CNV
	
	Duration: 24 months
	
	Similarity between intervention and comparator: Intervention was lemon flavoured effervescent tablet made of citric acid containing saccharine and sorbitol and placebo was as treatment, but without the zinc sulfate

Outcomes	Primary: not specified Secondary: not specified Outcomes reported in paper: • 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 Follow-up: 6, 12, 18, and 24 months Eyes: one eye per person, CNV in one eye and not in the fellow eye. The fellow eye was the "study eye."
Notes	A priori sample size estimate was 500 participants, but trial stopped early because interim analysis showed no detectable trend

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Stur 1996 *(Continued)*

Funders: Astra, Linz, Austria; Austrian Foundation for the Propagation of Scientific Research

Source of funding: "Supported in part by the Austrian Foundation for the Propagation of Scientific Research (Ostetreichischer Fonds zur Forderung der xuissenschaftlichen Forschung), Project 7215-MED." and "The authors thank the staff at Astra GmbH, Linz, Austria, for providing the coded doses of zinc sulfate and placebo."

Declaration of interest: "Proprietary interest category: No"

Date study conducted: March 1990 to June 1992

Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This was a double-masked, randomised, placebo-controlled study conducted at a single center. The randomization between zinc and placebo was performed in a ratio 1:1" Judgement comment: 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	Quote: "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."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "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."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "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."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "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."

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Stur 1996 *(Continued)*

Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "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."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "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 scheduled 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." Quote: "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."
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

VECAT 2002

Methods	Parallel group RCT Method of allocation: coded bottles Masking: participant - yes; provider - yes; outcome - yes Losses to follow-up: 11 participants excluded after randomisation
Participants	Country: Australia Number of people randomised: 1204 (eyes unknown) randomised, but 11 participants excluded after randomisation, and reported 1193 (eyes unknown) randomised by group Number of people followed up: 1179 (98%) Average age (range): 66 years (55 to 80) Percentage women: 56% Ethnic group: unknown Baseline visual acuity: 99% ≥ 40 letters on logMAR chart Comorbidities affecting the eye: only 19% with AMD; 4% with diabetes; approximately 20% with lens opacity Percentage current smokers: 2% Inclusion criteria: • lens and retina of at least 1 eye available for documentation Exclusion criteria: • previous cataract surgery or advanced cataract in both eyes

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VECAT 2002 *(Continued)*

	• steroid or anticoagulation use • serious disease • regular use or sensitivity to vitamin E

Interventions	Intervention:
	• vitamin E 500 IU per day: natural vitamin E in soybean oil medium
	  * 595 people randomised (eyes unknown)
	  * 587 (99%) people followed up (eyes unknown)
	Comparator:
	• placebo of soybean oil medium
	  * 598 people randomised (eyes unknown)
	  * 592 (99%) people followed up (eyes unknown)
	Duration: 4 years
	Similarity between intervention and comparator: Quote: "Vitamin E and placebo capsules were of identical appearance and taste."

Outcomes	Primary: • development of early AMD Secondary: • progression of early AMD • development of late AMD • changes in visual acuity (the number of letters read on the logMAR chart) • changes in visual function (VF14 score). Follow-up: annual follow-up for 4 years Eyes: Quote: "Participants were categorised by their worse eye."
Notes	Source of funding: "The VECAT study was funded in part by grants from the National Health and Medical Research Council, Jack Brockhoff Foundation, the Eirene Lucas Foundation, the Stoicesco Foundation, the Carleton Family Charitable Trust, Je Hope Knell Trust Fund, Smith and Nephew, Australia, and Henkel Australia." Declaration of interest: no competing interests declared Date study conducted: January 1995 to January 2000 Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were then randomly allocated to treatment group. This random allocation was performed by using a “permuted blocks” allocation scheme."
Allocation concealment (selection bias)	Low risk	Quote: "Study numbers were allocated sequentially by the study coordinator as participants were enrolled in the study." Quote: "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

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VECAT 2002 *(Continued)*

		avoid confusion. Identical containers were used. The jars were packed in numerical order and then dispensed by study personnel."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "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."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "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."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "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."
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "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." Quote: "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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: 78/595 (13%) participants in vitamin E group and 72/598 (12%) of placebo group withdrew over the course of the study. Reasons for withdrawal reported in table form.
Selective reporting (reporting bias)	High risk	Judgement comment: For visual acuity, trial report states that outcome was analysed but only reports that result was not significant.

Veterans LAST study 2004

Methods	Parallel group RCT 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 or antioxidant), 80% compared with other 2 groups (lutein alone 86%, placebo 87%).
Participants	Country: USA Number of people randomised: 90 (eyes unknown) Number of people followed up: 76 (84%) (eyes unknown) Average age (range): approximate 75 years Percentage women: 4% Ethnic group: unknown Baseline visual acuity: average ranged from 0.279 to 0.445 logMAR by eye and treatment group Comorbidities affecting the eye: unknown

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Veterans LAST study 2004 *(Continued)*

	Percentage current smokers: unknown Inclusion criteria: • atrophic AMD diagnosed by ophthalmoscopy • 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	Intervention:
	
	• lutein 10 mg non-esterified lutein (FloraGlo from Kemin Foods International, Des Moines, Iowa)
	  * 29 people randomised (eyes unknown)
	  * 25 (86%) people followed up (eyes unknown)
	• lutein plus additional antioxidants and nutrients (OcuPower, Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida)
	  * 30 people randomised (eyes unknown)
	  * 24 (80%) people followed up (eyes unknown)
	
	Comparator:
	
	• placebo, maltodextrin
	  * 31 people randomised (eyes unknown)
	  * 27 (87%) people followed up (eyes unknown)
	
	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
	
	Similarity between intervention and comparator: "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food"

Outcomes	Primary: • macular pigment optical density Secondary: • not specified 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

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Veterans LAST study 2004 *(Continued)*

- VFQ-14 (activities of daily living, night driving, glare recovery symptoms)
- Amsler grid
- self reported vision

It was difficult to extract data on outcomes of relevance to this review: i.e. visual acuity and progression of AMD.

Follow-up: 12 month

Eyes: reported right and left eyes separately

Notes	Source of funding: "This material is based on work supported by the DVA Medical Center, North Chicago, Illinois and the Department of Veteran's Affairs, Hines, Illinois." and "Grant sponsors are Kemin Foods, Inc. (Des Moines, Iowa); L/itacost.com, with its subsidiary Nutraceutical Sciences Institute (NSI: Boynton Beach, Florida); and Great Smokies Diagnostic Laboratory (Asheville, North Carolina). FloraGloB non-esterified lutein is a product of Kemin Foods. The FloraGloB lutein antioxidant supplement evaluated is known as OcuPower@, U.S. Patent #6,103,756-Wayne Gorsek, inventor; L/itacost.com assignee." Declaration of interest: unknown Date study conducted: August 1999 to May 2001 Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... were randomly assigned to one of three capsule groups by consecutive random card-3-choice, allocation sequence"
Allocation concealment (selection bias)	Low risk	Quote: "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." "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study." "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Quote: "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study." Quote: "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study." Quote: "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of outcome assessment (detection bias) Progression AMD	Low risk	Quote: "All personnel at the DVA Medical Cetnter were unaware of the masked allocation codes during the 12-month clinical study."

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Veterans LAST study 2004 *(Continued)*

		Quote: "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: Loss to follow-up 14/90: 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	Judgement comment: Difficult to assess with the information available.

Wang 2004

Methods	Parallel group RCT Method of allocation: unknown Masking: participant - unknown; provider - unknown; outcome - unknown Losses to follow-up: unknown
Participants	Country: China Number of people randomised: 400 (400 eyes) Number of people followed up: unknown Average age (range): 65 years (52 to 76) Percentage women: 53% Ethnic group: unknown Baseline visual acuity: unknown Comorbidities affecting the eye: unknown Percentage current smokers: unknown

Interventions	Intervention:
	
	• zinc oxide 80 mg daily, vitamin C, vitamin E
	  * unknown number people randomised (eyes unknown)
	  * unknown number (%) people followed up (eyes unknown)

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Wang 2004 *(Continued)*

	Comparator:
	• placebo
	  * unknown number people randomised (eyes unknown)
	  * unknown number (%) people followed up (eyes unknown)
	Duration: 24 to 32 months
	Similarity between intervention and comparator: unknown

Outcomes	Primary: • not specified Secondary: • not specified Outcomes: • visual acuity • early and late AMD Follow-up: every 6 months for 24 to 32 months Eyes: one eye per person, worse eye was selected
Notes	Limited information available on this trial. AMD participants were stratified into early and late-stage disease Source of funding: unknown Declaration of interest: unknown Date study conducted: unknown Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
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

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Wang 2004 *(Continued)*

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
AREDS: Age-Related Eye Disease Study
ARM: Age-related maculopathy
CNV: Choroidal neovascularisation
ERG: electroretinogram
ETDRS: Early Treatment Diabetic Retinopathy Study
GA: Geographic atrophy
LOCF: last observation carried forward
logMAR: logarithm of the minimal angle of resolution
mfERG: multifocal electroretinogram
MPOD: macular pigment optical density
NEI: National Eye Institute
RCT: randomised controlled trial
RDA: recommended dietary allowance
RPE: retinal pigment epithelium
SD: standard deviation
VFQ: Visual function questionnaire
ZMC: zinc-monocysteine

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

Study	Reason for exclusion
Akuffo 2015	No placebo or untreated group in the study
Anonymous 2015	Review
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
CREST 2014	Lutein and zeaxanthin compared to placebo with the aim of enhancing vision in healthy people. Some of the participants had AMD but they were all given supplementation i.e. no control group.

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Study	Reason for exclusion
Cumurcu 2006	Not an RCT
Falsini 2010	Trial of saffron
Franciose 2006	Bioavailability study
Goodrow 2006	Bioavailability study
ISRCTN35481392	Participants had no ocular pathology www.controlled-trials.com/ISRCTN35481392/ISRCTN35481392
ISRCTN57556290	No comparator group www.biomedcentral.com/1471-2415/7/3
ISRCTN81595685	Comparison of two active formulations
Kamburoglu 2006	Not an RCT, not antioxidant
Khachik 2006	Bioavailability study
Kolber 2013	Review
Kopsell 2006	Bioavailability study
Landrum 2012	Pilot study of effects of lutein supplementation on serum and macular pigment
Lim 2006	Not antioxidant
LUNA 2007	Bioavailability study
LUTEGA 2013	Antioxidants combined with omega-3 fatty acids
LUXEA 2006	only MPOD measured; no clinical outcomes
Meagher 2013	Conference abstract reporting MPOD only
Moeller 2006	Not an 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
NCT00800995	Not antioxidant vitamin or mineral (superoxide dismutase)
NCT00893724	Antioxidants combined with inosine
NCT02264938	No control group

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Study	Reason for exclusion
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 2012	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.
Sabour-Pickett 2014	No control group
Sasamoto 2011	Not an RCT
Scalinci 2002	Antioxidants combined with omega-3
Scorolli 2002	Antioxidants combined with PDT
Souied 2013	Not an antioxidant supplement (omega-3)
Told 2014	Small study of physiological effects in healthy volunteers
Told 2015	Small study of physiological effects in healthy volunteers
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
Wolf-Schnurrbusch 2015	Antioxidant compared to antioxidant plus omega-3
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 ongoing studies *[ordered by study ID]*

NCT01694680

Trial name or title	Intervention trial in early age-related macular degeneration

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NCT01694680 *(Continued)*

Methods	Parallel group RCT
Participants	N = 120
Interventions	Dietary Supplement: Lutein-enriched-egg beverage (NWT-02) Dietary Supplement: Placebo
Outcomes	from clinicaltrials.gov "Primary Outcome Measures: Visual function (time frame: 12 months; designated as safety issue: No) Secondary Outcome Measures: Carotenoid levels (time frame: 12 months; designated as safety issue: No); Levels of lutein and Zeaxanthin"
Starting date	October 2012 to April 2016
Contact information	EJ Johnson PhD Jean Mayer USDA Human Nutrition research Centyer on Aging (HNRCA), Boston
Notes	

NCT02625376

Trial name or title	Resveratrol for exudative age-related macular degeneration
Methods	Parallel group RCT
Participants	N = 489
Interventions	Dietary Supplement: Resvega Dietary Supplement: Trans-Resveratrol Dietary Supplement: placebo
Outcomes	from clinical trials.gov "Primary Outcome Measures: Comparaison of incidence of choroidal neovascularization between resveratrol group and placebo group at 24 months (time frame: 24 months; designated as safety issue: Yes) What is the influence of the daily intake of 500 mg of resveratrol on the incidence of neovascularization of the second eye? Secondary Outcome Measures: Comparaison of incidence of choroidal neovascularization between Resvega group and placebo group at 24 months (time frame: 24 months; designated as safety issue: Yes) What is the influence of the daily intake resvega on the incidence of neovascularization of the second eye?"
Starting date	August 2015 to August 2019
Contact information	Nicolas LEVEZIEL, MD, Ph Dpt of Ophthalmology, University Hospital of Poitiers, France
Notes	

DATA AND ANALYSES

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Comparison 1. Antioxidant multivitamin and mineral supplement versus placebo

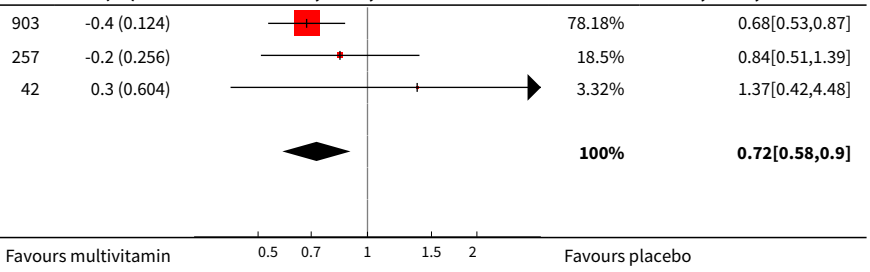
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression to late AMD (neovascular AMD or geographic atrophy)	3	2445	Odds Ratio (Fixed, 95% CI)	0.72 [0.58, 0.90]
2 Progression to neovascular AMD	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
3 Progression to geographic atrophy	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
4 Progression to visual loss (loss of 3 or more lines on logMAR chart)	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
5 Mean visual acuity	5	595	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.03, 0.07]
5.1 Mean visual acuity at end of study	1	59	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.13, 0.21]
5.2 Change in visual acuity	4	536	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.03, 0.07]
6 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Antioxidant multivitamin and mineral supplement versus placebo, Outcome 1 Progression to late AMD (neovascular AMD or geographic atrophy).

Study or subgroup	Multivitamin N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Weight	Odds Ratio IV, Fixed, 95% CI
AREDS 2001	888	903	-0.4 (0.124)		78.18%	0.68[0.53,0.87]
CARMA 2013	252	257	-0.2 (0.256)		18.5%	0.84[0.51,1.39]
CARMIS 2011	103	42	0.3 (0.604)		3.32%	1.37[0.42,4.48]
Total (95% CI)					**100%**	**0.72[0.58,0.9]**

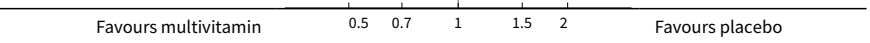
Heterogeneity: Tau^2=0; Chi^2=1.71, df=2(P=0.42); I^2=0%

Test for overall effect: Z=2.94(P=0)



Analysis 1.2. Comparison 1 Antioxidant multivitamin and mineral supplement versus placebo, Outcome 2 Progression to neovascular AMD.

Study or subgroup	Multivitamin N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
AREDS 2001	610	596	-0.5 (0.143)		0.62[0.47,0.82]



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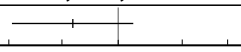
Analysis 1.3. Comparison 1 Antioxidant multivitamin and mineral supplement versus placebo, Outcome 3 Progression to geographic atrophy.

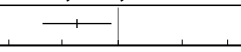
Study or subgroup	Multivitamin N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
AREDS 2001	610	596	-0.3 (0.197)		0.75[0.51,1.1]



Favours multivitamin — Favours placebo

Analysis 1.4. Comparison 1 Antioxidant multivitamin and mineral supplement versus placebo, Outcome 4 Progression to visual loss (loss of 3 or more lines on logMAR chart).

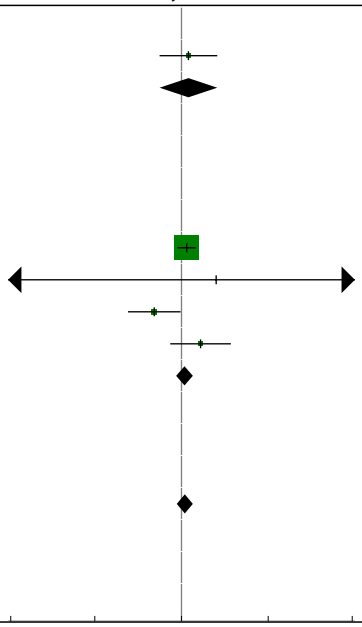
Study or subgroup	Multivitamin N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
AREDS 2001	888	903	-0.3 (0.112)		0.77[0.62,0.96]



Favours multivitamin — Favours placebo

Analysis 1.5. Comparison 1 Antioxidant multivitamin and mineral supplement versus placebo, Outcome 5 Mean visual acuity.

Study or subgroup	Multivitamin N	Multivitamin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Mean visual acuity at end of study							
AMDSG 1996	35	0.3 (0.4)	24	0.3 (0.2)		7.74%	0.04[-0.13,0.21]
Subtotal ***	**35**		**24**			**7.74%**	**0.04[-0.13,0.21]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.47(P=0.64)							
1.5.2 Change in visual acuity							
Bartlett 2007	20	0 (0.1)	10	-0 (0.1)		75.85%	0.03[-0.02,0.08]
CARMA 2013	172	-0.1 (7)	173	-0.3 (7.7)		0.09%	0.2[-1.35,1.75]
CARMIS 2011	84	-0.1 (0.5)	26	0 (0.3)		9.31%	-0.16[-0.31,-0.01]
Veterans LAST study 2004	24	-0 (0.2)	27	-0.1 (0.4)		7.01%	0.11[-0.06,0.28]
Subtotal ***	**300**		**236**			**92.26%**	**0.02[-0.03,0.07]**
Heterogeneity: Tau^2=0; Chi^2=6.43, df=3(P=0.09); I^2=53.34%							
Test for overall effect: Z=0.71(P=0.48)							
Total ***	**335**		**260**			**100%**	**0.02[-0.03,0.07]**
Heterogeneity: Tau^2=0; Chi^2=6.49, df=4(P=0.17); I^2=38.41%							
Test for overall effect: Z=0.81(P=0.42)							
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.8), I^2=0%							



Favours multivitamin — Favours placebo

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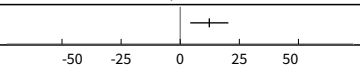
Analysis 1.6. Comparison 1 Antioxidant multivitamin and mineral supplement versus placebo, Outcome 6 Quality of life.

Study or subgroup	Multivitamin N	Multivitamin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
CARMIS 2011	84	3.6 (14.3)	26	-8.7 (19.4)		12.3[4.24,20.36]

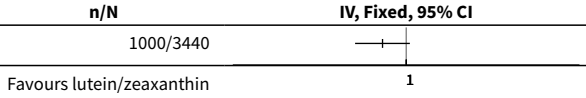


Comparison 2. Lutein and/or zeaxanthin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression to late AMD (neovascular AMD and/or geographic atrophy	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Progression to neovascular AMD	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Progression to geographic atrophy	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4 Progression to visual loss (loss of 3 or more lines on logMAR chart)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5 Distance visual acuity: mean	3	231	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.05, 0.05]
5.1 Mean visual acuity at end of study	1	72	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.06, 0.06]
5.2 Change in visual acuity	2	159	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.09, 0.08]
6 Visual Function Quality (VFQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Lutein and/or zeaxanthin versus placebo, Outcome 1 Progression to late AMD (neovascular AMD and/or geographic atrophy.

Study or subgroup	Lutein/zeaxanthin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
AREDS2 2013	940/3451	1000/3440		0.94[0.87,1.01]



Analysis 2.2. Comparison 2 Lutein and/or zeaxanthin versus placebo, Outcome 2 Progression to neovascular AMD.

Study or subgroup	Lutein/zeaxanthin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
AREDS2 2013	607/3451	655/3440		0.92[0.84,1.02]

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Analysis 2.3. Comparison 2 Lutein and/or zeaxanthin versus placebo, Outcome 3 Progression to geographic atrophy.

Study or subgroup	Lutein/zeaxanthin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
AREDS2 2013	367/3451	398/3440		0.92[0.8,1.05]

Favours lutein/zeaxanthin 1 Favours placebo

Analysis 2.4. Comparison 2 Lutein and/or zeaxanthin versus placebo, Outcome 4 Progression to visual loss (loss of 3 or more lines on logMAR chart).

Study or subgroup	Lutein/zeaxanthin n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
AREDS2 2013	1015/3332	1034/3324		0.98[0.91,1.05]

Favours lutein/zeaxanthin 1 Favours placebo

Analysis 2.5. Comparison 2 Lutein and/or zeaxanthin versus placebo, Outcome 5 Distance visual acuity: mean.

Study or subgroup	Lutein/zeaxanthin N	Lutein/zeaxanthin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.5.1 Mean visual acuity at end of study							
CLEAR 2013	36	0.1 (0.1)	36	0.1 (0.1)		64%	0[-0.06,0.06]
Subtotal ***	**36**		**36**			**64%**	**0[-0.06,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.5.2 Change in visual acuity							
Ma 2012	80	-0 (0.2)	27	0 (0.2)		27.85%	-0.02[-0.11,0.07]
Veterans LAST study 2004	25	-0.1 (0.2)	27	-0.1 (0.4)		8.15%	0.04[-0.13,0.21]
Subtotal ***	**105**		**54**			**36%**	**-0.01[-0.09,0.08]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%							
Test for overall effect: Z=0.15(P=0.88)							
Total ***	**141**		**90**			**100%**	**-0[-0.05,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.9), I^2=0%							

Favours lutein/zeaxanthin -0.4 -0.2 0 0.2 0.4 Favours placebo

Analysis 2.6. Comparison 2 Lutein and/or zeaxanthin versus placebo, Outcome 6 Visual Function Quality (VFQ).

Study or subgroup	Lutein/zeaxanthin N	Lutein/zeaxanthin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Ma 2012	80	78.8 (13.9)	28	77.3 (17.1)		1.48[-5.53,8.49]

Favours placebo -50 -25 0 25 50 Favours lutein/zeaxanthin

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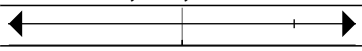
Comparison 3. Vitamin E versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression to late AMD (neovascular AMD and/or geographic atrophy	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Progression to visual loss (loss of 3 or more lines on logMAR chart)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Vitamin E versus placebo, Outcome 1 Progression to late AMD (neovascular AMD and/or geographic atrophy.

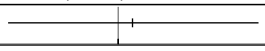
Study or subgroup	Vitamin E n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
VECAT 2002	4/494	3/504		1.36[0.31,6.05]



Favours vitamin E — Favours placebo

Analysis 3.2. Comparison 3 Vitamin E versus placebo, Outcome 2 Progression to visual loss (loss of 3 or more lines on logMAR chart).

Study or subgroup	Vitamin E n/N	Placebo n/N	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
VECAT 2002	59/587	57/592		1.04[0.74,1.47]



Favours vitamin E — Favours placebo

Comparison 4. Zinc versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression to late AMD (neovascular AMD or geographic atrophy)	3	3790	Odds Ratio (Fixed, 95% CI)	0.83 [0.70, 0.98]
2 Progression to neovascular AMD	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
3 Progression to geographic atrophy	1		Odds Ratio (Fixed, 95% CI)	Totals not selected
4 Progression to visual loss (loss of 3 or more lines on logMAR chart)	2	3791	Odds Ratio (Fixed, 95% CI)	0.87 [0.75, 1.00]
5 Distance visual acuity: mean	2	155	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.04]
5.1 Mean visual acuity at end of study	1	78	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.04, 0.08]

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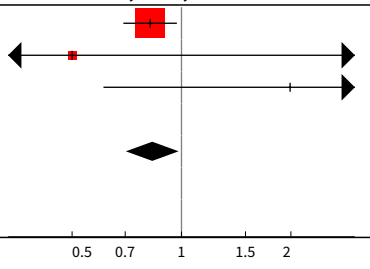
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.2 Change in visual acuity	1	77	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.14, 0.02]

Analysis 4.1. Comparison 4 Zinc versus placebo, Outcome 1 Progression to late AMD (neovascular AMD or geographic atrophy).

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 2001	1792	1848	-0.2 (0.086)		97.15%	0.82[0.69,0.97]
Holz 1993	28	30	-0.7 (0.922)		0.85%	0.5[0.08,3.05]
Stur 1996	46	46	0.7 (0.603)		1.99%	1.99[0.61,6.49]
Total (95% CI)					**100%**	**0.83[0.7,0.98]**

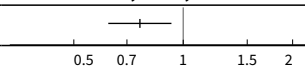
Heterogeneity: Tau^2=0; Chi^2=2.42, df=2(P=0.3); I^2=17.47%

Test for overall effect: Z=2.17(P=0.03)



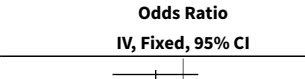
Analysis 4.2. Comparison 4 Zinc versus placebo, Outcome 2 Progression to neovascular AMD.

Study or subgroup	Zinc N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
AREDS 2001	1209	1233	-0.3 (0.102)		0.76[0.62,0.93]



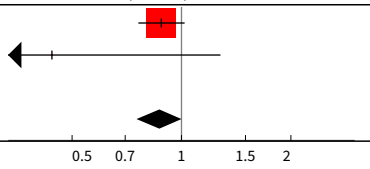
Analysis 4.3. Comparison 4 Zinc versus placebo, Outcome 3 Progression to geographic atrophy.

Study or subgroup	Zinc N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
AREDS 2001	1209	1233	-0.2 (0.139)		0.84[0.64,1.1]



Analysis 4.4. Comparison 4 Zinc versus placebo, Outcome 4 Progression to visual loss (loss of 3 or more lines on logMAR chart).

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 2001	1792	1848	-0.1 (0.074)		98.18%	0.88[0.76,1.02]
Newsome 1988	80	71	-0.8 (0.545)		1.82%	0.44[0.15,1.28]
Total (95% CI)					**100%**	**0.87[0.75,1]**



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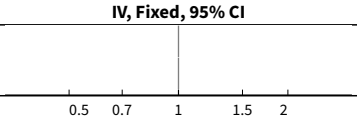
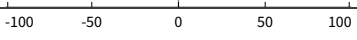
Study or subgroup	Zinc N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Weight	Odds Ratio IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.59, df=1(P=0.21); I²=37.05%						
Test for overall effect: Z=1.91(P=0.06)						



Analysis 4.5. Comparison 4 Zinc versus placebo, Outcome 5 Distance visual acuity: mean.

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.5.1 Mean visual acuity at end of study							
Stur 1996	37	0 (0.1)	41	0 (0.1)		65.96%	0.02[-0.04,0.08]
Subtotal ***	**37**		**41**			**65.96%**	**0.02[-0.04,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.65(P=0.52)							
4.5.2 Change in visual acuity							
Newsome 1988	40	0.1 (0.1)	37	0.1 (0.2)		34.04%	-0.06[-0.14,0.02]
Subtotal ***	**40**		**37**			**34.04%**	**-0.06[-0.14,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.46(P=0.14)							
Total ***	**77**		**78**			**100%**	**-0.01[-0.05,0.04]**
Heterogeneity: Tau²=0; Chi²=2.45, df=1(P=0.12); I²=59.18%							
Test for overall effect: Z=0.33(P=0.74)							
Test for subgroup differences: Chi²=2.45, df=1 (P=0.12), I²=59.18%							



ADDITIONAL TABLES

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Table 1. Multivitamin supplements

Study	AMDSG 1996	AREDS 2001	Berrow 2013	Bartlett 2007	CARMA 2013	CARMIS 2011	Kaiser 1995	Veterans LAST study 2004	Wang 2004
Brand name of supplement if reported	**OcuGuard (Twin Lab Inc, Ronkonkoma, NY)**	**-**	**Ocuvite Duo (Bausch and Lomb, Berlin)**	**-**	**Ocuvite (Bausch and Lomb, Berlin)**	**-**	**Visaline (Novopharma Cham, Switzerland).**	**OcuPower (Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida** **FloraGlo (Kemin Foods International, Des Moines, Iowa)**	**-**
Vitamin A	-	-	-	retinol 750 mg	-	-	-	2500 IU	-
Vitamin C	750 mg	500 mg	150 mg	250 mg	150 mg	180 mg	100 mg	1500 mg vitamin C (as calcium ascorbate)	dose not specified
Vitamin E	200 IU	400 IU	15 mg	34 mg	15 mg	30 mg	10 mg	500 IU natural vitamin E (d-alpha tocopherol succinate)	dose not specified
Beta-carotene	20,000 IU	15 mg	-	-	-	-	10 mg	15,000 IU natural beta carotene (Betatenem)	-
Lutein	-	-	12 mg	6 mg	12 mg	10 mg	-	10 mg	-
Zeaxanthin	-	-	0.6 mg	-	0.6 mg	1 mg plus astaxanthin 4 mg	-	-	-
Zinc	12.5 mg as zinc picolinate	80 mg as zinc oxide with cupric oxide 2 mg	25 mg as zinc oxide with cupric oxide 0.4 mg	10 mg with copper 0.5 mg	20 mg as zinc oxide with copper gluconate 0.4 mg	zinc 22.5 mg copper 1 mg	-	25 mg as zinc L-methionine-L-OptiZincB 1 mg copper	-
Selenium	50 µg	-	-	-	-	-	-	200 µg	-
Other ingredients	citrus bioflavonoid complex 125 mg	-	omega-3 fatty acids: EPA	-	-	-	1.5 mg buphenine HCl	400 IU vitamin D3 50 mg vitamin B1	-

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Table 1. Multivitamin supplements *(Continued)*

quercitin (bioflavonoid) 50 mg	240 mg and DHA 840 mg	10 mg vitamin B2
bilberry extract (bioflavonoid) 5 mg		70 mg vitamin B3
rutin (bioflavonoid) 50 mg		50 mg vitamin B
taurine 100 mg		550 mg vitamin B6
N-acetyl cysteine 100 mg		500 µg vitamin B12
L-glutathione 5 mg		800 µg folic acid
vitamin B2 25 mg		300 µg biotin
chromium 100 µg		500 mg calcium
		300 mg magnesium
		75 µg iodine
		2 mg manganese
		200 µg chromium
		75 µg molybdenum
		600 µg lycopene
		160 mg bilberry extract (standardized to 25% anthocyanosides)
		150 mg alpha lipoic acid
		200 mg N-acetyl cysteine
		100 mg quercetin
		100 mg rutin
		250 mg citrus bioflavonoids
		50 mg plant enzymes
		5 mg black pepper extract (BioperineB)
		325 mg malic acid
		900 mg taurine
		100 mg L-glycine

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Table 1. Multivitamin supplements *(Continued)*

	10 mg L-glutathione
	2 mg boron

Table 2. Characteristics of included trials

Study	Type of AMD	Treatment (dose/day)	Treatment duration	Follow-up	Data on eyes or people	Visual acuity	Progression AMD	Notes
AMDSG 1996	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) 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	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	-

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Table 2. Characteristics of included trials *(Continued)*

		Chromium 100 µg						
AREDS 2001	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	-
AREDS2 2013	bilateral large drusen or non-foveal geographic atrophy (no advanced AMD) or large drusen or non-foveal geographic atrophy in one eye and advanced AMD in the fellow eye (AREDS Simple Scale Score of 2, 3 or 4)	lutein 10 mg and zeaxanthin 2 mg (1 tablet/day) Almost all participants in both intervention and comparator groups took AREDS supplement and multivitamin with the study medication. Other study arm: There was another study arm looking at docosahexaenoic acid (DHA) 350 mg and eicosapentaenoic acid (EPA) 650 mg (2 soft-gel capsules/day); it was not included in this review	5 years (median)	5 years (median)	Eyes adjusted for within person correlation	Progression to moderate vision loss using ETDRS charts.	Progression to advanced AMD	-
Bartlett 2007	Soft or	Lutein esters 6 mg Retinol 750 mg Vitamin C 250 mg	9 months	9 months	Trial eye selected (initial visit only); If both	Change in logMAR acuity measured using ETDRS chart	Fundus photographs graded using AREDS classi-	-

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Table 2. Characteristics of included trials *(Continued)*

	hard drusen, and areas of increased or decreased pigment associated with these drusen	Vitamin E 34 mg Zinc 10 mg Copper 0.5 mg			eyes were eligible for inclusion, the right eye was used		fication system (4 categories). Mean (SD) grade was reported	
Berrow 2013	ARM	Ocuvite Duo (Bausch and Lomb) vitamin C 150 mg, cupric oxide 400 µg, vitamin E 15 mg, zinc oxide 20 mg, lutein 12 mg, zeaxanthin 0.6 mg, EPA 240 mg, DHA 840 mg	40 weeks	40 weeks and 60 weeks	One eye per participant	NA	NA	-
CARMA 2013	any severity of early AMD in one eye and late AMD (neovascular AMD or central geographic atrophy) in the fellow eye. The study eye was the eye free of late-stage AMD.	Ocuvite (Bausch and Lomb, Berlin, Germany) lutein 12 mg, zeaxanthin 0.6 mg, vitamin E 15 mg, vitamin C 150 mg, zinc oxide 20 mg, copper 0.4 mg (daily dose) one tablet twice daily	3 years	every 6 months for 3 years	Mixture of one and two eyes	ETDRS charts (logMAR)	Grading of colour fundus photographs	-
CARMIS 2011	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	-
CLEAR 2013	AMD grade 0 to 4 in one eye (Rotterdam grading) and visual acuity 0.5 or better	Lutein 10 mg	12 months	12 months	One eye per participant	Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart at 4 m	Not reported	-

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Table 2. Characteristics of included trials *(Continued)*

Holz 1993	People with drusen	Zinc sulfate 200 mg	Not stated but assume same as follow-up duration	12 to 24 months	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 months	6 months	Study eye identified	Decimal acuity measured using a Snellen chart	Not reported	-
LISA 2011	AREDS categories 2, 3, or 4	Lutein 20 mg a day for 3 months and then lutein 10 mg a day for 3 months	6 months	6 months	Study eye identified; if both eyes were eligible, one eye was selected randomly	Reported in graph form, not possible to extract data. Measured using ETDRS chart	Not reported	-
Ma 2012	Early AMD (drusen, pigmentary abnormalities)	Lutein 10mg Lutein 20mg Lutein 10mg and zeaxanthin 10mg	12 months	12 months	Unclear how many eyes included	Unclear how measured but reported in logMAR	Not reported	-
Newsome 1988	Drusen or pigmentary change (or both), VA 20/80 or better	Zinc sulfate 200 mg	12 to 24 months	12 to 24 months	Reported by eye; 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	-

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Table 2. Characteristics of included trials *(Continued)*

Stur 1996	Neovascular AMD in 1 eye, VA better than 20/40 in other eye	Zinc sulfate 200 mg	24 months	24 months	Study eye, which was fellow eye; other eye had neovascular AMD	Mean logMAR score measured using Bailey-Lovie chart Note: participants 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 participants at 24 months follow-up "did not show any treatment benefit"
VECAT 2002	Early AMD (18%) Late AMD (0.5%) Rest presumably had no signs of AMD	Vitamin E 500 IU	48 months	48 months	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 2004	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	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	-

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Table 2. Characteristics of included trials *(Continued)*

	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 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% anthocyano-sides) Alpha lipoic acid 150 mg

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Table 2. Characteristics of included trials *(Continued)*

	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)
	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

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Table 3. Adverse effects in the included studies.

Study number	Study name	Intervention	Adverse effects
1	AMDSG 1996	Multivitamin (Ocuguard)	One person developed an "allergic reaction", although it was not clear whether or not this was related to the treatment.
2	AREDS 2001	Multivitamin and zinc	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). No important effect on mortality associated with multivitamin use (hazard ratio for mortality 0.87, 95% CI 0.60 to 1.25). 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).
3	AREDS2 2013	Lutein and zeaxanthin	Quote "No clinically or statistically significant differences in reported serious adverse events, including rates of development of neoplasms, were noted across the treatment groups in the primary randomization. However, secondary randomization excluding participants who were smokers showed more lung cancers in the beta carotene group than in the no beta carotene group (23 [2.0%] vs 11 [0.9%]) (nominal P=.04)." and "Rates of reported gastrointestinal disorders and hospitalizations for genitourinary diseases were similar in the 2 randomly assigned groups (high-dose zinc, low-dose zinc) in AREDS2" "The HR for mortality comparing lutein zeaxanthin vs no lutein zeaxanthin was 1.06 (95% CI, 0.87-1.31;P=.56) for lutein zeaxanthin vs no lutein zeaxanthin"
4	Bartlett 2007	Multivitamin	"There were no reported adverse effects from any of the study participants."
5	Berrow 2013	Multivitamin (Ocuvite)	Did not report adverse effects.
6	CARMA 2013	Multivitamin (Ocuvite)	Did not report adverse effects.
7	CARMIS 2011	Multivitamin	Quote "There were no significant systemic or ocular adverse events related to the nutritional supplementation."
8	CLEAR 2013	Lutein	3/42 in the lutein group and 1/42 in the placebo group "discontinued due to medical reasons", but it was unclear if these were complications, per se.
9	France 1998	Zinc	Unpublished study, no data available.
10	Holz 1993	Zinc	Quote "the zinc therapy was well-tolerated".
11	Kaiser 1995	Multivitamin	Did not report adverse effects.
12	LISA 2011	Lutein (Lutamax)	Quote "In two subjects, the withdrawal was due to serious adverse events. One subject had a myocardial infarction, and the other subject developed CNV in the study eye."
13	Ma 2012	Lutein and zeaxanthin	Quote "No adverse events were observed or reported." and "No significant adverse events or changes in biochemical or hematologic profiles were observed or reported in any subject throughout the study. No subject developed or reported occasional skin pigmentation (carotenodermia)."

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Table 3. Adverse effects in the included studies. *(Continued)*

14	Newsome 1988	Zinc	Did not report adverse effects.
15	Newsome 2008	Zinc mono-cysteine	Quote "ZMC (zinc mono-cysteine) appeared to be well tolerated"; 1/40 had gastrointestinal symptoms attributable to treatment.
16	Stur 1996	Zinc	4/56 in the zinc-treated group and 2/56 in the placebo group withdrew because of gastrointestinal symptoms.
17	VECAT 2002	Vitamin E	11 in the vitamin E and 7 in the control group died; 16 in the vitamin E group and 17 in the control group had an adverse reaction.
18	Veterans LAST study 2004	Multivtamin (OcuPower) and lutein (FloraGlo)	The number of adverse effects were tabulated, but the study was underpowered to detect any differences.
19	Wang 2004	Multivitamin and zinc	Did not report adverse effects.

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

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#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 Ovid 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/

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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 2006.

Appendix 3. Embase Ovid 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/

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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 Ovid 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

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Appendix 5. OpenGrey search strategy

(macular degeneration OR AMD) AND (antioxidant OR vitamin OR carotene OR selenium OR tocopherol)

Appendix 6. ISRCTN search strategy

(macular degeneration OR AMD) AND (antioxidant OR vitamin OR carotene OR selenium OR tocopherol)

Appendix 7. ClinicalTrials.gov search strategy

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

Appendix 8. ICTRP search strategy

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

Appendix 9. MEDLINE Ovid 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")

WHAT'S NEW

Date	Event	Description
22 September 2017	Amended	Correction of discrepancy between Analysis 1.5 and text in Effects of interventions section. Sources of support and Acknowledgements updated.

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 1, 1998

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Date	Event	Description
29 March 2017	New search has been performed	Issue 7, 2017: Electronic searches were updated.
29 March 2017	New citation required but conclusions have not changed	Issue 7, 2017: Six new trials (AREDS2 2013; Berrow 2013; CARMA 2013; CLEAR 2013; France 1998; Ma 2012) were included in this 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.
11 July 2012	New search has been performed	Issue 9, 2012: John Lawrenson assisted with this review update.
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 the 2012 and 2017 updates, 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.
- National Institute for Health Research (NIHR), UK.

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  The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol was published in 1999. Since that time, there have been methodological improvements within Cochrane, and the methods have been updated to include assessment of risk of bias, 'Summary of findings' tables, GRADE assessment, and better consideration of unit of analysis issues.

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Previous versions of this review have included a comparison "Any multivitamin or single component antioxidant supplement versus placebo". We have dropped this comparison for the current review because the majority of the data for this review come from AREDS 2001 and AREDS2 2013. Given that all participants in AREDS2 2013 received the supplements trialled in AREDS 2001 it did not make much sense to pool these data.

For the update in 2017, we modified the outcome measures to ensure they were in line with those being used as part of the macular degeneration guidelines being prepared by NICE (NICE 2016). We also applied the default minimum important difference interval for dichotomous outcomes of 0.8 to 1.25 for downgrading for imprecision.

Table: Comparing outcome measures in current review with outcome measures in last published version

Current review (2017)*	Last published version (2012)
Progression to late AMD (neovascular AMD, geographic atrophy, or both) Progression to neovascular AMD Progression to geographic atrophy	Progression of the disease (secondary) • as defined by study investigators
Progression to visual loss • loss of 3 or more lines • continuous	Visual acuity (primary) • loss of 3 or more lines • continuous
Quality of life	Quality of life (secondary)
Resource use and costs	
Adverse effects	Adverse effects

* In the current review no primary / secondary outcomes are specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Antioxidants [*therapeutic use]; Dietary Supplements; Disease Progression; Geographic Atrophy [prevention & control]; Lutein [therapeutic use]; Macular Degeneration [*prevention & control]; Minerals [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Vitamin E [therapeutic use]; Vitamins [*therapeutic use]; Zeaxanthins [therapeutic use]; Zinc [therapeutic use]

MeSH check words

Aged; Humans

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