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

Evans JR, Lawrenson JG

Evans JR, Lawrenson JG.
Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration.
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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

Age-related macular degeneration (AMD) is a degenerative condition of the back of the eye that occurs in people over the age of 50 years. 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 AMD. This is the third update of the review.

### Objectives

To assess the effects of antioxidant vitamin and mineral supplements on the progression of AMD in people with AMD.

### Search methods

We searched CENTRAL, MEDLINE, Embase, one other database, and three trials registers, most recently on 29 November 2022.

### Selection criteria

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

### Data collection and analysis

We used standard methods expected by Cochrane.

### Main results

We included 26 studies conducted in the USA, Europe, China, and Australia. These studies enroled 11,952 people aged 65 to 75 years and included slightly more women (on average 56% women). We judged the studies that contributed data to the review to be at low or unclear risk of bias.

Thirteen studies compared multivitamins with control in people with early and intermediate AMD. Most evidence 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; 3 studies, 2445 participants; moderate-certainty evidence). In people with early AMD, who are at low risk of progression, this means there would be approximately four fewer cases of progression to late AMD for every 1000 people taking vitamins (one fewer to six fewer cases). In people with intermediate AMD at higher risk of progression, this corresponds to approximately 78 fewer cases of progression for every 1000 people taking vitamins (26 fewer to 126 fewer). AREDS also provided evidence of 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


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0.62 to 0.96; moderate-certainty evidence). Low-certainty evidence from one study of 110 people suggested higher quality of life scores (measured with the Visual Function Questionnaire) in treated compared with non-treated people after 24 months (mean difference (MD) 12.30, 95% CI 4.24 to 20.36). In exploratory subgroup analyses in the follow-on study to AREDS (AREDS2), replacing beta-carotene with lutein/zeaxanthin gave hazard ratios (HR) of 0.82 (95% CI 0.69 to 0.96), 0.78 (95% CI 0.64 to 0.94), 0.94 (95% CI 0.70 to 1.26), and 0.88 (95% CI 0.75 to 1.03) for progression to late AMD, neovascular AMD, geographic atrophy, and vision loss, respectively.

Six studies compared lutein (with or without zeaxanthin) with placebo and one study compared a multivitamin including lutein/zeaxanthin with multivitamin alone. The duration of supplementation and follow-up ranged from six months to five years. Most evidence came from the AREDS2 study in the USA; almost all participants in AREDS2 also took the original AREDS supplementation formula. People taking lutein/zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94, 95% CI 0.87 to 1.01), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05) compared with control (1 study, 4176 participants, 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15 or more letters was seen in the lutein/zeaxanthin and control groups (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; low-certainty evidence). Quality of life (Visual Function Questionnaire) was similar between groups (MD 1.21, 95% CI -2.59 to 5.01; 2 studies, 308 participants; moderate-certainty evidence).
One study in Australia randomised 1204 people to vitamin E or placebo with four years of follow-up; 19% of participants 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 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 neovascular AMD, geographic atrophy, or quality of life.
Five studies compared zinc with placebo. Evidence largely drawn from the largest study (AREDS) found a lower progression to late AMD over six years (OR 0.83, 95% CI 0.70 to 0.98; 3 studies, 3790 participants; moderate-certainty evidence), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; moderate-certainty evidence), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; moderate-certainty evidence), or visual loss (OR 0.87, 95% CI 0.75 to 1.00; 2 studies, 3791 participants; moderate-certainty evidence). There were no data on quality of life. Gastrointestinal symptoms were the main reported adverse effect. In AREDS, zinc was associated with a higher risk of genitourinary problems in men, but no difference was seen between high- and low-dose zinc groups in AREDS2.

Most studies were too small to detect rare adverse effects. Data from larger studies (AREDS/AREDS2) suggested there may be little or no effect on mortality with multivitamin (HR 0.87, 95% CI 0.60 to 1.25; low-certainty evidence) or lutein/zeaxanthin supplementation (HR 1.06, 95% CI 0.87 to 1.31; very low-certainty evidence), but confirmed the increased risk of lung cancer with beta-carotene, mostly in former smokers.

**Authors' conclusions**

Moderate-certainty evidence suggests that antioxidant vitamin and mineral supplementation (AREDS: vitamin C, E, beta-carotene, and zinc) probably slows down progression to late AMD. People with intermediate AMD have a higher chance of benefiting from antioxidant supplements because their risk of progression is higher than people with early AMD. Although low-certainty evidence suggested little effect with lutein/zeaxanthin alone compared with placebo, exploratory subgroup analyses from one large American study support the view that lutein/zeaxanthin may be a suitable replacement for the beta-carotene used in the original AREDS formula.

## PLAIN LANGUAGE SUMMARY

### Do antioxidant vitamin and mineral supplements slow down the progression of age-related macular degeneration (AMD)?

**Key messages**
- Taking an antioxidant multivitamin supplement may slow down the progression of age-related macular degeneration (AMD), an eye disease that blurs your central vision.

- People with intermediate AMD have a higher chance of benefiting from antioxidant supplements because their risk of progression is higher than for people with early AMD.

- 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 is age-related macular degeneration?**

Age-related macular degeneration (AMD) is an eye disease that blurs your central vision. It is usually only diagnosed in people aged 50 years and above. AMD affects the central area (macula) of the back of the eye (retina), as the macula degenerates with age.

In early AMD, yellow spots (called drusen) can be seen under the retina by an eye health professional. The affected person will probably be unaware that they have a problem. As the disease progresses, the drusen become larger (intermediate AMD). In the later stages of the disease, there may be loss of the cells – needed for vision – in the back of the eye. This is known as geographic atrophy. Sometimes, new (harmful) blood vessels grow in the macula. These new blood vessels may bleed and cause scarring. This is known as neovascular AMD. Neovascular AMD and geographic atrophy are known as late AMD.

**Why might antioxidant vitamins and minerals be helpful?**


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Antioxidant vitamins and minerals may help to protect the macula against this deterioration and loss of vision. Antioxidants are natural molecules that may prevent or delay some types of cell damage. Vitamins C and E, beta-carotene, lutein, zeaxanthin, and zinc are examples of antioxidants commonly found in dietary supplements.

**What did we want to find out?**
We wanted to find out whether antioxidant vitamin and mineral supplements slow down the progression of age-related macular degeneration (AMD) and prevent visual loss.

**What did we do?**

We searched for studies that compared antioxidant vitamin and mineral supplements with placebo (a 'dummy' treatment not containing any supplements) or no treatment. We 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. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

**What did we find?**

We found 26 studies from the USA, Europe, China, and Australia that enroled 11,952 people with AMD. These studies compared multivitamin supplements, zinc, vitamin E, lutein (with or without zeaxanthin) with placebo. Participants were aged 65 to 75 years and there were slightly more women than men in the studies.

**Main findings**

• Taking an antioxidant multivitamin supplement (AREDS formula containing vitamins E and C, beta-carotene plus zinc) probably slows down the progression of AMD to late AMD and vision loss. This may result in a small improvement in quality of life.

• People with intermediate AMD have a higher risk of progression to late AMD and so may be more likely to benefit from supplements (78 fewer cases of progression for every 1000 people taking supplements). People with early AMD have a low risk of progression and so may be less likely to benefit (4 fewer cases of progression to late AMD for every 1000 people taking supplements).

• Lutein with or without zeaxanthin may have little or no effect on progression to late AMD but may be a suitable replacement for beta-carotene in the AREDS formula. Beta-carotene may increase the chance of lung cancer in people who have smoked.

• The effects of vitamin E alone on the progression to late AMD and vision loss are uncertain.

Although vitamin supplements are generally regarded as safe, the studies included in this review did not provide good evidence about safety because most of the studies were small and reported on harmful effects inconsistently.

**What are the limitations of the evidence?**

Our confidence in the evidence ranged from moderate to very low. This is because most of the included studies were small, and they did not cover all the comparisons and outcomes we were interested in.

**How up to date is this review?**
This review updates our previous version. The evidence is up to date to 29 November 2022.


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**Summary of findings 1. Antioxidant multivitamin and mineral supplement versus placebo or no treatment for slowing the progression of age-related macular degeneration**

Antioxidant multivitamin and mineral supplement versus placebo or no treatment for slowing the progression of age-related macular degeneration

**Patient or population:** people with AMD
**Setting:** community
**Intervention:** AREDS formula: 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)
**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 antioxidant multivitamin and 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[a] | Most evidence from AREDS study with average follow-up of 6 years.<br>AREDS formula (minus beta-carotene) with lutein/zeaxanthin versus AREDS formula with beta-carotene: hazard ratio (HR) 0.82 (95% CI 0.69 to 0.96) |
| | 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[a] | Average follow-up of 6 years. Estimate of effect from study population including AMD categories 3 & 4 only.<br>AREDS formula (minus beta-carotene) with lutein/zeaxanthin versus AREDS formula with beta-carotene: HR 0.78 (95% CI 0.64 to 0.94). |
| | 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[a] | Average follow-up of 6 years. Estimate of effect from study population including AMD categories 3 & 4 only. |
| | 10 per 1000 | 8 per 1000 (5 to 11) | | | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | High | | | | | AREDS formula (minus beta-carotene) with lutein/zeaxanthin versus AREDS formula with beta-carotene: HR<br><br>0.94 (95% CI 0.70 to 1.26). |
| | 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[a] | Average follow-up of 6 years<br><br>AREDS formula (minus beta-carotene) with lutein/zeaxanthin versus AREDS formula with beta-carotene: HR 0.88 (95% CI 0.75 to 1.03) |
| | 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[b] | Follow-up of 24 months |
| Adverse effects | Most studies were too small to detect rare adverse effects. Data from AREDS suggested little or no effect on mortality (HR 0.87, 95% CI 0.60 to 1.25). Participants in the antioxidant arms of AREDS more frequently reported yellow skin (8.3% versus 6.0%, P = 0.008). Additional data from AREDS2 found increased risk of lung cancer in the beta-carotene versus no beta-carotene group (23 (2.0%) versus 11 (0.9%)), mostly in former smokers. | | | | ⊕⊕⊖⊖ Low[c] | - |
| Resource use and costs | - | - | - | - | - | Not reported |

*__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.

**AMD:** age-related macular degeneration; **AREDS:** Age-Related Eye Disease Study; **CI:** confidence interval; **logMAR:** logarithm of the minimum angle of resolution; **OR:** odds ratio; **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


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**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

[a]Downgraded one level for imprecision because upper confidence interval within range 0.8 to 1.25.
[b]Downgraded one level for risk of bias because study was not placebo-controlled and at high risk of performance and detection bias, and one level for imprecision because confidence intervals included clinically insignificant effect.
[c]Downgraded one level for imprecision because included studies were underpowered to look at adverse events, and one level for risk of bias as adverse events were reported inconsistently.

**Summary of findings 2. Lutein with or without zeaxanthin versus placebo for slowing the progression of age-related macular degeneration**

Lutein with or without zeaxanthin versus placebo for slowing the progression of age-related macular degeneration

**Patient or population:** people with AMD
**Setting:** community
**Intervention:** lutein 10 mg, zeaxanthin 2 mg
**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/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[a] | Average follow-up of 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[a] | Average follow-up of 5 years |
| | 15 per 1000 | 9 per 1000 (8 to 10) | | | | |
| | High | | | | | |
| | 430 per 1000 | 276 per 1000 (252 to 306) | | | | |
| Progression to geographic atrophy | Low | | RR 0.92 (0.80 to 1.05) | 6891 eyes | ⊕⊕⊖⊖ Low[a] | Average follow-up of 5 years |


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| | | | | | | |
|---|---|---|---|---|---|---|
| | 15 per 1000 | 9 per 1000 (8 to 11) | | (1 RCT) | | |
| | High | | | | | |
| | 430 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[a] | Average follow-up of 5 years<br>On average, visual acuity was the same: 0.00 logMAR (95% CI -0.05 to 0.05; 3 studies, 231 participants; follow-up of 12 months) |
| | 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 ranged from 73.1 to 77.3 | The mean VFQ quality of life score in the intervention group was 1.21 higher (better) (2.59 lower to 5.01 higher) | - | 308 (2 RCT) | ⊕⊕⊕⊖ Moderate[b] | Follow-up of 12 months |
| Adverse effects | Most studies were too small to detect rare adverse effects. Data from AREDS2 suggested little or no effect on mortality (HR 1.06, 95% CI 0.87 to 1.31). | | | | ⊕⊖⊖⊖ Very low[c] | - |
| Resource use and costs | - | - | - | - | - | Not reported |

*__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.

**AMD:** age-related macular degeneration; **AREDS:** Age-Related Eye Disease Study; **CI:** confidence interval; **HR:** hazard ratio; **logMAR:** logarithm of the minimum angle of resolution; **OR:** odds ratio; **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.


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[a]Downgraded one level for imprecision, as confidence interval includes 1 null effect, and one level for indirectness, as study was not placebo-controlled.
[b]Downgraded one level for imprecision, as confidence interval includes 0 null effect, and one level for risk of bias, as studies were poorly reported.
[c]Downgraded one level for imprecision as studies were small to detect adverse effects and (for mortality in AREDS2) confidence interval includes 1 null effect; downgraded one level for indirectness as study was not placebo-controlled; downgraded one level as adverse effects were inconsistently reported.

**Summary of findings 3. Vitamin E versus placebo for slowing the progression of age-related macular degeneration**

Vitamin E versus placebo for slowing the progression of age-related macular degeneration

**Patient or population:** people with AMD
**Setting:** community
**Intervention:** vitamin E (500 IU per day: natural vitamin E in soybean oil medium)
**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 vitamin E 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[a,b] | Average follow-up of 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[a,b] | Average follow-up of 4 years |
| | 15 per 1000 | 16 per 1000 (11 to 22) | | | | |
| | High | | | | | |
| | 430 per 1000 | 447 per 1000 (318 to 632) | | | | |





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| | | | | | | |
|---|---|---|---|---|---|---|
| Quality of life | Not reported | | | | | |
| Adverse effects | No serious adverse effects were seen. Similar numbers of people in the vitamin E and placebo groups withdrew due to adverse effects (4 versus 7), reported any adverse effect (91 versus 83), or ocular adverse effect (105 versus 90). | | | | ⊕⊖⊖⊖ Very low[c] | - |
| Resource use and costs | - | - | - | - | - | Not reported |

*__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.

**AMD:** age-related macular degeneration; **AREDS:** Age-Related Eye Disease Study; **CI:** confidence interval; **HR:** hazard ratio; **logMAR:** logarithm of the minimum angle of resolution; **OR:** odds ratio; **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.

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

### Summary of findings 4. Zinc versus placebo for slowing the progression of age-related macular degeneration

Zinc versus placebo for slowing the progression of age-related macular degeneration

**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) | ⊕⊕⊕⊖ Moderate[a] | Most evidence from AREDS study with average follow-up of 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[a] | Average follow-up of 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[b] | Average follow-up of 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 logMAR chart) | Low | | OR 0.87 (0.75 to 1.00) | 3791 (2 RCTs) | ⊕⊕⊕⊖ Moderate[b] | 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 were reported as a reason for withdrawal. Of 286 people randomised into studies 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[b] | - |


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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.

**AMD:** age-related macular degeneration; **AREDS:** Age-Related Eye Disease Study; **CI:** confidence interval; **HR:** hazard ratio; **logMAR:** logarithm of the minimum angle of resolution; **OR:** odds ratio; **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.

[a]Downgraded one level for imprecision because upper confidence interval within range 0.8 to 1.25.
[b]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 atrophy). 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.

There have been a number of different clinical classifications of the condition, based on observations of drusen, pigmentary abnormalities, neovascular AMD, and geographic atrophy. In this review, we use the Beckman Initiative classification (Table 1; Ferris 2013). In this classification, people with no drusen, or small drusen only and no pigmentary abnormalities, are considered to have no AMD or normal ageing changes. The term 'early AMD' is restricted to people with medium-sized drusen (≥ 63 µm and < 125 µm) and no pigmentary abnormalities. 'Intermediate AMD' refers to people with large drusen (≥ 125 µm) and pigmentary abnormalities. 'Late AMD' defines people with neovascular AMD, geographic atrophy, or both. Table 1 also shows how this classification maps on to the categories used in the Age-Related Eye Disease Study (AREDS) (AREDS 2001).

In general, the early stages of the disease are asymptomatic. In the later stages, there may be a considerable distortion of vision and complete loss of visual function, particularly in the central area of vision.

Large genome-wide association studies have identified several AMD-associated genetic variants (Warwick 2018). Variations in two genes, in particular, appear to be most strongly associated with both the development of AMD and its progression to the advanced stages of the disease. These are the complement factor H (CFH) gene on chromosome 1 and the age-related maculopathy susceptibility 2 (ARMS2) gene on chromosome 10.

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

Antioxidants micronutrients 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. These supplements are taken orally and may be taken alone or in combination.

Supplementation has two aims: either to prevent nutritional deficiency, by ensuring recommended daily intakes are achieved; or to provide a high pharmaceutical dose with potentially therapeutic effects. Table 2 shows the recommended daily intakes for these micronutrients, along with examples of 'high dose' amounts seen in eye health supplements. Currently, there are no recommended daily intakes for carotenoids. Some carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) can be converted into retinol (vitamin A), and others not (lycopene, lutein, and zeaxanthin).

There have been many observational studies reporting the association between dietary antioxidants and AMD, with inconsistent findings (see examples of reviews: Chong 2007; Fletcher 2010). Data on vitamin intake in observational studies should be considered with caution, 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. People who take supplements may adopt a more healthy lifestyle (e.g. not smoking, taking regular exercise), which may reduce their risk of AMD. These differences may not be adequately controlled by statistical analysis. A randomised controlled trial (RCT) design, whereby people are randomly allocated to supplements or placebo, is the best study design to answer questions about associations between antioxidants and the progression of AMD.

## How the intervention might work

A dietary antioxidant is defined as "a substance in foods which significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiologic function in humans" (Young 1998). Antioxidants may also help to maintain membrane stability (Food and Agriculture Organization 2001).

Photoreceptors in the retina are subject to oxidative stress throughout life, due to combined exposures to light and oxygen. As part of normal physiological processes involving oxygen, reactive oxygen species (including radicals superoxide and hydroxyl ions, hydrogen peroxide, and singlet oxygen) are produced (Cai 2000). These active and potentially damaging molecules have to be cleared by antioxidant defence systems, including enzymes (e.g. superoxide dismutase, glutathione peroxidase, catalase). Antioxidant vitamins, such as vitamin C, vitamin E, and carotenoids, may also play a role. There are many carotenoids but lutein and zeaxanthin are the main constituents of the macular pigment and are thought both to mop up reactive singlet oxygen and play a role in filtering blue light to avoid damage to the sensory neurons (Cai 2000). One theory for the pathology of age-related macular degeneration is that the balance between the development and elimination of the reactive oxygen species is affected, leading to damage to the retinal tissues. 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 (Christen 1996).

The vitamins and minerals considered in this review may also have anti-inflammatory, neuroprotective, immune-modulating effects, effects on gene expression, or both (Azzi 2018; Food and Agriculture Organization 2001; Young 1998). These other physiological effects may also be important in the progression of AMD, in addition to the antioxidant effects proposed.


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## Why it is important to do this review

Antioxidant vitamin and mineral supplements are increasingly being marketed for use in age-related eye diseases, including AMD. A critical appraisal and summary of the evidence will be of use to the following groups: (1) people with AMD, who need reliable information in order to decide whether to take vitamin supplements; (2) people who are treating or supporting individuals with AMD, who need reliable information to share with patients; (3) eye care clinicians, who need appraised evidence to inform their practice; and (4) healthcare professionals preparing clinical guidelines, who need high-quality evidence syntheses. This is the third update of this review.

# OBJECTIVES

To assess the effects of antioxidant vitamin and mineral supplements 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 (RCTs).

### Types of participants

Participants in the studies were people with AMD in one or both eyes. We did not place any restrictions on participants but note that AMD is usually diagnosed in people aged 50 years and above and increases with increasing age; therefore, most participants in included studies were older adults.

### Types of interventions

We included studies which compared antioxidant vitamin or mineral supplementation, alone or in combination, with placebo or no intervention. We defined antioxidants as any vitamin or mineral known to have antioxidant properties in vivo, or 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. We excluded studies where antioxidant vitamins were combined with other potentially active ingredients.

The overall objective of the review was to assess the impact of antioxidant vitamin and mineral supplements on the progression of AMD. Studies 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). We considered the following comparisons in this review.

- Multivitamin formulation versus placebo. All the formulations which include two or more antioxidant vitamins or minerals fall into this category.
- 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 update in 2017 to include outcomes specified by the UK National Institute for Health and Care Excellence (NICE) macular degeneration guideline panel (NICE 2018); 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 logarithm of the minimum angle of resolution (logMAR) chart)*;
- 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.

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 databases listed below for randomised controlled trials and controlled clinical trials. There were no restrictions on language or year of publication. The date of the search was 29 November 2022.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 11) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 29 November 2022) (Appendix 1).
- MEDLINE Ovid (1946 to 29 November 2022) (Appendix 2).
- Embase Ovid (1980 to 29 November 2022) (Appendix 3).
- AMED (Allied and Complementary Medicine Database) (1985 to 29 November 2022) (Appendix 4).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 29 November 2022) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 29 November 2022) (Appendix 6).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp; searched 29 November 2022) (Appendix 7).

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 8 for search strategy.

For the 2022 update, we did not search OpenGrey as this resource has now been archived.


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### Searching other resources

We searched the reference lists of identified study reports to find additional studies. We used the Science Citation Index to find studies that cited the identified studies. We contacted investigators of included studies to identify additional published and unpublished studies.

## Data collection and analysis

### Selection of studies

Both review authors independently assessed the titles and abstracts of all reports of studies identified by the electronic searches. We obtained the full texts of possibly relevant studies. 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 investigators of all studies included in the review. In the 2012 and current updates, both review authors independently extracted data. We compared our datasets and resolved any disagreements through discussion. One author cut and pasted the data into Review Manager Web (Review Manager Web 2023), and the other author checked for accuracy and fidelity. In the current update, we screened citations and extracted duplicate data 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 2019).

### Measures of treatment effect

We used the risk ratio (RR) for dichotomous outcomes where possible. As one of the main large studies 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 study (AREDS 2001).

For continuous outcomes, we used the mean difference (MD). Where possible, we checked for skewness using methods outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

### Unit of analysis issues

The main study design method in this area is the parallel-group randomised controlled trial. Cluster-randomised studies were unlikely, but we would have considered them. Cross-over studies would not generally be appropriate in this area because of the uncertain and complex natural history of AMD. If we identify eligible cross-over studies 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 study, 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 studies with high (over 95%) follow-up.

Two studies specifically excluded people who experienced a neovascular event (one component of late-stage AMD) from the 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. We interpreted an $I^2$ statistic value of 50% or more to indicate considerable inconsistency of results, such that a pooled result may be inaccurate and should not be reported. The $I^2$ statistic aims to assess the consistency of the study results in meta-analyses: it describes the percentage of variation across studies that is due to heterogeneity rather than chance (Higgins 2003).

The main clinical heterogeneity was the type of supplement. We incorporated this into the analysis strategy by considering the formulations by type.

### Assessment of reporting biases

In future versions of this review, when sufficient studies 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 studies, we would use the fixed-effect model. Most of our analyses fell into the latter category, and so we largely used a fixed-effect model.

### Subgroup analysis and investigation of heterogeneity

Currently, there are insufficient included studies to perform useful subgroup analyses; thus, subgroup analyses are not proposed for this version of the review. Characteristics that may be important are the type and severity of AMD, and we may consider these in future review updates.

### Sensitivity analysis

We did not plan any sensitivity analyses.

### Summary of findings and assessment of the certainty of the evidence

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


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We assessed the certainty of the evidence (GRADE) for each outcome using customised software (GRADEpro). JE carried out the initial assessment of evidence certainty; JL checked the assessments. We considered risk of bias, inconsistency, indirectness, imprecision, and publication bias when judging the certainty of the evidence (Schünemann 2019).

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

Please see Table 3 for a summary of searches for previous versions of this review.

Update searches run on 29 November 2022 yielded a further 1175 records (Figure 1). After 237 duplicates were removed, the Cochrane Information Specialist screened the remaining 938 records and removed 723 references that were not relevant to the scope of the review. We screened the remaining 215 references. For 191 of these 215 references, it was clear from the title and abstract that the study was not relevant to the review. We obtained 24 full-text reports for further assessment. These reports comprised:


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**Figure 1. PRISMA study flow diagram**

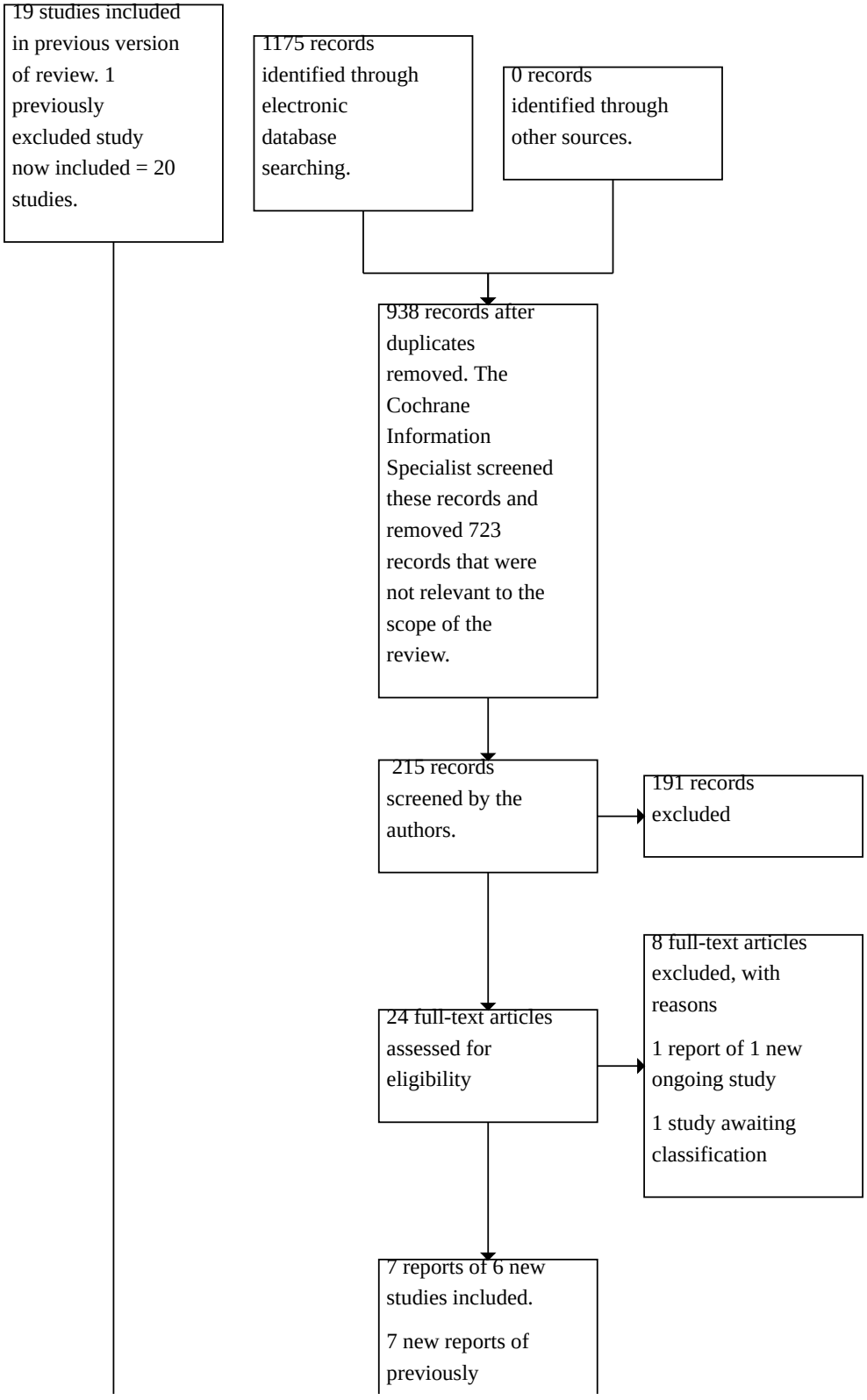



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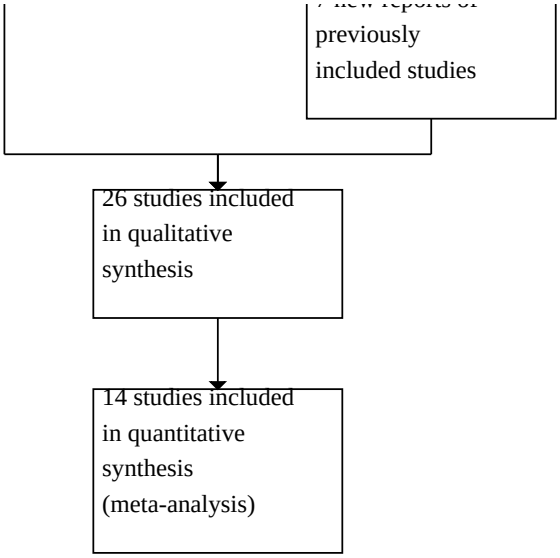
**Figure 1. (Continued)**




- six new studies (published in seven reports): Azar 2017, Garcia-Layana 2021, Li 2017, Li 2018, Parravano 2019, and Piatti 2020;
- ancillary publications (seven reports) for two already included studies, AREDS 2001 and AREDS2 2013;
- one study (one report) awaiting classification, as it is currently published only as an abstract (Chiosi 2020);
- one new ongoing study (one report): NCT03845582; and
- eight excluded studies (eight reports).

### Included studies

A total of 26 studies are now included in the review (20 studies already identified in previous versions of the review and six new studies). A total of 11,952 people were enroled in these studies. Below is a summary of the 26 studies. See Characteristics of included studies for detailed information on individual studies and Table 4 for a summary.

Three studies had more than one treatment arm:

- AREDS 2001 had a multivitamin arm and a zinc arm; we considered these separately in this review;
- LAST 2004 had both multivitamin and lutein/zeaxanthin arms; we considered these separately;
- the two intervention groups in LUTEGA 2013 were similar, differing only in dose; we combined these groups for this review.

In the following discussion, we use the Beckman Initiative terminology for the clinical classification of AMD (Ferris 2013, Table 1).

#### *Multivitamin supplements (13 studies)*

Eleven studies compared multivitamin supplements with placebo (AMDSG 1996; AREDS 2001; Bartlett 2007; CARMA 2013; Garcia-Layana 2021; Kaiser 1995; LAST 2004; LUTEGA 2013; Parravano 2019; Piatti 2020; Wang 2004), and two studies compared multivitamin supplements with no treatment (Berrow 2013; CARMIS 2011). Table 5 summarises the daily dose of key antioxidant vitamin and mineral supplements considered. These studies were conducted in the USA (AMDSG 1996; AREDS 2001; LAST 2004), Europe (Bartlett 2007; Berrow 2013; CARMA 2013; CARMIS 2011; Garcia-Layana 2021; Kaiser 1995; LUTEGA 2013; Parravano 2019; Piatti 2020), and China (Wang 2004).

AMDSG 1996, Bartlett 2007, Berrow 2013, CARMIS 2011, and LAST 2004 only enroled people with early AMD. AREDS 2001 and Wang 2004 recruited people with both early and late AMD. CARMA 2013 enroled 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 and LUTEGA 2013 with non-exudative AMD. Parravano 2019 and Piatti 2020 recruited people with intermediate AMD. Garcia-Layana 2021 enroled people with unilateral neovascular AMD.

People taking part in the studies were identified by referral from local ophthalmologists (Kaiser 1995), from people attending Department of Veterans Medical Centers (AMDSG 1996; LAST 2004), from retinal speciality clinics and general population volunteers (AREDS 2001), from eye outpatient clinics (Berrow 2013; Piatti 2020; 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 and Parravano 2019, it was not clear how they identified participants. In LUTEGA 2013, participants were from the "local population" but it was not clear how they were identified.

The number of participants enroled in multivitamin supplement studies ranged from 14 (Berrow 2013) to 3640 (AREDS 2001). Apart from AREDS 2001, all these studies recruited fewer than 500 people; the median number randomised was 85. The average age of participants ranged from 65 to 75 years; the median percentage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of women was 56%, and two studies recruited mainly men (AMDSG 1996; LAST 2004).

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

***Lutein (with or without zeaxanthin) supplements (eight studies)***

Six studies compared lutein supplements with placebo (AREDS2 2013; CLEAR 2013; Li 2017; LISA 2011; LAST 2004; Ma 2012). In AREDS2 2013, all participants also took the AREDS formula (Table 5). The daily dose of lutein used in these studies was 10 mg (AREDS2 2013; CLEAR 2013; LAST 2004; Ma 2012) and 20 mg (Li 2017; LISA 2011; Ma 2012). Two of these studies combined lutein with zeaxanthin, either a dose of 2 mg (AREDS2 2013), or 10 mg (Ma 2012). These studies were conducted in the USA (AREDS2 2013; LAST 2004), Europe (CLEAR 2013; LISA 2011), and China (Li 2017; Ma 2012).

CLEAR 2013, LAST 2004, Li 2017, and Ma 2012 only considered people with early AMD. AREDS2 2013 enroled 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).

One study compared lutein (5 mg) and zeaxanthin (1 mg) combined with omega-3 fatty acids, vitamins and zinc with a control of omega-3 fatty acids, vitamins and zinc (Azar 2017). One study compared a multivitamin supplement, including lutein 10 mg and zeaxanthin 2.6 mg, with a supplement without lutein or zeaxanthin but including beta-carotene 800 mg (Garcia-Layana 2021). Both studies were from Europe and recruited people with stage 4 exudative AMD in one eye (AREDS criteria) and followed up the fellow eye.

People taking part in the studies were identified from people attending Department of Veterans Medical Centers (LAST 2004), from "clinical centers" (AREDS2 2013) or sites (Garcia-Layana 2021), hospital (Azar 2017; Li 2017), 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 enroled in lutein and zeaxanthin supplement studies ranged from 79 (Azar 2017) to 4203 (AREDS2 2013). Apart from AREDS2 2013, all of these studies recruited fewer than 250 people. The average age of participants ranged from 69 to 75 years; the median percentage of women was 57%, and one study recruited mainly men (LAST 2004).

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

***Vitamin E (one study)***

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

***Zinc (six studies)***

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 sulphate 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 enroled people with early AMD; AREDS 2001 and Newsome 1988 recruited people with both early and late AMD; Stur 1996 only enroled people with late AMD in one eye.

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

People taking part in the studies were identified by referral from local ophthalmologists (Newsome 1988), eye outpatient clinics (Stur 1996), retinal speciality 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 studies ranged from six months to seven years.

***Other (one study)***

One study in China compared goji berry supplement to usual diet and followed up for 90 days (Li 2018). Goji berries are a source of carotenoids and zinc.

**Excluded studies**

We have listed 59 excluded studies, including the eight studies identified in this review update, in the Characteristics of excluded studies section.

The reasons for exclusion were as follows:

- ineligible population: participants did not have AMD in one or both eyes (n = 21);
- ineligible design: not an RCT (n = 18);
- ineligible intervention: not an antioxidant vitamin or mineral supplement (n = 8);
- ineligible comparator: no placebo or untreated group in the study (n = 8);
- ineligible intervention: supplement combined with other active intervention (n = 3);
- ineligible outcome: review outcomes were not measured (n = 1).


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### Risk of bias in included studies

Figure 2 and Figure 3 summarise the risk of bias assessment. Overall, we considered the studies 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 studies, except Berrow 2013, CARMIS 2011, and Li 2018 had a placebo control. Five studies were not well reported (Holz 1993; LISA 2011; Li 2017; Li 2018; Wang 2004), and one study 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**

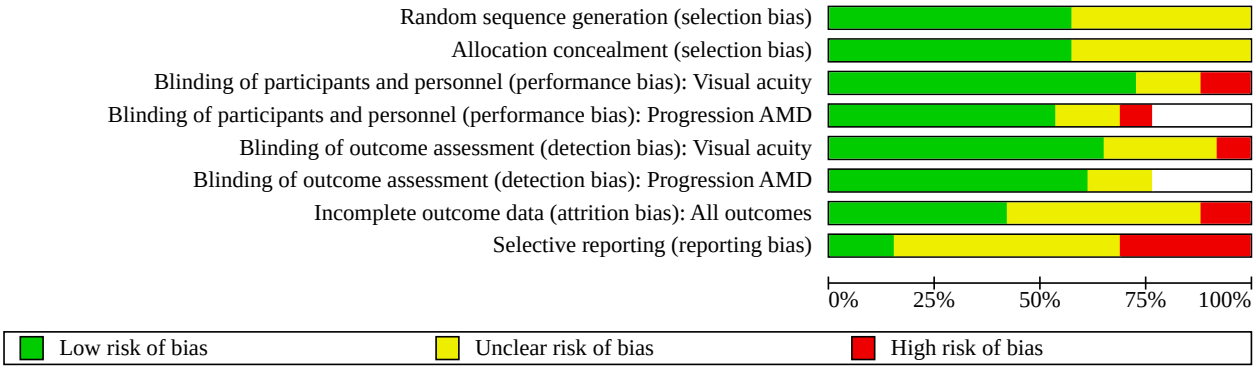



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**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**

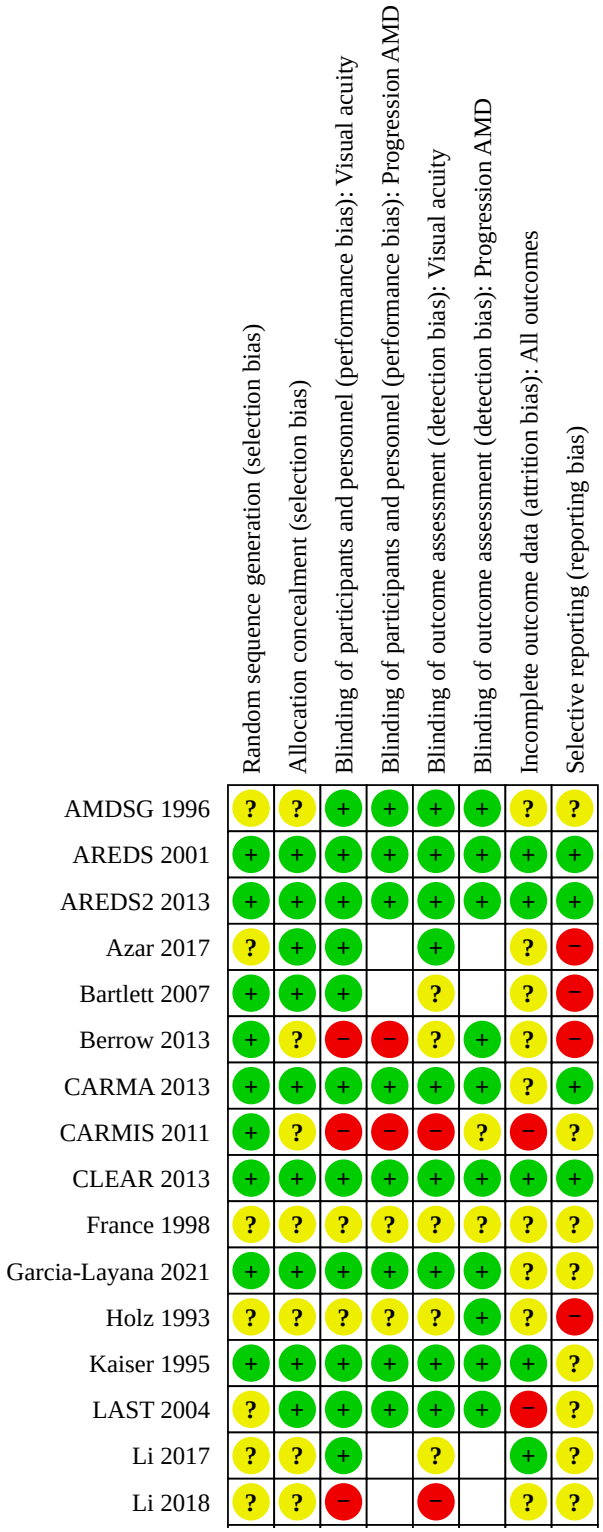



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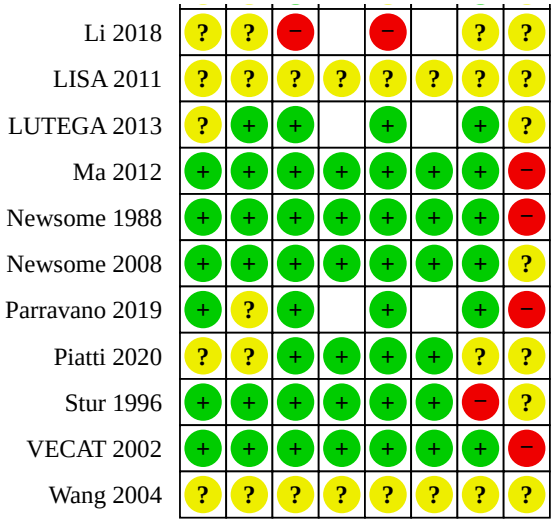
**Figure 3. (Continued)**




### Allocation

In 12 studies, randomisation appeared to have been executed properly; that is, an unpredictable sequence of treatment allocation was adequately concealed from people recruiting participants into the study. In the remaining studies, the judgements were unclear for one or both of these aspects of study conduct because of poor reporting.

### Blinding

Three studies had a 'no treatment' control group; we considered these to be at high risk for performance and detection bias (Berrow 2013; CARMIS 2011; Li 2018).

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 LAST 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

Included studies did not always clearly report information that would allow us to assess the likelihood of attrition bias. We judged three studies 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 LAST 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 endpoint of late-stage AMD (neovascularisation) was withdrawn from the study. Contact with the study 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 (CNV). Similarly, CARMA 2013 excluded people with CNV from analyses of visual acuity.

### Selective reporting

There was some evidence of selective reporting in eight studies (Azar 2017; Bartlett 2007; Berrow 2013; Holz 1993; Ma 2012; Newsome 1988; Parravano 2019; VECAT 2002), 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 1** Antioxidant multivitamin and mineral supplement versus placebo or no treatment for slowing the progression of age-related macular degeneration; **Summary of findings 2** Lutein with or without zeaxanthin versus placebo for slowing the progression of age-related macular degeneration; **Summary of findings 3** Vitamin E versus placebo for slowing the progression of age-related macular degeneration; **Summary of findings 4** Zinc versus placebo for slowing the progression of age-related macular degeneration

We provide more information on the outcomes and follow-up times relating to the data included in these analyses in Table 4.

### Antioxidant multivitamin and mineral supplement versus placebo or no treatment

See Summary of findings 1.


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Table 5 summarises the multivitamin supplements in the 13 studies included here. There was considerable heterogeneity in constituents of these supplements, but as most of the evidence comes from the AREDS study, we have focused on the AREDS formula here (i.e. vitamin C, vitamin E, carotenoids, and zinc).

Only three studies reported data on our primary outcome of progression to late AMD (AREDS 2001; CARMA 2013; CARMIS 2011), and only one of these studies 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 LAST 2004 measured visual acuity using a Snellen chart and converted the score into logMAR units. AREDS 2001, Bartlett 2007, CARMIS 2011, and LUTEGA 2013 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, Parravano 2019, and Wang 2004. Only one study reported on quality of life, using the Italian version of the National Eye Institute Visual function questionnaire (NEI-VFQ) (CARMIS 2011).

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. 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; LAST 2004), selected a study eye (Bartlett 2007; Kaiser 1995; LUTEGA 2013; 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 less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 3 studies, 2445 participants; moderate-certainty evidence; Analysis 1.1). Most evidence came from AREDS 2001, with follow-up of six years. In people with early AMD, who are at low risk of progression, this would equate to approximately four fewer cases of progression to late AMD for every 1000 people taking vitamins (one fewer to six fewer cases). In people with intermediate AMD at higher risk of progression, this would correspond to approximately 78 fewer cases of progression for every 1000 people taking vitamins (26 fewer to 126 fewer). The other two studies were smaller and provided different estimates (OR after 12 months of follow-up: 0.84, 95% CI 0.51 to 1.39; 509 participants in CARMA 2013; and OR after 24 months of follow-up: 1.37, 95% CI 0.42 to 4.48; 145 participants in CARMIS 2011). We did not downgrade for inconsistency because the confidence intervals were completely overlapping for the three studies.

Over six years, evidence from AREDS 2001 suggests people taking antioxidant vitamins and zinc were probably less likely to progress to neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; 1 study, 1206 participants; moderate-certainty evidence; Analysis 1.2) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; 1 study, 1206 participants; 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; 1 study, 1791 participants; moderate-certainty evidence; Analysis 1.4).

Studies 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; LAST 2004; LUTEGA 2013). No effect of treatment on visual acuity was seen from these analyses. The pooled mean difference (MD) was 0.0 logMAR (95% CI -0.04 to 0.03; $I^2$ = 46%; 6 studies, 740 participants; Analysis 1.5).

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 (CARMIS 2011) (mean difference (MD) 12.30, 95% CI 4.24 to 20.36; Analysis 1.6).

In exploratory subgroup analyses in the follow-on study to AREDS (AREDS2 2013), replacing beta-carotene with lutein/zeaxanthin gave hazard ratios (HR) of 0.82 (95% CI 0.69 to 0.96), 0.78 (95% CI 0.64 to 0.94), 0.94 (95% CI 0.70 to 1.26) and 0.88 (95% CI 0.75 to 1.03) for progression to late AMD, neovascular AMD, geographic atrophy, and vision loss, respectively. One study comparing Retulit (AREDS with lutein/zeaxanthin) versus Theavit (AREDS with beta-carotene) found little evidence of a difference in visual acuity (difference in ETDRS letters −1.63, 95% CI −0.83 to 4.09; P = 0.192) in 93 people after 12 months of follow-up (Garcia-Layana 2021) (Table 5).

Table 6 summarises information available on adverse effects. Low-certainty evidence was available on adverse effects from these included studies. They were underpowered to look at adverse effects and reported them inconsistently. 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). Additional data from AREDS2 2013 found an increased chance of lung cancer in the beta-carotene versus no beta-carotene group (23 (2.0%) versus 11 (0.9%)), mostly in former smokers.

None of the studies reported resource use and costs.

The study comparing goji berries to usual diet was small (57 in each group) and followed participants for only 90 days (Li 2018). Best-corrected visual acuity was similar in the two groups at the end of follow-up (0.21 standard deviation (SD) 0.18 in the intervention group compared with 0.22 SD 0.19 in the control). The authors reported in the discussion only that there were "no detectable adverse effects".

**Lutein (with or without zeaxanthin) versus placebo**

See Summary of findings 2.

Six studies compared lutein supplements (10 mg or 20 mg) with placebo and followed participants for six months to five years (AREDS2 2013; CLEAR 2013; LAST 2004; LISA 2011; Li 2017; Ma 2012). In AREDS2 2013, all participants also took the AREDS formula.

Only one study 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. LAST 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. Data from Li 2017 could not be used because it was not clear how visual acuity


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was measured and reported. Two studies reported on quality of life, using the Chinese version of the NEI-VFQ (Li 2017; 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. Some studies reported findings on right eyes and left eyes separately (LAST 2004), or selected a study eye (CLEAR 2013; LISA 2011). In some studies, there was insufficient information to establish their approach (Li 2017; Ma 2012).

Compared to placebo, people taking lutein with or without zeaxanthin may have similar or slightly reduced risk of progression to late AMD over five years (risk ratio (RR) 0.94, 95% CI 0.87 to 1.01; 1 study, 6891 eyes; low-certainty evidence), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 1 study, 6891 eyes; low-certainty evidence), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 1 study, 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15 or more letters was seen in both the lutein/zeaxanthin and control groups (RR 0.98, 95% CI 0.91 to 1.05; 1 study, 6656 eyes; low-certainty evidence).

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; $I^2$ = 0%; 231 participants; Analysis 2.5).

There was moderate-certainty evidence of little or no difference between lutein with or without zeaxanthin and control groups in quality of life from 308 participants in two studies (MD 1.21, 95% CI -2.59 to 5.01; Analysis 2.6).

Table 6 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 reported them inconsistently. Data from AREDS2 2013 suggested no serious adverse effects associated with lutein and zeaxanthin use. The hazard ratio for mortality comparing lutein/zeaxanthin to no lutein/zeaxanthin was 1.06 (95% CI 0.87 to 1.31).

None of the studies reported resource use and costs.

Azar 2017 compared lutein/zeaxanthin plus omega-3 fatty acids and vitamins with omega-3 fatty acids and vitamins but did not report any of our review outcomes, aside from a comment to the effect that there were no serious adverse effects observed.

**Vitamin E versus placebo**

See Summary of findings 3.

Only one included study investigated vitamin E alone (VECAT 2002). This study randomised 587 participants to vitamin E supplementation and 592 to placebo, and followed them for an average of four years. Over 80% of the participants in this study had no signs of AMD. The study included one eye per person.

The number of late AMD events was low (4/494 in the vitamin E and 3/504 in the placebo group). Therefore, the estimate of effect was very uncertain (RR 1.36, 95% CI 0.31 to 6.05). We judged this to be very low-certainty evidence as there were only seven 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 for this outcome.

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 studies 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 study investigated zinc-monocysteine (Newsome 2008).

Three studies reported data on our primary outcome of progression to late AMD (AREDS 2001; Holz 1993; Stur 1996); only one of these studies 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; this 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 study 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 insufficient information to establish 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 covariates 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; 3 studies, 3790 participants; moderate-certainty evidence; Analysis 4.1), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 1 study, 2442 participants; moderate-certainty evidence; Analysis 4.2), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 1 study, 2442 participants; moderate-certainty evidence; Analysis 4.3), and visual loss (OR 0.87, 95% CI 0.75 to 1.00; 2 studies, 3791 participants; moderate-certainty evidence; Analysis 4.4).

Most of the data came from AREDS 2001, with follow-up over six years. The other two studies were smaller and provided different estimates for progression to late AMD. We did not downgrade for


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inconsistency because the confidence intervals were completely overlapping for the three studies.

Only one study 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 chart 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 6 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 reported them inconsistently.

The main reported adverse effect leading to withdrawal from the studies was gastrointestinal symptoms. Of 286 people randomised into studies of zinc sulphate 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 intake 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). AREDS2 2013 reported that gastrointestinal disorders and hospitalisations for genitourinary diseases were similar between high-dose and low-dose zinc groups.

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

## DISCUSSION

### Summary of main results

The current update (2023) identified six new included studies (Azar 2017; Garcia-Layana 2021; Li 2017; Li 2018; Parravano 2019; Piatti 2020). We also included a study that we had previously excluded because lutein was combined with omega-3 fatty acids (LUTEGA 2013). We revised our decision for this update because some of the multivitamin supplements used in other included studies include omega-3 fatty acids, plus there is little evidence that omega-3 fatty acids are an active ingredient (Lawrenson 2015).

These six new included studies were small and scant useable data could be extracted.

The studies contributing to this review fall into two categories. There were three large studies with reasonably long treatment duration and follow-up of four to six years (AREDS 2001; AREDS2 2013; VECAT 2002). The other 23 studies were smaller (ranging from 20 to 500 participants) and had shorter durations of treatment and follow-up (six to 24 months).

The large studies provide answers to different questions. The AREDS 2001 study provided evidence that long-term supplementation with vitamins C, E, beta-carotene, and zinc in people with AMD probably reduces the risk of progression to late AMD and loss of visual acuity. The overall benefit demonstrated in that study was modest, with a relative risk reduction in the order of 20% to 25% over five years. However, given that treatment options for AMD are limited, and vision loss is rarely recovered, this may be of interest to people with AMD, particularly intermediate AMD where the risk of progression is higher.

People with early AMD have a low risk of progression to late AMD and visual loss. The evidence as to the effect of antioxidant supplements in this group is uncertain. In the AREDS study, there were too few events to assess the effects of supplementation in people with early AMD. The authors concluded that the "low event rate makes it impossible to assess treatment effects in this category (category 2) for the AMD outcome and less likely that any of the treatments would be recommended. Therefore, analyses are also presented for those participants most likely to benefit from an effective treatment (Categories 3 and 4)". The results of AREDS are often interpreted as evidence that the supplements do not work to stop progression in early AMD. For example, the US National Eye Institute website makes the following statement: "AREDS 2 supplements can’t prevent early AMD from developing into intermediate AMD" (National Eye Institute 2023). We think this is wrong, as the evidence is uncertain. However, our review demonstrates that, even if the effects of supplements are similar at every stage of AMD, few people with early AMD will benefit from antioxidant supplementation because of the low risk of progression in that group. In Summary of findings 1 for the comparison of multivitamin and mineral supplement versus placebo or no treatment, we show that many people with early AMD would have to take vitamin supplements for few people to benefit. We estimate that there would be approximately four fewer cases of progression to late AMD for every 1000 people taking vitamins (one fewer to six fewer cases). In contrast, people at high risk of progression (i.e. people with intermediate AMD) are more likely to benefit, with approximately 78 fewer cases of progression for every 1000 people taking vitamins (26 fewer to 126 fewer).

AREDS2 2013 compared lutein/zeaxanthin supplements with placebo; almost all participants also took the AREDS formula. Secondary analyses from this study suggested that there may be some benefit in replacing beta-carotene with lutein, but these analyses were only exploratory (AREDS2 2014). Other studies of lutein with or without 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 results of the VECAT 2002 study did not support vitamin E supplementation to prevent the incidence or progression of AMD. However, the study was underpowered to answer 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 study on vitamin E supplementation and AMD progression.


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The other studies of multivitamin preparations were either too small to provide evidence either way, or the data were not available in a format suitable to include in this review. Pooling results, where possible, did not provide evidence of any benefit of supplementation. However, these studies were of relatively short duration.

A total of four published studies investigated zinc supplementation (AREDS 2001; Holz 1993; Newsome 1988; Stur 1996), and one study 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 studies provided 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 intended 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 studies 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 is probably of benefit comes from the AREDS 2001 study. 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. Alternatively, the retinal fundus photographs might have been different in some way, such that the graders' response was affected by treatment group. However, these scenarios are unlikely, and there was little evidence that unblinding was a problem in the study. The extent to which the results from this one study – conducted in a well-nourished American population where supplementation is common – can be extrapolated to other settings and populations is unclear.

It is worth noting that pooling data from studies other than AREDS 2001 revealed little evidence for the 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. Investigators found little evidence of harm, but there was an increased risk of hospital admission due to genitourinary complications in people taking zinc supplements (80 mg per day). Other studies have questioned the safety of some of the components of the AREDS formulation. Two large randomised controlled studies have indicated that smokers who take beta-carotene may be at increased risk of developing lung cancer (ATBC 1994; Omenn 1996). Subsequent analyses of AREDS studies confirmed this. The Heart Outcomes Prevention Evaluation (HOPE) study found that amongst people with vascular disease or diabetes, vitamin E supplementation was associated with a higher risk of heart failure (Lonn 2005).

We identified two, somewhat dated, systematic reviews addressing the harms of vitamin supplements. Huang and colleagues did not identify any consistent adverse effects of mineral and vitamin supplements, but only included nine RCTs in their review (Huang 2006). A subsequent Cochrane Review that investigated antioxidant supplements for preventing all-cause mortality included 78 studies with 296,707 participants (Bjelakovic 2012). Bjelakovic and colleagues "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). A systematic search of the literature for systematic reviews addressing the harms of vitamin supplements did not identify any further relevant evidence.

Whether specific genetic subgroups of people with AMD experience a different risk of benefit or harm from antioxidant supplements remains controversial. Currently, we have not included genetic factors as a planned subgroup analysis in this review. Several different analyses of AREDS data have yielded conflicting results (Assell 2018; Awh 2013; Awh 2015; Chew 2014b; Chew 2015; Klein 2008; Seddon 2016; Vavvas 2018). The most comprehensive and recent analysis concludes that genetic polymorphisms of the complement factor H (CFH) and the age-related maculopathy susceptibility 2 (ARMS2) genes do not predict response to antioxidant and zinc supplementation in people with AMD (Assell 2018).

### Certainty of the evidence

As the majority of the studies were placebo-controlled, we mostly assessed them as being at overall low risk of bias. In particular, we judged the two studies that contributed most of the data to this review as at low risk of bias (AREDS 2001; AREDS2 2013). Three studies compared supplements to no treatment (Berrow 2013; CARMIS 2011; Li 2018); we judged these to be at high risk of performance bias. However, these studies were small and did not contribute significant amounts of data to the analysis. There was some variable reporting of the smaller studies; 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 several studies that did not report non-significant data on visual acuity, which might be expected as a key outcome in such studies. Another problem is the variety of ways in which visual acuity can be analysed and reported; for example, as a dichotomous outcome with a variety of potential cut-points, or as a continuous variable reporting change or final value. It was possible that investigators had analysed visual acuity in a variety of ways and reported the most significant finding. However, in these studies, we did not find evidence of improved visual acuity associated with treatment.

The main reasons for downgrading the certainty of the evidence were imprecision (due to small study size) and indirectness. In particular, since all participants in AREDS2 2013 took multivitamin supplements, the results may not have been a true reflection of the effect of lutein/zeaxanthin supplementation alone.


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### 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). Improvements in Cochrane methods, the structure of the data, and collaboration with relevant partners (such as the National Institute for Health and Care Excellence (NICE)) have guided these changes, and we have aimed to avoid data-driven changes.

Our choice of outcome measures for the current update remains the same as for the last update (Evans 2017), when we revised the outcome measures in order to collect outcomes relevant to the development of the NICE guideline on macular degeneration (NICE 2018). Since then, two core outcome sets relevant to macular degeneration have been published (Krezel 2019; Rodrigues 2016). These outcome sets suggest additional potential outcomes, such as reading speed and near visual acuity, which are not currently included in our review. However, these outcomes are not commonly reported, if at all, in the studies included in this review, and we have not amended our review outcomes. We may consider these outcomes in future updates if studies amend their outcomes in the light of consensus core outcome sets (as we believe they should do). Contrast sensitivity is reported in some studies of age-related macular degeneration but is not currently included in our review. Neither of the core outcome sets mentioned above lists contrast sensitivity as an important outcome. In Rodrigues 2016, for example, clinical measures such as contrast sensitivity were specifically dismissed in favour of patient-reported outcome measures (PROMs), which are included in the current review in the form of quality of life measures. In Krezel 2019, which included a substantial number of participants with age-related macular degeneration, contrast sensitivity was not reflected in the final choice of outcomes. For this reason, we did not amend our review outcomes to include contrast sensitivity. Macular pigment optical density (MPOD) is often reported in studies of lutein/zeaxanthin. However, MPOD level in itself is not a direct measure of AMD and is not currently listed on core outcome sets.

For the current update, we consulted with the GRADE group as to how best to grade the evidence on lutein/zeaxanthin in AREDS2. One suggestion was that we should consider indirect comparisons between AREDS and AREDS2 to obtain an estimate of the effect of lutein/zeaxanthin. Unfortunately, as almost all participants in AREDS2 also took AREDS formula, such an analysis would not provide any additional information on the comparison between lutein/zeaxanthin and placebo. This means that we have no high-quality, large-scale, placebo-controlled comparisons for lutein/zeaxanthin, as specified in our protocol. Nevertheless, we have included data from AREDS2 in two ways. Firstly, we have included the prespecified comparisons in that study but downgraded the evidence to reflect the lack of a true placebo control. Secondly, we have reported the post hoc analyses conducted by the AREDS2 investigators, suggesting that lutein/zeaxanthin may replace beta-carotene in the AREDS supplement. We consider the evidence for lutein/zeaxanthin is rather indirect and, moreover, is not currently supported by other admittedly small, poorer quality, and shorter duration studies. However, other systematic reviews consider this to be high-quality evidence and suggest that the lack of a placebo control group in AREDS2 may mean that the effects of lutein/zeaxanthin are under-estimated rather than over-estimated (Waugh 2018). We feel this view ignores the fact that people in the lutein/zeaxanthin group also took the AREDS formula.

### Agreements and disagreements with other studies or reviews

There have been a number of reviews published on this topic (Andreatta 2014; Angelo 2015; Broadhead 2015; Buschini 2015; Carneiro 2017; Chew 2014a; Csader 2022; Downie 2014; Grover 2014; Hanus 2016; Liu 2015; Manikandan 2016; Pameijer 2022; Prasad 2014; Sacconi 2017; Schmidl 2015; Waugh 2018; Zampatti 2014). In general, these reviews have provided narrative assessments 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 some people with AMD, in harmony with our conclusion.

One systematic review of lutein and zeaxanthin supplementation pooled data from eight studies (Liu 2015). We identified the same eight studies for this 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 this review. Liu 2015 used the Jadad scale to assess the quality of the included studies, but did not factor this assessment into the review's 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.

There have been two recent reviews of the effect of lutein and zeaxanthin supplementation on macular pigment optical density, which was not an outcome in the current review (Fitzpatrick 2022; Liu 2022).

The authors of AREDS2 2013 concluded in the main study 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 on to 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 study data from AREDS2 2013 suggested a benefit of lutein/zeaxanthin versus beta-carotene in this study population, all of whom were taking supplements. For this reason, the authors of AREDS2 2013 recommend replacing beta-carotene with lutein (https://nei.nih.gov/areds2/PatientFAQ). In the last version of this review, we did not consider these secondary analyses of AREDS2 2013 due to their exploratory nature. However, we reconsidered this decision for the current review, and we discuss the judgements involved under Potential biases in the review process above.


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# AUTHORS' CONCLUSIONS

## Implications for practice

People with age-related macular degeneration (AMD) probably experience moderate delay in progression of the disease with antioxidant vitamin and mineral supplementation. This finding was drawn from one large study conducted in a relatively well-nourished American population. Until it is replicated by other large-scale studies in other populations, we will not know whether these findings can be applied more generally. People with intermediate AMD have a higher chance of benefiting from antioxidant supplements because their risk of progression is higher than people with early AMD. Although low-certainty evidence suggested little effect with lutein/zeaxanthin alone compared with placebo, exploratory subgroup analyses from one large study in the USA suggest lutein/zeaxanthin may be a suitable replacement for beta-carotene as used in the original Age-Related Eye Disease Study (AREDS) formula. Beta-carotene is known to be associated with an increased risk of lung cancer in people who have smoked or have been exposed to asbestos.

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. 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. Participants in the study providing most of the evidence took supplements for an average of six years. 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 studies included in this review.

## Implications for research

Studies in other populations, preferably with a variety of nutritional statuses, are required. These studies should have large enough sample sizes, and long enough durations, to demonstrate effects that are meaningful for people. They should also include outcomes relevant to people affected by AMD, including quality of life assessment. Core outcome sets should be used as much as possible. 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.

Study reporting should include enough information to assess the risk 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 participant 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 sources of evidence broader than randomised controlled studies alone.

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### AMDSG 1996

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: sponsor prepared coded tablets<br>Masking: participant - not clear; provider - yes; outcome - yes<br>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<br><br>Number of people randomised: 71 (eyes unknown)<br><br>Number (%) of people followed up: 59 (83%) (eyes unknown)<br><br>Average age (range): 72 years (unknown)<br><br>Percentage women: 7%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• 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<br><br>Exclusion criteria:<br><br>• longer than 1 year's use of vitamins<br>• ex-prisoners of war<br>• chronic alcoholics with tobacco or nutritional amblyopia<br>• gastrointestinal absorption disorders |
| Interventions | Intervention:<br><br>• 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 |


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**AMDSG 1996** *(Continued)*

| | |
|---|---|
| | µg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 µg (daily)<br>○ unknown number people randomised (eyes unknown )<br>○ 39 (unknown %) people followed up (eyes unknown )<br><br>Comparator:<br><br>• placebo, starch<br>○ unknown number people randomised (eyes unknown)<br>○ 32 (unknown %) people followed up (eyes unknown)<br><br>Duration: 18 months<br><br>Similarity between intervention and comparator: treatment and placebo may not have been identical |
| Outcomes | Primary: not specified<br><br>Secondary: not specified<br><br>Outcomes reported in the paper:<br><br>• Snellen acuity with best refraction converted to logMAR units for analysis<br>• near vision M units with dual sided Bailey-Lovie chart<br>• contrast sensitivity<br>• retinal grading score (adapted from Chesapeake Bay Study)<br>• subjective perception of vision; adverse gastrointestinal reactions<br><br>Follow-up: 18 months<br><br>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<br><br>Declaration of interest: unknown<br><br>Date study conducted: unknown<br><br>Trial registration number: unknown |

***Risk of bias***

| 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"<br><br>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, |


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**AMDSG 1996** *(Continued)*

| | | |
|---|---|---|
| | | labelling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"<br><br>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)<br>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"<br><br>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)<br>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)<br>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"<br><br>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 outcome assessment (detection bias)<br>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"<br><br>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)<br>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. |


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**AMDSG 1996** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Difficult to assess with the information given – no access to study protocol and study was not registered. |

**AREDS 2001**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>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.<br><br>Method of allocation: coded bottles<br>Masking: participant - yes; provider - yes; outcome - yes<br>Losses to follow-up: 2.4% balanced across study groups |
| Participants | Country: USA<br><br>Number of people randomised: 3640 (eyes unknown)<br><br>Number (%) of people followed up: 2.4% lost to follow up<br><br>Average age (range): 69 years (55 to 80)<br><br>Percentage women: 56%<br><br>Ethnic group: 96% white<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: 8%<br><br>Inclusion criteria:<br><br>• 20/32 or better in at least 1 eye<br>• ocular media clear and therefore able to obtain adequate stereoscopic fundus photographs<br>• at least 1 eye free from eye disease that could complicate assessment of AMD<br><br>Exclusion criteria:<br><br>• illness or disorders that would make long-term follow-up or compliance with study protocol unlikely or difficult |
| Interventions | Intervention:<br><br>• antioxidants vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg (daily)<br>• zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide (daily)<br>  ◦ 2737 people randomised (eyes unknown) (945 antioxidants only, 904 zinc only, 888 antioxidants plus zinc)<br>  ◦ 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."<br><br>Comparator:<br><br>• placebo<br>  ◦ 903 people randomised (eyes unknown) |


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**AREDS 2001** *(Continued)*

| | |
|---|---|
| | ○ 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."<br><br>Duration: average follow-up 6.3 years<br><br>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:<br><br>• progression to advanced AMD (assessed using stereoscopic fundus colour photograph)<br>• 15-letter or more decrease in visual acuity score (EDTRS logMAR chart)<br><br>Secondary:<br><br>• safety outcomes included: reported adverse events; serum levels of haemoglobin; hospitalisations; and mortality.<br><br>Follow-up: annual follow-up for at least 5 years<br><br>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."<br><br>Declaration of interest: Quote: "The AREDS investigators have no commercial or proprietary interest in the supplements used in this study."<br><br>Date study conducted: 1992 to 2001<br><br>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"<br><br>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". |
| 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)<br>Visual acuity | Low risk | Quote: "The 4 treatment interventions were double-masked..."<br><br>"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"<br><br>Quote: "Four participants (0.1%) were reported to have been unmasked during the trial" |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "The 4 treatment interventions were double-masked..." |


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**AREDS 2001** *(Continued)*

| | | |
|---|---|---|
| Progression AMD | | 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"<br><br>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."<br><br>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"<br><br>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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: coded tablets<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>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.<br><br>Quote "The original AREDS trial involved 4,757 participants, ages 55-80 at the time of enrollment. Of 4,203 surviving participants, 3,549 (about 84%) took part in the follow-on AREDS2 trial." www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#:~:text=How%20many%20people%20participated%20in,participants%2C%20ages%2050%2D85. |
| Participants | Country: USA<br><br>Number of people randomised: 4203 (6916 eyes)<br><br>Number (%) of people followed up: 4176 (99%) using LOCF (6891 eyes)<br><br>Average age (range): 74 years (68 to 79)<br><br>Percentage women: 56% |


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**AREDS2 2013** *(Continued)*

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 long-chain polyunsaturated fatty acids (LCPUFAs) (specifically docosahexaenoic acid (DHA) plus eicosapentaenoic acid (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 standardised 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 randomisation. (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 neovascularisation or cancer

| | |
|---|---|
| Interventions | Intervention:<br>• lutein 10 mg and zeaxanthin 2 mg (1 tablet/day)<br>  ◦ 2123 people randomised (3468 eyes)<br>  ◦ 2107 (99%) people followed up (3451 eyes)<br>Comparator:<br>• placebo (1 tablet/day)<br>  ◦ 2080 people randomised (3448 eyes)<br>  ◦ 2069 (99%) people followed up (3440 eyes) |


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**AREDS2 2013** *(Continued)*

| | |
|---|---|
| | Almost all participants in both intervention and comparator groups took AREDS supplement and multivitamin with the study medication.<br><br>Duration: 5 years (median)<br><br>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.<br><br>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:<br><br>• progression to advanced AMD in people at moderate to high risk for progression<br><br>Secondary:<br><br>• progression to moderate vision loss<br>• adverse events<br>• progression of lens opacity or incidence of cataract surgery<br>• effect of study supplements on cognitive function<br>• effect of DHA/EPA on cardiovascular morbidity and mortality<br><br>Follow-up: annual follow-up for 5 years<br><br>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)"<br><br>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."<br><br>Date study conducted: September 2006 to October 2012 (from clinicaltrials.gov entry)<br><br>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-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 |


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**AREDS2 2013** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias) Visual acuity | Low risk | Judgement comment: placebo-controlled trial. Personnel measuring visual acuity unaware of allocation.<br>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.<br>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.<br>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.<br>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. |

**Azar 2017**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: sponsor prepared coded tablets<br>Masking: participant - yes; provider - yes; outcome - yes<br>Losses to follow-up: not reported |
| Participants | Country: France<br>Number of people randomised: 79 (79 eyes)<br>Number (%) of people followed up: not reported<br>Average age (range): 77 years (unknown)<br>Percentage women: 58%<br>Ethnic group: unknown<br>Baseline visual acuity: unknown<br>Comorbidities affecting the eye: unknown<br>Percentage current smokers: 11% |


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**Azar 2017** *(Continued)*

| | |
|---|---|
| | Inclusion criteria:<br>• people with stage 4 exudative AMD in only one eye (AREDS criteria)<br>• people undergoing cataract surgery with no retinal pathology (not included in this review)<br><br>Exclusion criteria:<br>• intolerance of or taking supplements<br>• allergy to mydriatic agents<br>• ocular disease or other conditions that might interfere with MPOD measurements<br>• other severe diseases<br>• unable to give informed consent |
| Interventions | Intervention:<br>• lutein (5 mg), zeaxanthin (1 mg)<br>• omega-3 fatty acids (DHA 560 mg and GLA 420 mg), vitamin C (80 mg), vitamin E (10 mg), vitamin B6 (2 mg), vitamin B9 (200 micrograms), vitamin B12 (1 microgram), zinc (10 mg), (2 tablets/day)<br>  ○ 40 people randomised (40 eyes)<br>  ○ unclear number of people followed up<br><br>Comparator:<br>• omega-3 fatty acids (DHA 560 mg and GLA 420 mg), vitamin C (80 mg), vitamin E (10 mg), vitamin B6 (2 mg), vitamin B9 (200 micrograms), vitamin B12 (1 microgram), zinc (10 mg),(2 tablets/day)<br>  ○ 39 people randomised (39 eyes)<br>  ○ unclear number of people followed up<br><br>Duration: 2 years<br><br>Similarity between intervention and comparator: Quote: "Both tablets, manufactured by the same laboratory (Laboratorios Thea, Barcelona, Spain), presented with the same look, packaging, taste and smell".<br><br>Other study arm: study had two different participant groups: people with no AMD undergoing cataract surgery and people with AMD in one eye. We have extracted data for the second group only. |
| Outcomes | Primary:<br>• not specified<br><br>Other outcomes:<br>• Amsler grid<br>• BCVA<br>• IOP<br>• macular thickness (measured with OCT)<br>• MPOD (measured with the VIsucam 200)<br><br>Follow-up: 8, 16, 24, and 32 weeks<br><br>Eyes: one eye per person - the eye with non-exudative AMD |
| Notes | Source of funding: Quote: "Funding was received from Thea Laboratories in support of this study as the form of supplementation provision."<br><br>Declaration of interest: reported no competing interests<br><br>Date study conducted: not reported |


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**Azar 2017** *(Continued)*

| | |
|---|---|
| | Trial registration number: this was reported as NCT0140845 but this number does not exist. Unable to locate a comparable trial on clinicaltrials.gov |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Judgement comment: described as "randomized double-masked, comparative multicenter trial". "Patients were randomly assigned", but otherwise no information on sequence generation. |
| Allocation concealment (selection bias) | Low risk | Quote: "Both participants and ophthalmologists were blinded as to which subgroup was taking which supplement. Both tablets, manufactured by the same laboratory (Laboratorios Thea, Barcelona, Spain), presented with the same look, packaging, taste and smell". |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Quote: "Both participants and ophthalmologists were blinded as to which subgroup was taking which supplement. Both tablets, manufactured by the same laboratory (Laboratorios Thea, Barcelona, Spain), presented with the same look, packaging, taste and smell". |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Low risk | Quote: "Both participants and ophthalmologists were blinded as to which subgroup was taking which supplement. Both tablets, manufactured by the same laboratory (Laboratorios Thea, Barcelona, Spain), presented with the same look, packaging, taste and smell". |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Judgement comment: follow-up not reported |
| Selective reporting (reporting bias) | High risk | Judgement comment: clinical trials register entry not found - NCT0140845 does not seem to exist. Outcomes reported in methods but not the findings, including visual acuity. |

**Bartlett 2007**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: sponsor prepared coded tablets<br>Masking: participant - yes; provider - yes; outcome - yes<br>Losses to follow-up: 5 (2 treatment, 3 control) |
| Participants | Country: UK<br>Number of people randomised: 30 (30 eyes)<br>Number (%) of people followed up: 25 (83%) (25 eyes)<br>Average age (range): 69 years (55 to 82)<br>Percentage women: 53%<br>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:<br>• lutein esters 6 mg, retinol 750 mg, vitamin C 250 mg, vitamin E 34 mg, zinc 10 mg, copper 0.5 mg (daily)<br>  ◦ 17 people randomised (17 eyes)<br>  ◦ 15 (88%) people followed up (15 eyes)<br>Comparator:<br>• placebo tablets containing cellulose (daily)<br>  ◦ 13 people randomised (13 eyes)<br>  ◦ 10 (77%) people followed up (10 eyes)<br>Duration: 9 months<br>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<br>Secondary: unknown<br>Outcome measures specified on trial registration entry:<br>• distance and near visual acuity (VA) measured using Bailey-Lovie logMAR charts<br>• contrast sensitivity (CS) measured using a Pelli-Robson chart (Clement Clarke International, Harlow Essex, UK)<br>• colour vision measured using the PV-16 quantitative colour vision test<br>• Macular Mapping (MM) test<br>• Eger Macular Stressometer (EMS) used to assess glare recovery<br>• fundus photographs of the macula will be assessed using colour and edge analysis software<br>Study publication provided data on contrast sensitivity at 9-month follow-up.<br>Protocol listed more outcomes (see risk of bias table under selective reporting) and specified 9 and 18 months of follow-up.<br>Follow-up: 9 months (reported) and 18 months (not reported) |


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**Bartlett 2007** *(Continued)*

| | |
|---|---|
| | Eyes: study 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)."<br><br>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."<br><br>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."<br><br>Declaration of interest: unknown<br><br>Date study conducted: March 2003 and December 2004<br><br>Trial registration number: ISRCTN78467674 (registered retrospectively) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "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."<br><br>Quote: "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 | Quote: "Enrolment was carried out by HB, who, along with FE, was masked to group assignment."<br><br>Quote: "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."<br><br>Quote: "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)<br>Visual acuity | Low risk | Quote: "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 outcome assessment (detection bias)<br>Visual acuity | Unclear risk | Quote: "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."<br><br>Quote: "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 |


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**Bartlett 2007** *(Continued)*

| | | |
|---|---|---|
| | | 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." |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Quote: "Statistical analysis was carried out on a per protocol basis." |
| Selective reporting (reporting bias) | High risk | Protocol report listed the following outcomes: visual acuity, contrast sensitivity, colour vision, macular mapping test, glare recovery, fundus photographs analysed by colour and edge analysis software.<br><br>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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: unclear<br><br>Masking: participant - no; provider - no; outcome - yes<br><br>Loss to follow-up: unclear, either no loss to follow-up or 2/16 (12.5%) loss to follow-up |
| Participants | Country: UK<br><br>Number of people randomised: 14 (14 eyes)<br><br>Number (%) of people followed up: 14 (100%) (14 eyes)<br><br>Average age (range): 68 years (56 to 83)<br><br>Percentage women: unknown<br><br>Ethnic group: Caucasian (understood to be white)<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown but average 7 pack-years in antioxidant group and 13.5 pack-years in the placebo group<br><br>Inclusion criteria:<br><br>• best-corrected distance VA of 0.2 logMAR or better (for good mfERG central fixation)<br>• clear optical media, as determined by a clear view of the fundus<br>• no signs of other retinal or optic nerve disease other than ARM (as determined by fundal photography and questionnaire) in the study eye<br>• good general health (as determined by health questionnaire)<br>• no prescribed medication that could affect the retina (as determined by health questionnaire)<br><br>Exclusion criteria:<br><br>• moderate-to-dense lens opacities<br>• intraocular lens |


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**Berrow 2013** *(Continued)*

- 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:<br>• 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<br>  ○ 8 people randomised (8 eyes)<br>  ○ 8 (100%) people followed up (8 eyes)<br>Comparator:<br>• no treatment<br>  ○ 6 people randomised (6 eyes)<br>  ○ 6 (100%) people followed up (6 eyes)<br>Duration: 40 weeks<br>Similarity between intervention and comparator: different because no placebo group |
| Outcomes | From clinical trial registry entry<br>Primary:<br>• multifocal electroretinogram amplitudes and latencies, assessed every 20 weeks for a period of 80 weeks<br>Secondary:<br>• macular pigment optical density, assessed every 20 weeks for a period of 80 weeks<br>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."<br>Follow-up: 40 weeks and 60 weeks<br>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. 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."<br>Declaration of interest: Quote: "The authors declare no competing financial interests"<br>Date study conducted: January 2009 to December 2011 |


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**Berrow 2013** *(Continued)*

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)<br>Visual acuity | High risk | Judgement comment: no placebo; control group did not receive any intervention |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | High risk | Judgement comment: no placebo; control group did not receive any intervention |
| Blinding of outcome assessment (detection bias)<br>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)<br>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)<br>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"<br><br>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. |

**CARMA 2013**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: labelled containers<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>Loss to follow-up: high attrition after 12 months - 9% follow-up at 3 years |


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**CARMA 2013** *(Continued)*

| | |
|---|---|
| Participants | Country: Ireland<br><br>Number of people randomised: 433 (614 eyes)<br><br>Number (%) of people followed up: at 12 months, 493 eyes (80%); at 24 months, 260 eyes (42%); and at 36 months, 58 eyes (9%)<br><br>Average age (range): 74 years (unknown)<br><br>Percentage women: 57%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: average 80 letters on logMAR chart<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: 14%<br><br>Inclusion criteria:<br><br>• 50 years and older<br>• 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.<br>• 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.<br>• 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<br><br>Exclusion criteria:<br><br>• not explicitly stated |
| Interventions | Intervention:<br><br>• 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<br>  ◦ 216 people randomised (304 eyes)<br>  ◦ unknown number (unknown %) people followed up (243 eyes) at 12 months<br><br>Comparator:<br><br>• placebo (cellulose microcrystalline, lactose and magnesium stearate) (twice daily)<br>  ◦ 217 people randomised (310 eyes)<br>  ◦ unknown number (unknown %) people followed up (250 eyes) at 12 months<br><br>Duration: total study duration 3 years but high attrition after 12 months<br><br>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:<br><br>• distance visual acuity<br><br>Secondary:<br><br>• retinal visual acuity<br>• morphological progression of AMD (grading of stereoscopic colour fundus photographs)<br>• macular pigment levels and serum levels of antioxidants |


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**CARMA 2013** *(Continued)*

| | |
|---|---|
| | Follow-up: every 6 months for 3 years, but high attrition after 12 months<br><br>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." Analyses 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."<br><br>Declaration of interest: Quote: "The author(s) have no proprietary or commercial interest in any materials discussed in this article."<br><br>Date study conducted: June 2004 to April 2008<br><br>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."<br><br>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)<br>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: "[p]articipants and study staff were masked to treatment assignments". |
| Blinding of participants and personnel (performance bias)<br>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: "[p]articipants and study staff were masked to treatment assignments". |
| Blinding of outcome assessment (detection bias)<br>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 |


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**CARMA 2013** *(Continued)*

| | | |
|---|---|---|
| | | were indistinguishable in all respects from each other." And: "[p]articipants 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; 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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: random list, unclear how delivered<br>Masking: participant - no; provider - no; outcome - unclear<br>Losses to follow-up: 18% in supplement group, 38% in no supplement group |
| Participants | Country: Italy<br>Number of people randomised: 145 (145 eyes)<br>Number (%) of people followed up: 84 (58%) (84 eyes)<br>Average age (range): 73 years (unknown)<br>Percentage women: 59%<br>Ethnic group: unknown<br>Baseline visual acuity: average 82 letters (ETDRS chart)<br>Comorbidities affecting the eye: 30% of intervention group had had cataract surgery but none of the control group<br>Percentage current smokers: 17%<br>Inclusion criteria:<br>• age 55 to 80<br>• 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<br>• best-corrected visual acuity in the trial eye ≥ 20/32 (0.2 logMAR), 74 letters of the ETDRS chart)<br>• able to understand and comply with the requirements of the trial<br>• no condition limiting view of the fundus (e.g. vitreous haemorrhage, cataracts, epiretinal membrane)<br>• available for a minimum trial duration of approximately 6 months<br>• agree to take only the nutritional supplement provided during this study |


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**CARMIS 2011** *(Continued)*

| | |
|---|---|
| | Exclusion criteria:<br>• ocular disease that causes irreversible reduction of visual acuity (amblyopia, uncontrolled glaucoma, anterior ischaemic optic neuropathy, clinically significant macular oedema)<br>• lens opacity and score 4+ (Lens Opacity Classification System II)<br>• insufficient pupil dilation<br>• previous laser treatment of the posterior pole for any other reason<br>• macular changes not attributable to AMD<br>• carotenoids intolerance<br>• major chronic disease<br>• life expectation lower than 6 months<br>• withdrawal of informed consent<br>• enrolment in another clinical study with experimental product within the last 4 weeks or during the current study |
| Interventions | Intervention:<br>• 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)<br>  ◦ 103 people randomised (103 eyes)<br>  ◦ 84 (82%) people followed up (84 eyes)<br>Comparator:<br>• no dietary supplementation<br>  ◦ 42 people randomised (42 eyes)<br>  ◦ 26 (62%) people followed up (26 eyes)<br>Duration: 24 months<br>Similarity between intervention and comparator: different, no placebo group |
| Outcomes | Reported in methods section of paper:<br>Primary:<br>• change in BCVA (the number of letters read on the logMAR chart)<br>Secondary:<br>• changes in macular function by CS using a Pelli-Robson chart (Clement Clarke International, Harlow Essex, UK) scored per lines<br>• changes in visual function via the Italian-validated version of the 25-item NEI VFQ<br>Reported in results section:<br>• multi-focal electroretinograms (ERG) at 6 and 12 months<br>Follow-up: 6, 12, and 24 months<br>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<br>Declaration of interest: Quote: "The authors report no proprietary interest or financial support."<br>Date study conducted: December 2003 to September 2006<br>Trial registration number: unknown |


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**CARMIS 2011** *(Continued)*

***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... "<br><br>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."<br><br>Quote: "Study drug was administered by an unmasked physician who had no other role in the study."<br><br>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)<br>Visual acuity | High risk | Quote: "A 24-month prospective open-label randomised study... " |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | High risk | Quote: "A 24-month prospective open-label randomised study... " |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | High risk | Quote: "A 24-month prospective open-label randomised study... "<br><br>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."<br><br>However, as participants were not masked, this could have affected the measurement of visual acuity. |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Unclear risk | Quote: "A 24-month prospective open-label randomised study... "<br><br>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)<br>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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: coded tablets prepared by manufacturer<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>Loss to follow-up: 13% |
| Participants | Country: the Netherlands and the UK<br><br>Number of people randomised: 84 (84 eyes)<br><br>Number (%) of people followed up: 73 (87%) (73 eyes)<br><br>Average age (range): 71 years (unknown)<br><br>Percentage women: 61% (56% in intervention group, 67% in control group)<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: average 0.1 logMAR in intervention group, and 0.05 logMAR in control group<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• 50 to 80 years<br>• AMD grade 0 to 4 in one eye (Rotterdam grading)<br>• best corrected visual acuity (BCVA) of logMAR 0.5 or better<br>• minimal cataract<br><br>Exclusion criteria:<br><br>• 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)<br>• history of glaucoma<br>• any dietary supplements containing lutein, zeaxanthin, or meso-zeaxanthin within 3 months of the start of the study<br>• unable to understand the study procedures or unable to give informed consent |
| Interventions | Intervention:<br><br>• lutein 10 mg (daily)<br>  ◦ 42 people randomised (42 eyes)<br>  ◦ 36 (86%) people followed up (36 eyes)<br><br>Comparator:<br><br>• placebo soya bean oil (daily)<br>  ◦ 42 people randomised (42 eyes)<br>  ◦ 37 (88%) people followed up (37 eyes)<br><br>Duration: 12 months<br><br>Similarity between intervention and comparator: Quote: "The [..] capsules and their packaging were completely indistinguishable" |


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**CLEAR 2013** *(Continued)*

| | |
|---|---|
| Outcomes | Primary:<br>• not described in paper but main aim was to investigate effects on MPOD and VA<br>Secondary:<br>• not described in paper<br>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."<br>From clinical trials registry entry (but not prospectively registered):<br>"Primary Outcome Measures: Macular Pigment Optical Density (time frame: baseline, 4 months, 8 months, 12 months; designated as safety issue: No)<br>Secondary Outcome Measures: Visual Acuity (time frame: baseline, 4 months, 8 months, 12 months; designated as safety issue: No)"<br>Follow-up: 3, 8, and 12 months<br>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."<br>Declaration of interest: all authors reported no declaration of interest<br>Date study conducted: August 2007 to August 2009 (from clinical trials registry entry)<br>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."<br>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)<br>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)<br>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)<br>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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: unknown<br>Masking: participant - unknown; provider - unknown; outcome - unknown<br>Loss to follow-up: unknown |
| Participants | Country: France<br>Number of people randomised: 170 (170 eyes)<br>Number (%) of people followed up: unknown<br>Average age (range): unknown<br>Percentage female: unknown<br>Ethnic group: unknown<br>Baseline visual acuity: unknown<br>Comorbidities affecting the eye: unknown<br>Percentage current smokers: unknown<br>Inclusion criteria: neovascular AMD in one eye and drusen in the other |
| Interventions | Intervention:<br>• zinc supplementation (30 mg/day)<br>• unknown number of people randomised (eyes unknown)<br>• unknown number of people followed up (eyes unknown)<br>Comparator:<br>• not known, but study described as "double blind"<br>• unknown number of people randomised (eyes unknown)<br>• unknown number of people followed up (eyes unknown)<br>Duration: unknown |


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**France 1998** *(Continued)*

| | |
|---|---|
| | Similarity between intervention and comparator: unknown |
| Outcomes | Primary: unknown<br>Secondary: unknown<br>Follow-up: unknown<br>Eyes: one eye per person |
| Notes | Trial is unpublished.<br>"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 Professor Soubrane, Universitaire de Creteil, France]<br>Source of funding: unknown<br>Declaration of interest: unknown<br>Date study conducted: unknown<br>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)<br>Visual acuity | Unclear risk | No information available |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | Unclear risk | No information available |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Unclear risk | No information available |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Unclear risk | No information available |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information available |
| Selective reporting (reporting bias) | Unclear risk | No information available |


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**Garcia-Layana 2021**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: sponsor prepared coded tablets<br>Masking: participant - yes; provider - yes; outcome - yes<br>Losses to follow-up: 16 (5 intervention, 11 comparator) |
| Participants | Countries: Spain and Portugal<br>Number of people randomised: 109 (109 eyes)<br>Number (%) of people followed up: 93 (85%) (93 eyes)<br>Average age (range): 77 years (unknown)<br>Percentage women: 49%<br>Ethnic group: unknown<br>Baseline visual acuity: 76 EDTRS letters<br>Comorbidities affecting the eye: 38% pseudophakic<br>Percentage current smokers: unknown<br>Inclusion criteria:<br>• aged 50 years or older<br>• unilateral choroidal neovascularisation secondary to AMD or any of its sequelae<br>• no exudative involvement in the contralateral eye (study eye)<br>Exclusion criteria:<br>• myopia of six dioptres<br>• posterior pole abnormalities that could lead to choroidal neovascularisation<br>• coexisting media opacities that prevent assessment of the fundus<br>• at risk of becoming lost to follow-up<br>• in a therapeutic trial within the last three months<br>• received any nutritional supplement within one month<br>• substance use disorder<br>• not able to understand the study procedures |
| Interventions | Intervention:<br>• Retilut (Laboratorios Thea, Barcelona, Spain) vitamin C 160 mg, vitamin E 24 mg, zinc 20 mg, copper 2 mg, lutein 10 mg, zeaxanthin 2.6 mg, DHA 400 mg, resveratrol 30 mg, hydroxytryosol 3 mg<br>Comparator:<br>• Theavit (Laboratorios Mayoli Spindler, Barcelona, Spain) vitamin C 120 mg, vitamin E 20 mg, zinc 15 mg, beta-carotene 800 mg, vitamin A 800 mg, manganese 2 mg, selenium 50 micrograms<br>Duration: 12 months<br>Similarity between intervention and comparator: Quote "The boxes containing the control and intervention products were identical in appearance". |
| Outcomes | Primary outcome: |


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**Garcia-Layana 2021** *(Continued)*

- BCVA

Secondary outcomes:

- biomicroscopy, fundus evaluation every 6 months
- digital retinography and biochemical analysis at baseline and 12 months
- adverse events at every study visit

Follow-up: 12 months

Eyes: one eye per person; "study eye" was the non-affected eye

| | |
|---|---|
| Notes | Source of funding: Quote: "The research was funded by Laboratorios Théa (Barcelona, Spain) and by research grants from the 'Instituto de Salud Carlos III/European Regional Development Fund' (ERDF) and RD16/0008/0011, OFTARED: Enfermedades oculares: 'Prevención, detección precoz, tratamiento y rehabilitación de las patologías oculares'. The authors thank Fernando Rico-Villademoros (COCIENTE SL Madrid, Spain) for his editorial assistance. This assistance has been funded by Laboratorios Théa (Barcelona, Spain)."<br><br>Declaration of interest: Quote "A.G.-L. has received consultant fees from Allergan, Bayer, Novartis, Roche, and Thea. S.R. declares no conflicts of interest. P.F.-R. declares no conflicts of interest. M.H. declares no conflicts of interest. M.J.A. has received consultant fees from Allergan, Bayer, Brill, Novartis, and Roche. J.N. has received consultant fees from Allergan, Novartis, and Zeiss. E.H.-G. declares no conflicts of interest. B.O.-A. declares no conflicts of interest. J.J.E.-B. has acted as the principal investigator in clinical trials from Roche, Novartis, and Kodiak. M.A.Z. declares no conflicts of interest. R.S. has received consultant fees from Allergan, Alimera, Bayer, Novartis, Roche, Thea, and NovoKordisk. M.C.A. declares no conflicts of interest. M.C.L.-S. declares no conflicts of interest. S.M.-M. declares no conflicts of interest. N.P.-B. declares no conflicts of interest. P.C. is a member of the advisory boards of Novartis and Bayer and a speaker for Novartis and Thea."<br><br>Date study conducted: November 2014 to April 2018<br><br>Trial registration number: NCT04756310 (registered February 2021) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomized in a 1:1 ratio with a block design". |
| Allocation concealment (selection bias) | Low risk | Quote: "The boxes containing the control and intervention products were identical in appearance and were consecutively numbered according to the randomization schedule." |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Quote: "The boxes containing the control and intervention products were identical in appearance and were consecutively numbered according to the randomization schedule. Patients were instructed to receive two capsules daily regardless of the assigned group." |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | Low risk | Quote: "The boxes containing the control and intervention products were identical in appearance and were consecutively numbered according to the randomization schedule. Patients were instructed to receive two capsules daily regardless of the assigned group." |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Low risk | Quote: "The boxes containing the control and intervention products were identical in appearance and were consecutively numbered according to the randomization schedule. Patients were instructed to receive two capsules daily regardless of the assigned group." |


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**Garcia-Layana 2021** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Progression AMD | Low risk | Quote: "The boxes containing the control and intervention products were identical in appearance and were consecutively numbered according to the randomization schedule. Patients were instructed to receive two capsules daily regardless of the assigned group." |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Quote: "Of the 109 randomized patients, 93 completed the trial. The number of participants discontinuing treatment prematurely was 5 (10%) with the intervention treatment and 11 (18.6%) with the control treatment".<br><br>Some imbalance in follow-up. Unclear if this would lead to attrition bias. |
| Selective reporting (reporting bias) | Unclear risk | Difficult to assess. Although study was registered, this was not done prospectively. |

**Holz 1993**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: not known<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>Losses to follow-up: not known |
| Participants | Country: UK<br><br>Number of people randomised: 58 (eyes not known)<br><br>Number (%) of people followed up: not known<br><br>Average age (range): 68 years (55 to 82)<br><br>Percentage women: not known<br><br>Ethnic group: not known<br><br>Baseline visual acuity: not known<br><br>Comorbidities affecting the eye: not known<br><br>Percentage current smokers: not known |
| Interventions | Intervention:<br><br>• zinc sulfate 200 mg (daily) 2 x 100 mg tablet<br>  ◦ 28 people randomised (eyes not known)<br>  ◦ unknown number of people followed up (eyes not known)<br><br>Comparator:<br><br>• placebo (lactose capsule) 2 x 1 tablet daily<br>  ◦ 30 people randomised (eyes not known)<br>  ◦ unknown number of people followed up (eyes not known)<br><br>Duration: 12 to 24 months<br><br>Similarity between intervention and comparator: not known |


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**Holz 1993** *(Continued)*

| | |
|---|---|
| Outcomes | Primary: not known<br><br>Secondary: not known<br><br>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".<br><br>Follow-up: 12 to 24 months<br><br>Eyes: unclear |
| Notes | Data available from abstract only.<br><br>Source of funding: Gertrud-Kusen-Stiftung, Hamburg, grant # Ho92/93-01-2<br><br>Declaration of interest: not known<br><br>Date study conducted: not known<br><br>Trial registration number: not known |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "randomised double-blind study" |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Unclear risk | Quote: "randomised double-blind study" |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | Unclear risk | Quote: "randomised double-blind study" |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Unclear risk | Quote: "randomised double-blind study" |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Low risk | Quote: "randomised double-blind study"<br><br>Quote: "Stereo fundus photographs and fluorescein angiograms were analyzed by investigators in a masked fashion using a standardized grading scheme". |
| Incomplete outcome data (attrition bias)<br>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 |


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**Kaiser 1995**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: sponsor prepared coded tablets<br>Masking: participant - yes; provider - yes; outcome - yes<br>Losses to follow-up: none |
| Participants | Country: Switzerland<br>Number of people randomised: 20 (20 eyes)<br>Number (%) of people followed up: 20 (20 eyes)<br>Average age (range): 73 years (50 to unknown)<br>Percentage women: 74%<br>Ethnic group: not known<br>Baseline visual acuity: not known<br>Comorbidities affecting the eye: not known<br>Percentage current smokers: not known<br>Inclusion criteria:<br>• 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.<br>Exclusion criteria:<br>• people with diabetes mellitus, endocrine problems, cardiac dysrhythmia, cardial infarction or hypotension, other ocular disorders |
| Interventions | Intervention:<br>• 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.<br>  ◦ 9 people randomised (9 eyes)<br>  ◦ 9 (100%) people followed up (9 eyes)<br>Comparator:<br>• placebo resembling active treatment prepared by sponsor<br>  ◦ 11 people randomised (11 eyes)<br>  ◦ 11 (100%) people followed up (11 eyes)<br>Duration: 6 months<br>Similarity between intervention and comparator: not known |
| Outcomes | Primary: not specified<br>Secondary: not specified<br>Outcomes reported:<br>• distance and near visual acuity |


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**Kaiser 1995** *(Continued)*

- 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<br>Declaration of interest: not known<br>Date study conducted: not known<br>Trial registration number: not known |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Sequence generation not described in the report but through contact with investigator<br>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<br>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)<br>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)<br>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)<br>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)<br>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)<br>All outcomes | Low risk | 20 participants enroled and 20 followed up |


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**Kaiser 1995** *(Continued)*

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

**LAST 2004**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: coded bottles<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>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<br><br>Number of people randomised: 90 (eyes unknown)<br><br>Number of people followed up: 76 (84%) (eyes unknown)<br><br>Average age (range): approximate 75 years<br><br>Percentage women: 4%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: average ranged from 0.279 to 0.445 logMAR by eye and treatment group<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• atrophic AMD diagnosed by ophthalmoscopy<br>• at least one visual abnormality reduced contrast sensitivity, photo-stress glare recovery deficit or deficit on Amsler grid<br>• clear ocular media<br>• free of any other ocular/systemic disease that could affect central or parafoveal macular visual function.<br><br>Exclusion criteria:<br><br>• cataract or retinal surgery within 6 months<br>• photosensitising drugs<br>• taken lutein supplements within the previous 6 months |
| Interventions | Intervention:<br><br>• lutein: 10 mg non-esterified lutein (FloraGlo from Kemin Foods International, Des Moines, Iowa)<br>  ◦ 29 people randomised (eyes unknown)<br>  ◦ 25 (86%) people followed up (eyes unknown)<br>• lutein plus additional antioxidants and nutrients (OcuPower, Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida)<br>  ◦ 30 people randomised (eyes unknown)<br>  ◦ 24 (80%) people followed up (eyes unknown) |


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**LAST 2004** *(Continued)*

| | |
|---|---|
| | Comparator:<br>• placebo, maltodextrin<br>  ○ 31 people randomised (eyes unknown)<br>  ○ 27 (87%) people followed up (eyes unknown)<br><br>Duration: 12 months<br><br>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<br><br>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:<br>• macular pigment optical density<br><br>Secondary:<br>• not specified<br><br>The following clinical measurements were made:<br>• lens opacity<br>• retinal images<br>• MPOD<br>• visual acuity (Snellen) distance and near<br>• glare testing<br>• glare recovery<br>• contrast sensitivity<br>• VFQ-14 (activities of daily living, night driving, glare recovery symptoms)<br>• Amsler grid<br>• self-reported vision<br><br>It was difficult to extract data on outcomes of relevance to this review: i.e. visual acuity and progression of AMD.<br><br>Follow-up: 12 month<br><br>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."<br><br>Declaration of interest: unknown<br><br>Date study conducted: August 1999 to May 2001<br><br>Trial registration number: unknown |
| ***Risk of bias*** | |


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**LAST 2004** *(Continued)*

| 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."<br><br>Quote: "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)<br>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."<br><br>Quote: "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)<br>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."<br><br>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)<br>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."<br><br>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)<br>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."<br><br>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)<br>All outcomes | High risk | Judgement comment: loss to follow-up 14/90:<br><br>Lutein 10 mg group N = 29<br>• 1 person lost to follow-up<br>• 1 person died<br>• 2 other withdrawals<br><br>Lutein 10 mg and antioxidant group N = 30<br>• 2 persons lost to follow-up<br>• 4 other withdrawals<br><br>Placebo group N = 31<br>• 1 person lost to follow-up<br>• 1 person died<br>• 1 other withdrawal<br><br>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 |


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**Li 2017**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: unclear<br>Masking: participant - yes; provider - unclear; outcome - unclear<br>Losses to follow-up: 206 randomised, 6 lost to follow-up |
| Participants | Country: China<br>Number of people randomised: 206 (eyes not reported)<br>Number (%) of people followed up: 200 (97%) (eyes not reported)<br>Average age (range): 70 years (not reported)<br>Percentage women: 51%<br>Ethnic group: Chinese<br>Baseline visual acuity: not reported<br>Comorbidities affecting the eye: not reported<br>Percentage current smokers: 20%<br>Inclusion criteria:<br>• aged 50 to 79 years old<br>• diagnosed as early-stage AMD<br>• best corrected visual acuity greater than 0.25<br>Exclusion criteria:<br>• suffering from other eye diseases<br>• laser treatment or medications<br>• patients have not taken lutein or similar supplements within 6 months. |
| Interventions | Intervention:<br>• lutein 20 mg/day<br>  ○ unknown number of people randomised (eyes unknown )<br>  ○ 100 (unknown %) people followed up (eyes unknown )<br>Comparator:<br>• placebo, not specified<br>  ○ unknown number of people randomised (eyes unknown)<br>  ○ 100 (unknown %) people followed up (eyes unknown)<br>Duration: 1 year (48 weeks)<br>The similarity between intervention and comparator was not reported. |
| Outcomes | Primary: not specified<br>Secondary: not specified<br>Outcomes reported in the paper: |


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**Li 2017** *(Continued)*

| | |
|---|---|
| | • serum lutein concentration<br>• Visual Function Questionnaire, 25 questions (VFQ25)<br>• spatial frequencies of contrast sensitivity<br>• macular pigment optical density<br>• best spectacle-corrected visual acuity<br><br>Follow-up: 1 year (48 weeks)<br><br>Eyes: unclear how reported |
| Notes | Source of funding: unknown<br><br>Declaration of interest: unknown<br><br>Date study conducted: unknown<br><br>Trial registration number: unknown |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Judgement comment: method of randomisation not reported |
| Allocation concealment (selection bias) | Unclear risk | Judgement comment: allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Judgement comment: described as double masked, placebo-controlled |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Unclear risk | Judgement comment: placebo-controlled but unclear from translation of report if investigators and outcome assessors masked |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Judgement comment: 206 people enroled and 200 followed-up |
| Selective reporting (reporting bias) | Unclear risk | Judgement comment: difficult to assess with the information available, although all stated outcomes were reported. No protocol or registration details were available. |

**Li 2018**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: unclear<br><br>Masking: participant - no; provider - no; outcome - no<br><br>Losses to follow-up: none |
| Participants | Country: China |


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**Li 2018** *(Continued)*

| | |
|---|---|
| | Number of people randomised: 114 (eyes unknown)<br><br>Number (%) of people followed up: 114 (100%) (eyes unknown)<br><br>Average age (range): 70 years (51 to 92)<br><br>Percentage women: 63%<br><br>Ethnic group: Chinese<br><br>Baseline visual acuity: 0.25 logMAR<br><br>Comorbidities affecting the eye: none (people with other ocular disorders excluded)<br><br>Percentage current smokers: 19%<br><br>Inclusion criteria:<br><br>• clinical diagnosis of early AMD, defined as the presence of soft distinct drusen and/or soft indistinct drusen and/or reticular drusen and/or pigmentary abnormalities<br><br>Exclusion criteria:<br><br>• other ocular disorders<br>• unstable systemic or chronic illness<br>• consumed dietary supplements containing antioxidants or carotenoids within the past 6 months<br><br>Group differences:<br><br>• slightly higher percentage of women in Goji group (67%) versus 60% in control group<br>• higher proportion of Goji group had hyperlipidaemia (51%) versus 33% in control |
| Interventions | Intervention:<br><br>• Goji berries (wolfberry)<br>  ◦ 57 people randomised (eyes unknown)<br>  ◦ 57 (100 %) people followed up (eyes unknown)<br><br>Comparator:<br><br>• usual diet<br>  ◦ 57 people randomised (eyes unknown)<br>  ◦ 57 (100 %) people followed up (eyes unknown)<br><br>Duration:<br><br>• 90 days |
| Outcomes | Primary: not specified<br><br>Secondary: not specified<br><br>Outcomes reported in the paper:<br><br>• visual performance - BCVA (logMAR)<br>• MPOD<br>• serum lutein/zeaxanthin<br><br>Follow-up: 90 days<br><br>Eyes: unclear how handled |
| Notes | Source of funding: "Supported by Special Foundation for Public Welfare Research of China (No.2013CZ-9)." |


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**Li 2018** *(Continued)*

| | |
|---|---|
| | Declaration of interest: all authors reported "none"<br>Date study conducted: unknown<br>Trial registration number: unknown |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "in this 90-day prospective, randomized controlled trial, all subjects were randomized by a 1:1 ratio to the Goji group and the control group."<br>Judgement comment: no other information on the generation of the allocation schedule |
| Allocation concealment (selection bias) | Unclear risk | Quote: "in this 90-day prospective, randomized controlled trial, all subjects were randomized by a 1:1 ratio to the Goji group and the control group."<br>Judgement comment: no other information on allocation concealment |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | High risk | Judgement comment: given the nature of the active (Goji berry supplement) and control (normal diet) condition, participants not blinded. No information on masking, and treatments were different |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | High risk | Judgement comment: no information on masking of visual acuity assessment; treatments were different |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Judgement comment: follow-up not reported. No evidence of missing data. Figure 4 [in study publication] seems to include all data from the Goji group |
| Selective reporting (reporting bias) | Unclear risk | Judgement comment: no trial registration or published protocol. However, all outcomes described in methods were reported. No access to protocol or trial register entry. |

**LISA 2011**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: 2:1 intervention:control<br>Masking: participant - yes; provider - yes; outcome - yes<br>Losses to follow-up: unclear |
| Participants | Country: Austria<br>Number of people randomised: 126 (126 eyes)<br>Number (%) of people followed up: 116 (92%) using LOCF (116 eyes)<br>Average age (range): 72 years (50 to 90)<br>Percentage women: 57% |


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**LISA 2011** *(Continued)*

| | |
|---|---|
| | Ethnic group: not known<br><br>Baseline visual acuity: 83.9% (visual acuity reported as a percentage)<br><br>Comorbidities affecting the eye: not known<br><br>Percentage current smokers: not known<br><br>Inclusion criteria:<br><br>• people in categories 2, 3, or 4, according to the AREDS grading scheme<br>• aged 50 to 90 years<br>• clear nonlenticular ocular media<br>• visual acuity > 0.4<br><br>Exclusion criteria:<br><br>• primary retinal pigment epithelium atrophy > 125 µm<br>• moderate or severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy<br>• participation in a clinical trial in the 3 weeks preceding the study<br>• ocular surgery within the last 6 months<br>• history of treatment with photosensitising drugs |
| Interventions | Intervention:<br><br>• 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<br>  ◦ 84 people randomised (84 eyes)<br>  ◦ unknown number of people followed up (eyes unknown)<br><br>Comparator:<br><br>• placebo<br>  ◦ 42 people randomised (42 eyes)<br>  ◦ unknown number of people followed up (eyes unknown)<br><br>Duration: 6 months<br><br>Similarity between intervention and comparator: unclear |
| Outcomes | Primary: not known<br><br>Secondary: not known<br><br>Outcomes reported in paper:<br><br>• macular pigment optical density<br>• mean differential light threshold<br>• distance visual acuity (ETDRS chart)<br>• mean arterial pressure<br>• pulse rate<br>• intraocular pressure<br><br>From clinical trials.gov, but retrospectively registered:<br><br>"Primary Outcome Measures: Macular pigment optical density (MPOD) as measured with optical reflectometry (time frame: 5 minutes; designated as safety issue: No)<br>Secondary Outcome Measures: visual acuity using ETDRS charts (time frame: 15 minutes; designated as safety issue: No)<br>Central visual field defects assessed with scanning laser scotometry (time frame: 30 minutes; designated as safety issue: No) |


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**LISA 2011** *(Continued)*

| | |
|---|---|
| | Changes in fundus appearance as documented with fundus photos (time frame: 5 minutes; designated as safety issue: No)<br>Determination of an increased systemic antioxidative state in plasma and low density lipoprotein and plasma lutein concentrations (time frame: 5 minutes; designated as safety issue: No)"<br><br>Follow-up: 1 month, 3 months, and 6 months<br><br>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"<br><br>Declaration of interest: all authors reported none.<br><br>Date study conducted: November 2006 to May 2011 (from clinicaltrials.gov)<br><br>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.”<br><br>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)<br>Visual acuity | Unclear risk | Quote: “All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting.”<br><br>No description of placebo. Potential for unmasking as to intervention received.<br><br>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)<br>Progression AMD | Unclear risk | Quote: “All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting.”<br><br>No description of placebo. Potential for unmasking as to intervention received.<br><br>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)<br>Visual acuity | Unclear risk | Quote: “All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting.”<br><br>No description of placebo. Potential for unmasking as to intervention received.<br><br>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)<br>Progression AMD | Unclear risk | Quote: “All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting.” |


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**LISA 2011** *(Continued)*

| | | |
|---|---|---|
| | | No description of placebo. Potential for unmasking as to intervention received.<br><br>No specific information provided as to the blinding of outcome assessors (grading of fundus images, assessment of MPOD or visual function) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 10 people were not included in the analysis, but not clear to which group these people were randomised.<br><br>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. In the placebo group, 6/42 (14.3%) 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. |

**LUTEGA 2013**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Parallel group RCT<br><br>Method of allocation: numbered blisters containing the capsules<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>Losses to follow-up: 16% |
| Participants | Country: Germany<br><br>Number of people randomised: 172 (172 eyes)<br><br>Number (%) of people followed up: 145 (84%)<br><br>Average age (range): 69 (range not reported)<br><br>Percentage women: 54%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• non-exudative AMD<br><br>Exclusion criteria:<br><br>• central geographic atrophy<br>• exudative forms of AMD<br>• pronounced opacity in the intended study eye |
| Interventions | Intervention: |


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**LUTEGA 2013** *(Continued)*

| | |
|---|---|
| | • lutein 10 mg, zeaxanthin 1 mg, concentrated fish oil 255 mg (DHA 100 mg, EPA 30 mg), vitamin C 60 mg, vitamin E 20 mg, zinc 10 mg, copper 0.25 mg<br>  ○ two groups: 1 capsule plus 1 placebo (60 people) and 2 capsules (66 people)<br>  ○ 17% lost to follow-up<br><br>Comparator:<br><br>• placebo<br>  ○ 46 people randomised (46 eyes)<br>  ○ 13% lost to follow-up<br><br>Duration: 12 months<br><br>Similarity between intervention and comparator: Quote: "capsules with an equal composition of ingredients but without any of the substances being investigated." |
| Outcomes | Primary:<br><br>• MPOD<br><br>Secondary:<br><br>• Unclear<br><br>Follow-up: 12 months<br><br>Eyes: Quote: "Only 1 eye of each patient was included in the trial for macular pigment measurements". Unclear how selected |
| Notes | Source of funding: Quote "The study was supported by Novartis GmbH, Germany, and Carl Zeiss Meditec, Jena, Germany."<br><br>Declaration of interest: see above<br><br>Date study conducted: May 2008 to October 2010<br><br>Trial registration number: NCT00763659 (study started May 2008, study registered October 2008)<br><br>Emailed authors: 2 August 2021 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of generation of allocation sequence not reported. |
| Allocation concealment (selection bias) | Low risk | Quote: "Allocation was concealed using numbered blisters containing the capsules." |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Quote: "[Placebo group] received capsules with an equal composition of ingredients but without any of the substances being investigated. Placebo and active treatment capsules were not outwardly distinguishable from each other." |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Low risk | Quote: "[Placebo group] received capsules with an equal composition of ingredients but without any of the substances being investigated. Placebo and active treatment capsules were not outwardly distinguishable from each other." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Judgement comment: some loss to follow-up: 83% followed-up in intervention groups and 87% in placebo group. Reasons for loss to follow-up include |


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**LUTEGA 2013** *(Continued)*

| | | |
|---|---|---|
| | | "exudative AMD, reduced mobility after prolonged illness, hospitalization, lack [of] time", but these were not disaggregated. |
| Selective reporting (reporting bias) | Unclear risk | Judgement comment: no access to study protocol. Only one outcome registered on trial register (MPOD) and this was reported. Visual acuity was measured but not reported. |

**Ma 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: not described<br>Masking: participant - yes; provider - yes; outcome - yes<br>Loss to follow-up: unclearly reported but could be 1/108 |
| Participants | Country: China<br>Number of people randomised: 108 (eyes unknown)<br>Number (%) of people followed up: 107 (99%) (eyes unknown)<br>Average age (range): 69 (unknown)<br>Percentage women: 58%<br>Ethnic group: unknown<br>Baseline visual acuity: 0.30 logMAR<br>Comorbidities affecting the eye: 23% early cataracts<br>Percentage current smokers: 6%<br>Inclusion criteria:<br>• 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<br>Exclusion criteria<br>• late AMD or other macular or choroidal disorders (e.g. macular oedema, macular holes, central serous chorioretinopathy, or macular epiretinal membrane)<br>• demonstrated the presence of significant central lens opacities precluding fundus autofluorescence<br>• had an implanted intraocular lens<br>• glaucoma<br>• unstable chronic illness<br>• history of intraocular inflammation<br>• ocular trauma<br>• laser treatment for retinal diseases<br>• retina-vitreous surgery<br>• photodynamic therapy<br>• currently taking medications affecting macular function (e.g. chloroquine or oxazepam)<br>• consumed dietary supplements containing vitamins or carotenoids within the 6 months before enrolment |


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**Ma 2012** *(Continued)*

| | |
|---|---|
| Interventions | Intervention:<br>• lutein 10 mg or lutein 20 mg or lutein 10 mg and zeaxanthin 10 mg (3 groups) (daily)<br>  ○ 80 people randomised (eyes unknown)<br>  ○ 79 (99%) people followed up (eyes unknown)<br>Comparator:<br>• placebo (daily)<br>  ○ 27 people randomised (eyes unknown)<br>  ○ 27 (100%) people followed up (eyes unknown)<br>Duration: 12 months<br>Similarity between intervention and comparator: unclear, placebo was not described |
| Outcomes | From the published paper:<br>Primary:<br>• macular pigment optical density<br>Secondary:<br>• best-corrected visual acuity<br>• contrast sensitivity<br>• photorecovery time<br>• Amsler grid testing<br>From clinical trials.gov (registered retrospectively):<br>"Primary Outcome Measures: MPOD and multifocal electroretinograms (time frame: 1 year)<br>Secondary Outcome Measures: risk of advanced AMD (time frame: 1 year)"<br>Follow-up: 24 weeks and 48 weeks<br>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."<br>Declaration of interest: Quote: "The author(s) have no proprietary or commercial interest in any materials discussed in this article."<br>Date study conducted: September 2009 to April 2012<br>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." |
| Allocation concealment (selection bias) | Low risk | Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment." |


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**Ma 2012** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment."<br><br>Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color." |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | Low risk | Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment."<br><br>Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color." |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Low risk | Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment."<br><br>Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color." |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Low risk | Quote: "All participants, the study investigators, and data analysts were masked to treatment assignment."<br><br>Quote: "To protect the blinding, the different capsules were indistinguishable by size, weight, or color." |
| Incomplete outcome data (attrition bias)<br>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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: computer-generated table of random numbers<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>Losses to follow-up: 23 (10 treatment, 13 placebo) |
| Participants | Country: USA<br><br>Number of people randomised: 174 (eyes unknown)<br><br>Number (%) of people followed up: 151 (87%) (258 eyes)<br><br>Average age (range): unknown (42 to 89 years)<br><br>Percentage women: 65%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: unknown |


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**Newsome 1988** *(Continued)*

| | |
|---|---|
| | Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• macular degeneration: clinically visible drusen with varying degrees of pigmentary change with visual acuity in 1 eye of 20/80 or better<br><br>Exclusion criteria:<br><br>• cataract reducing vision more than 1 line<br>• other known serious eye disease; diabetes mellitus<br>• other known systemic or metabolic disease or congenital condition, which might interfere with results |
| Interventions | Intervention:<br><br>• zinc sulfate 200 mg (daily) 1 x 100 mg twice daily<br>  ◦ 90 people randomised (eyes unknown)<br>  ◦ 80 (89%) people followed up (134 eyes)<br><br>Comparator:<br><br>• placebo<br>  ◦ 84 people randomised (eyes unknown)<br>  ◦ 71 (85%) people followed up (124 eyes)<br><br>Duration: 1 to 2 years<br><br>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<br><br>Secondary: not specified<br><br>Outcomes reported in paper:<br><br>• Pinhole corrected visual acuity using ETDRS charts<br>• changes in visible pigment, drusen, or atrophy from grading of macular photographs<br>• adverse effects of zinc, including copper deficiency anaemia<br><br>Follow-up: 6, 12, 18, and 24 months<br><br>Eyes: some people had one eye enroled 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<br><br>Declaration of interest: unknown<br><br>Date study conducted: unknown<br><br>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)<br>Visual acuity | Low risk | Quote: "All other personnel were masked to the study."<br><br>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)<br>Progression AMD | Low risk | Quote: "All other personnel were masked to the study."<br><br>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)<br>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)<br>Progression AMD | Low risk | Quote: "Two independent observers masked as to patient identity...". |
| Incomplete outcome data (attrition bias)<br>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."<br><br>Reasons for loss to follow-up zinc/placebo<br><br>• Stopped taking pills 5/6<br>• Started taking zinc 1/2<br>• Gastrointestinal symptoms 1/0<br>• Died 2/1<br>• Poor compliance 0/1<br>• Developed diabetes mellitus 0/1<br>• 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**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Parallel group RCT<br><br>Method of allocation: random allocation using a 50% likelihood scheme |


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**Newsome 2008** *(Continued)*

| | |
|---|---|
| | Masking: participant - yes; provider - yes; outcome - yes<br><br>Losses to follow-up: total of 6; 3 in each group of 40 participants |
| Participants | Country: USA<br><br>Number of people randomised: 80 (eyes unknown)<br><br>Number (%) of people followed up: 74 (93%) (74 right and 72 left eyes)<br><br>Average age (range): 74 years (unknown)<br><br>Percentage women: 80%<br><br>Ethnic group: 81% white<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• presence of macular drusen with or without pigment changes<br><br>Exclusion criteria:<br><br>• choroidal neovascular activity<br>• any condition preventing view of the fundus<br>• other conditions affecting eye: diabetes, eye surgery (except cataract). Chronic open angle glaucoma with stable intraocular pressures and visual fields was allowed.<br><br>Both zinc-monocysteine (ZMC) and placebo groups enroled 40 participants, with best-corrected visual acuity 20/25 to 20/70, macular drusen, and pigment changes |
| Interventions | Intervention:<br><br>• zinc-monocysteine 50 mg (daily 1 x 25 mg twice daily)<br>  ◦ 40 people randomised (eyes unknown)<br>  ◦ 37 (100%) people followed up (37 right and 25 left eyes)<br><br>Comparator:<br><br>• placebo<br>  ◦ 40 people randomised (eyes unknown)<br>  ◦ 37 (100%) people followed up (37 right and 37 left eyes)<br><br>Duration: 6 months<br><br>Similarity between intervention and comparator: unknown |
| Outcomes | Primary:<br><br>• change in acuity<br>• change in contrast sensitivity<br>• change in photorecovery time<br><br>Secondary: not specified<br><br>Follow-up: 6 months<br><br>Eyes: analysed right and left eyes separately |


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**Newsome 2008** *(Continued)*

| | |
|---|---|
| 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."<br><br>Declaration of interest: unknown<br><br>Date study conducted: unknown<br><br>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)<br>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)<br>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)<br>Visual acuity | Low risk | Quote: "Functional assessment....by masked trained examiners..."<br><br>Quote: "Masked examiners determined contrast sensitivity...." |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Low risk | Quote: "Functional assessment....by masked trained examiners..."<br><br>Quote: "Masked examiners determined contrast sensitivity...." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "Thirty-seven [out of 40] in each group competed all visits..."<br><br>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 |

**Parravano 2019**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: not reported<br><br>Masking: participant - yes; provider - yes; outcome - yes |


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**Parravano 2019** *(Continued)*

| | |
|---|---|
| | Losses to follow-up: 2 people (2 eyes) excluded. 1 in the intervention group for "lack of compliance" and 1 in the control group for IOP increase |
| Participants | Country: Italy<br><br>Number of people randomised: 30 (30 eyes)<br><br>Number (%) of people followed up: 28 (93%) (28 eyes)<br><br>Average age (range): 69 years (unknown)<br><br>Percentage women: 70%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• AREDS category 3 features (intermediate AMD)<br>• VA ≥ 20/32 [0.2 logMAR], 74 letters of the ETDRS charts<br>• extensive (as measured by drusen area) intermediate drusen, at least one large druse or GA not involving the center of the macula<br>• not taking supplements with carotenoids or antioxidants<br><br>Exclusion criteria:<br><br>• moderate to dense lens opacity<br>• implanted intraocular lens<br>• corneal opacities<br>• previous history of refractive surgery<br>• glaucoma or ocular hypertension<br>• previous history of intraocular inflammation such as anterior or posterior uveitis<br>• previous history of retinal detachment or laser treatment for peripheral retinal diseases<br>• diabetes or systemic hypertension under medical treatment<br>• previous history of ocular trauma<br>• usage of systemic treatments with known toxic effects on the macula (e.g. chloroquine, oxazepam), neurological diseases<br>• presence of any signs of advanced AMD (choroidal neovascularisation or central GA) |
| Interventions | Intervention:<br><br>• MacuPrev Farmaplus Italia s.r.l., Italy lutein 20 mg, zeaxanthin 4 mg, N-acetylcysteine 140 mg, bromelain 2500GDU 80 mg, vitamin D3 800 IU, vitamin B12 18 mg, alpha-lipoic acid 140 mg, rutin 157 mg, vitamin C 160 mg, zinc oxide 16 mg, Vaccinium myrtillus 36% anthocyanosides 90 mg, Ganoderma lucidum 600 mg zinc-monocysteine 50 mg (dose reflects daily amount taken in form of 2 tablets per day)<br>◦ 15 people randomised (15 eyes)<br>◦ 14 (93%) people followed up (14 eyes)<br><br>Comparator:<br><br>• placebo microcrystalline cellulose (885 mg), talcum (28 mg), calcium phosphate tribasic (688 mg), vegetable magnesium stearate (14 mg), and calcium carbonate (344 mg) (2 tablets per day)<br>◦ 15 people randomised (15 eyes)<br>◦ 14 (93%) people followed up (14 eyes)<br><br>Duration: 6 months |


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**Parravano 2019** *(Continued)*

| | |
|---|---|
| | Similarity between intervention and comparator: unknown |
| Outcomes | Primary: (not specifically described as primary but outcome on which the sample size was based.<br>• mfERG RAD<br>Secondary: (other outcomes)<br>• central macular thickness, inner retinal layer, outer retinal layers thickness and volume (measured using OCT)<br>Follow-up: 6 months<br>Eyes: one eye per person: Quote: "When both eyes fulfilled the inclusion criteria, the eye with the best VA was selected; when both eyes had the same VA, the right eye was chosen for analysis". |
| Notes | Source of funding: Quote: "Research for this study was financially supported by the Italian Ministry of Health and Fondazione Roma. Article processing charges were funded by Farmaplus Italia s.r.l., Italy".<br>Declaration of interest: authors reported none<br>Date study conducted: February to July 2017<br>Trial registration number: NCT03919019 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The random separation of AMD patients (screened by MT and MP) was performed by an electronically generated randomization system on the basis of age, gender, and mfERG ring 1 response amplitude density (RAD)". |
| Allocation concealment (selection bias) | Unclear risk | Judgement comment: allocation concealment not mentioned |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Judgement comment: placebo-controlled study |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Low risk | Judgement comment: placebo-controlled study. Quote: "The 4 operators were masked for each patient evaluation for both mfERG and OCT". |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Judgement comment: 28/30 participants completed the study |
| Selective reporting (reporting bias) | High risk | Judgement comment: outcomes on trial register reported but registered retrospectively. Some measured outcomes – e.g. visual acuity – not reported. |

**Piatti 2020**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT<br>Method of allocation: coded tablets |


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**Piatti 2020** *(Continued)*

| | |
|---|---|
| | Masking: participant - yes; provider - yes; outcome - yes<br><br>Losses to follow-up: unclear |
| Participants | Country: Italy<br><br>Number of people randomised: 80 (80 eyes)<br><br>Number (%) of people followed up: 74 (93%)<br><br>Average age (range): 72 (55 to 82)<br><br>Percentage women: 69%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: 49 ETDRS letters<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• age 55 to 80 years<br>• diagnosis of intermediate AMD, according to the AREDS Research Group classification<br>• BCVA for distance ≥ 20/32 Snellen decimal (LogMAR 0.2) and a minimum number of 43 letters read at the ETDRS chart<br>• BCVA for near ≥ 20/32 Snellen decimal (LogMAR 0.2) at the MNREAD chart<br><br>Exclusion criteria:<br><br>• not reported |
| Interventions | Intervention:<br><br>• lutein 10 mg, astaxanthin 4 mg, zeaxanthin 2 mg, vitamin C 90 mg, vitamin E 30 mg, zinc 22.5 mg plus copper 1 mg, omega-3 fatty acids (fish oil 500 mg, containing EPA 185 mg and DHA 140 mg)<br>  ◦ unclear how many randomised, 48 people included in analysis (48 eyes)<br><br>Comparator:<br><br>• placebo<br>  ◦ unclear how many randomised, 26 people included in analysis (26 eyes)<br><br>Duration: 24 months<br><br>Similarity between intervention and comparator: Quote: "Food supplement and placebo were packaged in identical containers and indistinguishable in terms of external appearance." Unclear about whether other differences |
| Outcomes | Primary:<br><br>• AMD progression<br><br>Secondary:<br><br>• visual acuity<br><br>Follow-up: 24 months<br><br>Eyes: one eye per person. Quote: "In case of bilateral AMD, eye with the best visual acuity (VA) was selected for the study; if both eyes had the same VA, the right eye was chosen. The fellow eye was always monitored in case of bilateral AMD. " |


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**Piatti 2020** *(Continued)*

| | |
|---|---|
| Notes | Source of funding: Quote: "The author(s) received no financial support for the research, authorship and/or publication of this article."<br><br>Declaration of interest: Quote: "The author(s) declared following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A.P. received consulting fees from Allergan, Bayer, Novartis and SIFI. D.M. received consulting fees from SIFI. All other authors have nothing to disclose."<br><br>Date study conducted: unknown<br><br>Trial registration number: unknown |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information on how allocation sequence was generated |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment not described |
| Blinding of participants and personnel (performance bias)<br>Visual acuity | Low risk | Supplement and placebo were packaged in identical containers and indistinguishable in terms of external appearance |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | Low risk | Supplement and placebo were packaged in identical containers and indistinguishable in terms of external appearance |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Low risk | Supplement and placebo were packaged in identical containers and indistinguishable in terms of external appearance |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Low risk | Supplement and placebo were packaged in identical containers and indistinguishable in terms of external appearance |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "Eighty patients with intermediate AMD were screened and randomized. Only patients without major protocol violations were included in the statistical analysis (full analysis subset); this subset included 74 patients (48 treated with food supplement and 26 with placebo)".<br><br>Unclear what the major protocol violations were. No other information about follow-up |
| Selective reporting (reporting bias) | Unclear risk | No access to protocol or trials registry entry |

**Stur 1996**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT |


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**Stur 1996** *(Continued)*

| | |
|---|---|
| | Method of allocation: sponsor-prepared coded bottles<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>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<br><br>Number of people randomised: 112 (112 eyes)<br><br>Number (%) of people followed up: 92 (82%) (92 eyes); 78 (70%) (78 eyes) included in the analyses because eyes that developed CNV were excluded<br><br>Average age (range): 71 years (50 to unknown)<br><br>Percentage women: 57%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: average 0.075 logMAR<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: 21%<br><br>Inclusion criteria:<br><br>• 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)<br><br>Exclusion criteria:<br><br>• dense senile cataract<br>• any other eye disease that could produce significant and permanent loss of visual acuity during follow-up<br>• physical status that could prevent follow-up; history of serious systemic or metabolic disease |
| Interventions | Intervention:<br><br>• zinc sulfate 200 mg (daily) 1 tablet<br>  ◦ 56 people randomised (56 eyes)<br>  ◦ unknown number (%) people followed up but 37 (37 eyes) included in the analyses, excluding eyes that developed CNV<br><br>Comparator:<br><br>• placebo 1 tablet<br>  ◦ people randomised (eyes unknown)<br>  ◦ unknown number (%) people followed up but 41 (41 eyes) included in the analyses, excluding eyes that developed CNV<br><br>Duration: 24 months<br><br>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<br><br>Secondary: not specified |


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**Stur 1996** *(Continued)*

| | |
|---|---|
| | Outcomes reported in paper:<br>• best-corrected logMAR visual acuity measured using Bailey-Lovie chart<br>• contrast sensitivity<br>• incidence of choroidal neovascularisation<br>• progression of disease (Wisconsin Age-related Maculopathy Grading System)<br>• copper deficiency anaemia<br>Follow-up: 6, 12, 18, and 24 months<br>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<br>Funders: Astra, Linz, Austria; Austrian Foundation for the Propagation of Scientific Research<br>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."<br>Declaration of interest: "Proprietary interest category: No"<br>Date study conducted: March 1990 to June 1992<br>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"<br>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)<br>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) | 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 |


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**Stur 1996** *(Continued)*

| | | |
|---|---|---|
| Progression AMD | | 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." |
| 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."<br><br>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**

| ***Study characteristics*** | |
|---|---|
| Methods | Parallel group RCT<br><br>Method of allocation: coded bottles<br><br>Masking: participant - yes; provider - yes; outcome - yes<br><br>Losses to follow-up: 11 participants excluded after randomisation |
| Participants | Country: Australia<br><br>Number of people randomised: 1204 (eyes unknown) randomised, but 11 participants excluded after randomisation, and reported 1193 (eyes unknown) randomised by group<br><br>Number of people followed up: 1179 (98%) |


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**VECAT 2002** *(Continued)*

| | |
|---|---|
| | Average age (range): 66 years (55 to 80)<br><br>Percentage women: 56%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: 99% ≥ 40 letters on logMAR chart<br><br>Comorbidities affecting the eye: only 19% with AMD; 4% with diabetes; approximately 20% with lens opacity<br><br>Percentage current smokers: 2%<br><br>Inclusion criteria:<br><br>• lens and retina of at least 1 eye available for documentation<br><br>Exclusion criteria:<br><br>• previous cataract surgery or advanced cataract in both eyes<br>• steroid or anticoagulation use<br>• serious disease<br>• regular use or sensitivity to vitamin E |
| Interventions | Intervention:<br><br>• vitamin E 500 IU per day: natural vitamin E in soybean oil medium<br>  ○ 595 people randomised (eyes unknown)<br>  ○ 587 (99%) people followed up (eyes unknown)<br><br>Comparator:<br><br>• placebo of soybean oil medium<br>  ○ 598 people randomised (eyes unknown)<br>  ○ 592 (99%) people followed up (eyes unknown)<br><br>Duration: 4 years<br><br>Similarity between intervention and comparator: Quote: "Vitamin E and placebo capsules were of identical appearance and taste." |
| Outcomes | Primary:<br><br>• development of early AMD<br><br>Secondary:<br><br>• progression of early AMD<br>• development of late AMD<br>• changes in visual acuity (the number of letters read on the logMAR chart)<br>• changes in visual function (VF14 score).<br><br>Follow-up: annual follow-up for 4 years<br><br>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."<br><br>Declaration of interest: no competing interests declared |


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**VECAT 2002** *(Continued)*

| | |
|---|---|
| | 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."<br><br>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 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)<br>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)<br>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)<br>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)<br>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."<br><br>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)<br>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. |

**Wang 2004**

***Study characteristics***

| | |
|---|---|
| Methods | Parallel group RCT |
| | Method of allocation: unknown |


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**Wang 2004** *(Continued)*

| | |
|---|---|
| | Masking: participant - unknown; provider - unknown; outcome - unknown<br><br>Losses to follow-up: unknown |
| Participants | Country: China<br><br>Number of people randomised: 400 (400 eyes)<br><br>Number of people followed up: unknown<br><br>Average age (range): 65 years (52 to 76)<br><br>Percentage women: 53%<br><br>Ethnic group: unknown<br><br>Baseline visual acuity: unknown<br><br>Comorbidities affecting the eye: unknown<br><br>Percentage current smokers: unknown<br><br>Inclusion criteria:<br><br>• people with early or advanced AMD (AREDS criteria)<br><br>Exclusion criteria:<br><br>• other eye diseases<br>• systemic illness |
| Interventions | Intervention:<br><br>• zinc oxide 80 mg daily, vitamin C, vitamin E<br>  ◦ unknown number of people randomised (eyes unknown)<br>  ◦ unknown number (%) of people followed up (eyes unknown)<br><br>Comparator:<br><br>• placebo<br>  ◦ unknown number of people randomised (eyes unknown)<br>  ◦ unknown number (%) of people followed up (eyes unknown)<br><br>Duration: 24 to 32 months<br><br>Similarity between intervention and comparator: unknown |
| Outcomes | Primary:<br><br>• not specified<br><br>Secondary:<br><br>• not specified<br><br>Outcomes:<br><br>• visual acuity<br>• early and late AMD<br><br>Follow-up: every 6 months for 24 to 32 months<br><br>Eyes: one eye per person, worse eye was selected |


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**Wang 2004** *(Continued)*

| | |
|---|---|
| Notes | Limited information available on this trial. AMD participants were stratified into early and late-stage disease<br><br>Source of funding: unknown<br><br>Declaration of interest: unknown<br><br>Date study conducted: unknown<br><br>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)<br>Visual acuity | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias)<br>Progression AMD | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias)<br>Visual acuity | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias)<br>Progression AMD | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>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
BCVA: best-corrected visual acuity
CNV: choroidal neovascularisation
CS: contrast sensitivity
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
ERG: electroretinogram
ETDRS: Early Treatment Diabetic Retinopathy Study
GA: geographic atrophy
IOP: intraocular pressure
LOCF: last observation carried forward


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logMAR: logarithm of the minimal angle of resolution
mfERG: multifocal electroretinogram
MPOD: macular pigment optical density
NEI: National Eye Institute
OCT: optical coherence tomography
RAD: response amplitude density
RCT: randomised controlled trial
RDA: recommended dietary allowance
RPE: retinal pigment epithelium
SD: standard deviation
VA: visual acuity
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 | Not an RCT |
| Bahrami 2006 | Participants did not have AMD in one or both eyes. |
| Barakat 2006 | Review outcomes were not measured. |
| Benzie 2006 | Participants did not have AMD in one or both eyes. |
| Berendschot 2015 | Not an antioxidant vitamin and/or mineral supplement |
| Bone 2007 | Participants did not have AMD in one or both eyes. |
| Broadhead 2019 | Not an antioxidant vitamin and/or mineral supplement |
| Cangemi 2007 | Not an RCT |
| Christen 2007 | Participants did not have AMD in one or both eyes. |
| Connolly 2011 | Participants did not have AMD in one or both eyes. |
| CREST 2014 | Not an RCT (participants with AMD were all given supplementation) |
| Cumurcu 2006 | Not an RCT |
| EXIT 2017 | Participants did not have AMD in one or both eyes. |
| Falsini 2010 | Not an antioxidant vitamin and/or mineral supplement |
| Franciose 2006 | Participants did not have AMD in one or both eyes. |
| Goodrow 2006 | Participants did not have AMD in one or both eyes. |
| ISRCTN35481392 | Participants did not have AMD in one or both eyes. |
| ISRCTN81595685 | No placebo or untreated group in the study |
| JPRN-UMIN000027962 | No placebo or untreated group in the study |


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| Study | Reason for exclusion |
|---|---|
| Kamburoglu 2006 | Not an RCT |
| Kolber 2013 | Not an RCT |
| Kopsell 2006 | Participants did not have AMD in one or both eyes. |
| Landrum 2012 | Participants did not have AMD in one or both eyes. |
| Lim 2006 | Not an antioxidant vitamin and/or mineral supplement |
| LIMPIA 2013 | Participants did not have AMD in one or both eyes. |
| LUNA 2007 | Not an RCT |
| LUXEA 2006 | No placebo or untreated group in the study |
| Meagher 2013 | No placebo or untreated group in the study |
| Moeller 2006 | Not an RCT |
| NCT00121589 | Not an RCT |
| NCT00718653 | Participants did not have AMD in one or both eyes. |
| NCT00800995 | Not an antioxidant vitamin and/or mineral supplement |
| NCT00893724 | Ineligible intervention: antioxidants combined with inosine |
| NCT02264938 | Not an RCT |
| NCT03205202 | Participants did not have AMD in one or both eyes. |
| NCT03478865 | Not an RCT |
| Nolan 2006 | Not an RCT |
| Nolan 2007 | Not an RCT |
| Nolan 2012 | Participants did not have AMD in one or both eyes. |
| Nussenblatt 2006 | Participants did not have AMD in one or both eyes. |
| Owsley 2006 | Not an antioxidant vitamin and/or mineral supplement |
| PHS II 2012 | Participants did not have AMD in one or both eyes. |
| Rosenthal 2006 | No placebo or untreated group in the study |
| Sabour-Pickett 2014 | No placebo or untreated group in the study |
| Saperstein 2015 | Participants did not have AMD in one or both eyes. |
| Sasamoto 2011 | Not an RCT |


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| Study | Reason for exclusion |
|---|---|
| Scorolli 2002 | Ineligible intervention: antioxidants combined with active treatment (photodynamic therapy (PDT)) |
| Souied 2013 | Not an antioxidant vitamin and/or mineral supplement |
| Told 2014 | Participants did not have AMD in one or both eyes. |
| Told 2015 | Participants did not have AMD in one or both eyes. |
| Vannas 1958 | Not an RCT |
| Vidal 2011 | Participants did not have AMD in one or both eyes. |
| Wang 2007 | Not an RCT |
| Wenzel 2006 | Bioavailability study |
| Wolf-Schnurrbusch 2015 | Ineligible comparator: antioxidant compared to antioxidant plus omega-3 |
| Wong 2010 | Not an antioxidant vitamin and/or mineral supplement |
| Zhao 2006 | Not an RCT |
| ZVF 2011 | No placebo or untreated group in the study |

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

### Characteristics of studies awaiting classification *[ordered by study ID]*

#### Chiosi 2020

| | |
|---|---|
| Methods | Randomised controlled trial |
| Participants | People with early-intermediate age-related macular degeneration (AMD) (n = 53)<br><br>Inclusion criteria:<br><br>• diagnosis of early-intermediate AMD according to Age-Related Eye Disease Study (AREDS) classification<br>• presence of small-medium drusen (≥ 63 µm, < 125 µm) in macular zone<br>• best-corrected visual acuity (BCVA) for distance ≥ 20/32 Early Treatment Diabetic Retinopathy Study (ETDRS) charts<br>• BCVA for near ≥ 20/32 Snellen Decimal (logarithm of the minimal angle of resolution (logMar) 0.2) at the MNREAD chart<br><br>Exclusion criteria:<br><br>• myopia > 3 diopter<br>• other macular disorders<br>• cataract and eye surgery 3 months prior to enrollment study |
| Interventions | Intervention: vitamin D 50 µg (1000%), homotaurine 50 mg plus complete AREDS 2 formula (1 tablet/day) |


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| | |
|---|---|
| **Chiosi 2020** *(Continued)* | |
| | Comparator: placebo<br>Duration: 12 months |
| Outcomes | Primary outcome:<br>• AMD progression assessed by optical coherence tomography of changes in drusen size<br>Other outcomes:<br>• retinography<br>• Amsler test<br>• visual function quality test (National Eye Institute Visual Function Questionnaire (NEI-VFQ))<br>• BCVA for distance and near |
| Notes | Abstract only |

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

**NCT01694680**

| | |
|---|---|
| Study name | Intervention trial in early age-related macular degeneration |
| Methods | Parallel group RCT |
| Participants | N = 120 |
| Interventions | Dietary supplement: lutein-enriched-egg beverage (NWT-02)<br>Dietary supplement: placebo |
| Outcomes | From clinicaltrials.gov:<br>"Primary Outcome Measures: Visual function (time frame: 12 months; designated as safety issue: No)<br>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 Center on Aging (HNRCA), Boston (MA) |
| Notes | |

**NCT02625376**

| | |
|---|---|
| Study name | Resveratrol for exudative age-related macular degeneration |
| Methods | Parallel group RCT |
| Participants | N = 489 |
| Interventions | Dietary supplement: Resvega<br>Dietary supplement: Trans-Resveratrol |


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**NCT02625376** *(Continued)*

| | |
|---|---|
| | Dietary supplement: placebo |
| Outcomes | From clinical trials.gov:<br><br>"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?<br>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 | |

**NCT03845582**

| | |
|---|---|
| Study name | Phase 3 Study of ALK-001 in geographic atrophy (SAGA) |
| Methods | Parallel group RCT |
| Participants | 300 people with geographic atrophy (GA) |
| Interventions | ALK-001 oral capsule (C20-D3-retinyl acetate or C20 deuterated vitamin A)<br><br>Placebo oral capsule |
| Outcomes | From clinicaltrials.gov:<br><br>"Primary Outcome Measures :<br><br>1. Growth rate of GA lesions, as assessed by Fundus Autofluorescence (FAF) [ Time Frame: Baseline to 24 months ]<br><br>Secondary Outcome Measures :<br><br>1. Safety and tolerability, as assessed by evaluation of adverse events [ Time Frame: Baseline to 24 months ]<br>2. Pharmacokinetics, as assessed by plasma concentrations of ALK-001 and metabolites [ Time Frame: Baseline to 24 months ]<br>3. Incidence of choroidal neovascularization (CNV) [ Time Frame: Baseline to 24 months ]<br>4. Changes in Visual Acuity [ Time Frame: Baseline to 24 months ]<br>5. Changes in Reading Speed [ Time Frame: Baseline to 24 months ]" |
| Starting date | May 2019. Estimated study completion May 2022 |
| Contact information | Leonide Saad, PhD sagainfo@sagastudy.com |
| Notes | |

RCT: randomised controlled trial


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## DATA AND ANALYSES

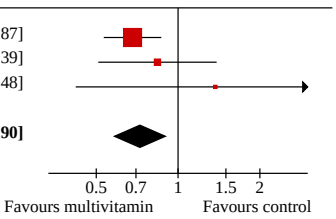
### Comparison 1. Antioxidant multivitamin and mineral supplement versus placebo or no treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Progression to late AMD (neovascular AMD and/or geographic atrophy) | 3 | 2445 | Odds Ratio (IV, Fixed, 95% CI) | 0.72 [0.58, 0.90] |
| 1.2 Progression to neovascular AMD | 1 | | Odds Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 1.3 Progression to geographic atrophy | 1 | | Odds Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 1.4 Progression to visual loss (loss of 3 or more lines on logMAR chart) | 1 | | Odds Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 1.5 Mean visual acuity | 6 | 740 | Mean Difference (IV, Fixed, 95% CI) | -0.00 [-0.04, 0.03] |
| 1.5.1 Mean visual acuity at end of study | 2 | 204 | Mean Difference (IV, Fixed, 95% CI) | -0.03 [-0.09, 0.02] |
| 1.5.2 Change in visual acuity | 4 | 536 | Mean Difference (IV, Fixed, 95% CI) | 0.02 [-0.03, 0.07] |
| 1.6 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 or no treatment, Outcome 1: Progression to late AMD (neovascular AMD and/or geographic atrophy)

| Study or Subgroup | log[Odds Ratio] | SE | Multivitamin Total | Placebo or no treatment Total | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| AREDS 2001 (1) | -0.3857 | 0.124375 | 888 | 903 | 78.2% | 0.68 [0.53 , 0.87] |
| CARMA 2013 (2) | -0.17435 | 0.255778 | 252 | 257 | 18.5% | 0.84 [0.51 , 1.39] |
| CARMIS 2011 (3) | 0.3164 | 0.603858 | 103 | 42 | 3.3% | 1.37 [0.42 , 4.48] |
| **Total (95% CI)** | | | **1243** | **1202** | **100.0%** | **0.72 [0.58 , 0.90]** |

Heterogeneity: Chi² = 1.71, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Not applicable




**Footnotes**
(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up
(2) Follow-up: 12 months
(3) Follow-up: 24 months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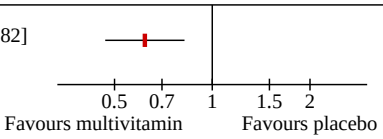
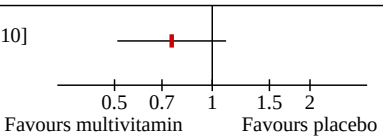
### Analysis 1.2. Comparison 1: Antioxidant multivitamin and mineral supplement versus placebo or no treatment, Outcome 2: Progression to neovascular AMD

| Study or Subgroup | log[Odds Ratio] | SE | Multivitamin Total | Placebo Total | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| AREDS 2001 | -0.478 | 0.143419 | 610 | 596 | 0.62 [0.47 , 0.82] |



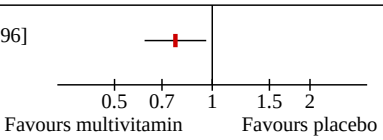

### Analysis 1.3. Comparison 1: Antioxidant multivitamin and mineral supplement versus placebo or no treatment, Outcome 3: Progression to geographic atrophy

| Study or Subgroup | log[Odds Ratio] | SE | Multivitamin Total | Placebo Total | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| AREDS 2001 | -0.2877 | 0.196819 | 610 | 596 | 0.75 [0.51 , 1.10] |




### Analysis 1.4. Comparison 1: Antioxidant multivitamin and mineral supplement versus placebo or no treatment, Outcome 4: Progression to visual loss (loss of 3 or more lines on logMAR chart)

| Study or Subgroup | log[Odds Ratio] | SE | Multivitamin Total | Placebo Total | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| AREDS 2001 (1) | -0.2614 | 0.111512 | 888 | 903 | 0.77 [0.62 , 0.96] |




**Footnotes**

(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up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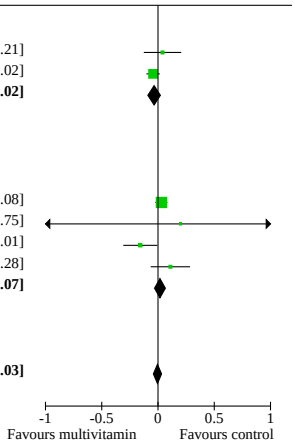
## Analysis 1.5. Comparison 1: Antioxidant multivitamin and mineral supplement versus placebo or no treatment, Outcome 5: Mean visual acuity

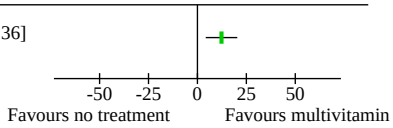
| Study or Subgroup | Multivitamin Mean [logMAR] | Multivitamin SD [logMAR] | Multivitamin Total | Placebo or no treatment Mean [logMAR] | Placebo or no treatment SD [logMAR] | Placebo or no treatment Total | Weight | Mean Difference IV, Fixed, 95% CI [logMAR] |
|---|---|---|---|---|---|---|---|---|
| **1.5.1 Mean visual acuity at end of study** | | | | | | | | |
| AMDSG 1996 (1) | 0.33 | 0.41 | 35 | 0.29 | 0.24 | 24 | 4.8% | 0.04 [-0.13 , 0.21] |
| LUTEGA 2013 (2) | 0.083048 | 0.170178 | 105 | 0.127 | 0.16 | 40 | 37.8% | -0.04 [-0.10 , 0.02] |
| **Subtotal (95% CI)** | | | **140** | | | **64** | **42.6%** | **-0.03 [-0.09 , 0.02]** |
| Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.21 (P = 0.23) | | | | | | | | |
| **1.5.2 Change in visual acuity** | | | | | | | | |
| Bartlett 2007 (3) | 0.01 | 0.07 | 20 | -0.02 | 0.07 | 10 | 47.1% | 0.03 [-0.02 , 0.08] |
| CARMA 2013 | -0.1 | 7 | 172 | -0.3 | 7.7 | 173 | 0.1% | 0.20 [-1.35 , 1.75] |
| CARMIS 2011 (4) | -0.121 | 0.4562 | 84 | 0.036 | 0.302 | 26 | 5.8% | -0.16 [-0.31 , -0.01] |
| LAST 2004 (5) | -0.03 | 0.2131 | 24 | -0.14 | 0.4045 | 27 | 4.4% | 0.11 [-0.06 , 0.28] |
| **Subtotal (95% CI)** | | | **300** | | | **236** | **57.4%** | **0.02 [-0.03 , 0.07]** |
| Heterogeneity: Chi² = 6.43, df = 3 (P = 0.09); I² = 53% | | | | | | | | |
| Test for overall effect: Z = 0.71 (P = 0.48) | | | | | | | | |
| **Total (95% CI)** | | | **440** | | | **300** | **100.0%** | **-0.00 [-0.04 , 0.03]** |
| Heterogeneity: Chi² = 9.19, df = 5 (P = 0.10); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.80) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.90, df = 1 (P = 0.17), I² = 47.3% | | | | | | | | |




**Footnotes**
(1) Right eye: LogMAR score (converted from Snellen decimal acuity) at 18 months
(2) Study eye: 12 months
(3) Study eye: Change in logMAR score (EDTRS chart) over 9 months
(4) Study eye: 12 months
(5) Right eye: Change in logMAR score (converted from Snellen decimal acuity) over 12 months

## Analysis 1.6. Comparison 1: Antioxidant multivitamin and mineral supplement versus placebo or no treatment, Outcome 6: Quality of life

| Study or Subgroup | Multivitamin Mean | Multivitamin SD | Multivitamin Total | No treatment Mean | No treatment SD | No treatment Total | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| CARMIS 2011 (1) | 3.6 | 14.2848 | 84 | -8.7 | 19.4103 | 26 | 12.30 [4.24 , 20.36] |




**Footnotes**
(1) NEI-VFQ at 24 months

## Comparison 2. Lutein with or without zeaxanthin versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Progression to late AMD (neovascular AMD and/or geographic atrophy) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.2 Progression to neovascular AMD | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.3 Progression to geographic atrophy | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.4 Progression to visual loss (loss of 3 or more lines on logMAR chart) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |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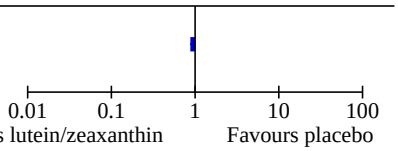
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.5 Distance visual acuity: mean | 3 | 231 | Mean Difference (IV, Fixed, 95% CI) | -0.00 [-0.05, 0.05] |
| 2.5.1 Mean visual acuity at end of study | 1 | 72 | Mean Difference (IV, Fixed, 95% CI) | 0.00 [-0.06, 0.06] |
| 2.5.2 Change in visual acuity | 2 | 159 | Mean Difference (IV, Fixed, 95% CI) | -0.01 [-0.09, 0.08] |
| 2.6 Quality of life | 2 | 308 | Mean Difference (IV, Fixed, 95% CI) | 1.21 [-2.59, 5.01] |

**Analysis 2.1. Comparison 2: Lutein with or without zeaxanthin versus placebo, Outcome 1: Progression to late AMD (neovascular AMD and/or geographic atrophy)**

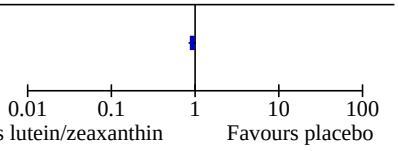
| | Lutein/zeaxanthin | | Placebo | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| AREDS2 2013 (1) | 940 | 3451 | 1000 | 3440 | 0.94 [0.87 , 1.01] | |




**Footnotes**
(1) Almost all participants took AREDS formula

**Analysis 2.2. Comparison 2: Lutein with or without zeaxanthin versus placebo, Outcome 2: Progression to neovascular AMD**

| | Lutein/zeaxanthin | | Placebo | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| AREDS2 2013 (1) | 607 | 3451 | 655 | 3440 | 0.92 [0.84 , 1.02] | |




**Footnotes**
(1) Almost all participants took AREDS formula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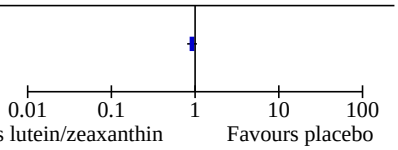
## Analysis 2.3. Comparison 2: Lutein with or without zeaxanthin versus placebo, Outcome 3: Progression to geographic atrophy

| Study or Subgroup | Lutein/zeaxanthin Events | Total | Placebo Events | Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| AREDS2 2013 (1) | 367 | 3451 | 398 | 3440 | 0.92 [0.80 , 1.05] | |

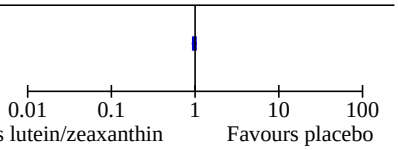



**Footnotes**

(1) Almost all participants took AREDS formula

## Analysis 2.4. Comparison 2: Lutein with or without zeaxanthin versus placebo, Outcome 4: Progression to visual loss (loss of 3 or more lines on logMAR chart)

| Study or Subgroup | Lutein/zeaxanthin Events | Total | Placebo Events | Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| AREDS2 2013 (1) | 1015 | 3332 | 1034 | 3324 | 0.98 [0.91 , 1.05] | |

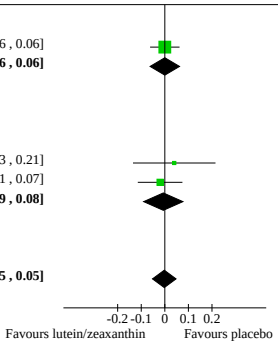



**Footnotes**

(1) Almost all participants took AREDS formula

## Analysis 2.5. Comparison 2: Lutein with or without zeaxanthin versus placebo, Outcome 5: Distance visual acuity: mean

| Study or Subgroup | Lutein/zeaxanthin Mean [logMAR] | SD [logMAR] | Total | Placebo Mean [logMAR] | SD [logMAR] | Total | Weight | Mean Difference IV, Fixed, 95% CI [logMAR] | Mean Difference IV, Fixed, 95% CI [logMAR] | Risk of Bias A B C D E F |
|---|---|---|---|---|---|---|---|---|---|---|
| **2.5.1 Mean visual acuity at end of study** | | | | | | | | | | |
| CLEAR 2013 (1) | 0.09 | 0.14 | 36 | 0.09 | 0.13 | 36 | 64.0% | 0.00 [-0.06 , 0.06] | | + + + + + + |
| **Subtotal (95% CI)** | | | **36** | | | **36** | **64.0%** | **0.00 [-0.06 , 0.06]** | | |
| Heterogeneity: Not applicable | | | | | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | | | | | |
| **2.5.2 Change in visual acuity** | | | | | | | | | | |
| LAST 2004 (2) | -0.1 | 0.218 | 25 | -0.14 | 0.4045 | 27 | 8.2% | 0.04 [-0.13 , 0.21] | | ? + + + - ? |
| Ma 2012 (3) | -0.02 | 0.1817 | 80 | 0 | 0.2275 | 27 | 27.9% | -0.02 [-0.11 , 0.07] | | + + + + + - |
| **Subtotal (95% CI)** | | | **105** | | | **54** | **36.0%** | **-0.01 [-0.09 , 0.08]** | | |
| Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0% | | | | | | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | | | | | | |
| **Total (95% CI)** | | | **141** | | | **90** | **100.0%** | **-0.00 [-0.05 , 0.05]** | | |
| Heterogeneity: Chi² = 0.36, df = 2 (P = 0.83); I² = 0% | | | | | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | | | | | |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.90), I² = 0% | | | | | | | | | | |




**Footnotes**

(1) Study eye: 12 months
(2) Right eye: 12 months
(3) Unclear eyes/people: 12 months

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Visual acuity
(D) Blinding of outcome assessment (detection bias): Visual acuity
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)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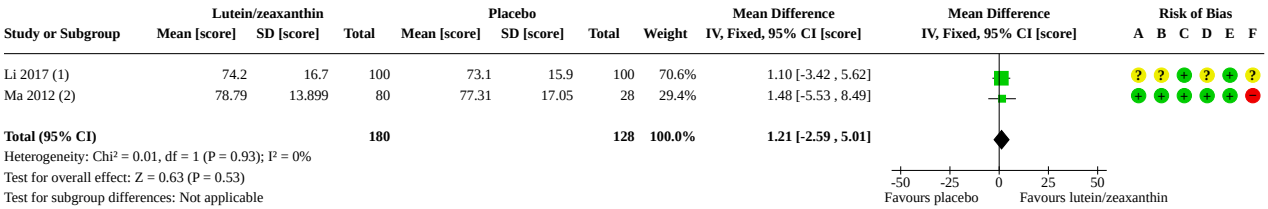
### Analysis 2.6. Comparison 2: Lutein with or without zeaxanthin versus placebo, Outcome 6: Quality of life




**Footnotes**

(1) National Eye Institute Visual Function Questionnaire 25: 48 weeks
(2) National Eye Institute Visual Function Questionnaire 25: 24 months

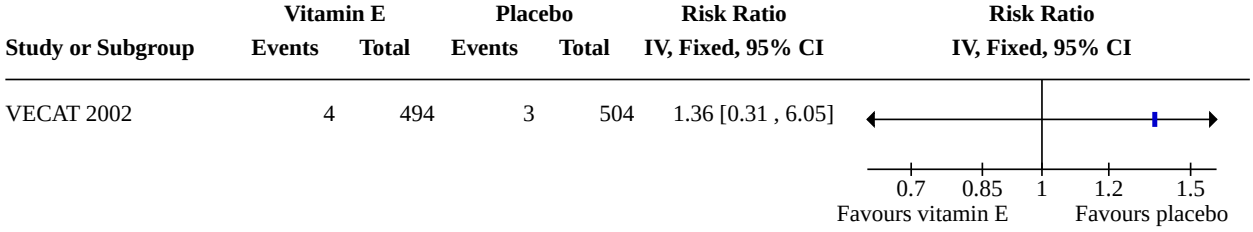
**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Visual acuity
(D) Blinding of outcome assessment (detection bias): Visual acuity
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)

## Comparison 3. Vitamin E versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Progression to late AMD (neovascular AMD and/or geographic atrophy | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 3.2 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





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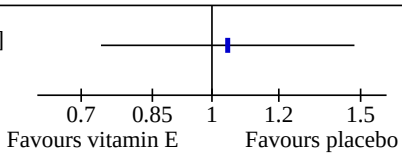
**Analysis 3.2. Comparison 3: Vitamin E versus placebo, Outcome 2: Progression to visual loss (loss of 3 or more lines on logMAR chart)**

| Study or Subgroup | Vitamin E Events | Vitamin E Total | Placebo Events | Placebo Total | Risk Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| VECAT 2002 (1) | 59 | 587 | 57 | 592 | 1.04 [0.74 , 1.47] |




**Footnotes**

(1) Loss of 2 lines (9 letters).

## Comparison 4. Zinc versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Progression to late AMD (neovascular AMD and/or geographic atrophy) | 3 | 3790 | Odds Ratio (IV, Fixed, 95% CI) | 0.83 [0.70, 0.98] |
| 4.2 Progression to neovascular AMD | 1 | | Odds Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 4.3 Progression to geographic atrophy | 1 | | Odds Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 4.4 Progression to visual loss (loss of 3 or more lines on logMAR chart) | 2 | 3791 | Odds Ratio (IV, Fixed, 95% CI) | 0.87 [0.75, 1.00] |
| 4.5 Distance visual acuity: mean | 2 | 155 | Mean Difference (IV, Fixed, 95% CI) | -0.01 [-0.05, 0.04] |
| 4.5.1 Mean visual acuity at end of study | 1 | 78 | Mean Difference (IV, Fixed, 95% CI) | 0.02 [-0.04, 0.08] |
| 4.5.2 Change in visual acuity | 1 | 77 | Mean Difference (IV, Fixed, 95% CI) | -0.06 [-0.14, 0.02] |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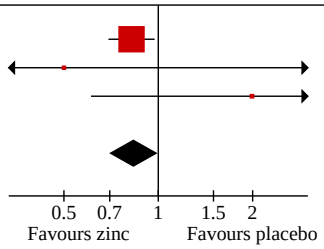
## Analysis 4.1. Comparison 4: Zinc versus placebo, Outcome 1: Progression to late AMD (neovascular AMD and/or geographic atrophy)

| Study or Subgroup | log[Odds Ratio] | SE | Zinc Total | Placebo Total | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| AREDS 2001 (1) | -0.1965 | 0.086422 | 1792 | 1848 | 97.2% | 0.82 [0.69 , 0.97] |
| Holz 1993 (2) | -0.6931 | 0.922 | 28 | 30 | 0.9% | 0.50 [0.08 , 3.05] |
| Stur 1996 (3) | 0.688135 | 0.603204 | 46 | 46 | 2.0% | 1.99 [0.61 , 6.49] |
| **Total (95% CI)** | | | **1866** | **1924** | **100.0%** | **0.83 [0.70 , 0.98]** |

Heterogeneity: Chi² = 2.42, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable

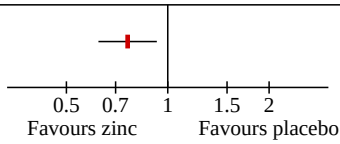



**Footnotes**

(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up
(2) By person: 'new exudative or dry macular lesions' over 12 to 24 months
(3) Study eye: incidence of exudative AMD over 24 months

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

| Study or Subgroup | log[Odds Ratio] | SE | Zinc Total | Placebo Total | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| AREDS 2001 (1) | -0.2744 | 0.101849 | 1209 | 1233 | 0.76 [0.62 , 0.93] |

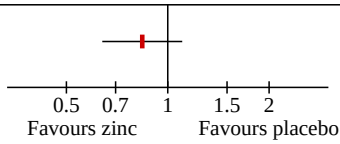



**Footnotes**

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

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

| Study or Subgroup | log[Odds Ratio] | SE | Zinc Total | Placebo Total | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| AREDS 2001 (1) | -0.1744 | 0.139467 | 1209 | 1233 | 0.84 [0.64 , 1.10] |




**Footnotes**

(1) By person (event in at least one eye): progression to advanced AMD over average 6.3 years follow-up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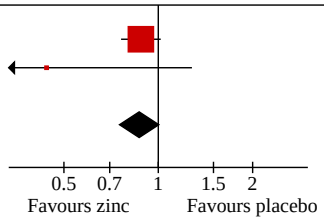
### Analysis 4.4. Comparison 4: Zinc versus placebo, Outcome 4: Progression to visual loss (loss of 3 or more lines on logMAR chart)

| Study or Subgroup | log[Odds Ratio] | SE | Zinc Total | Placebo Total | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| AREDS 2001 (1) | -0.1278 | 0.074246 | 1792 | 1848 | 98.2% | 0.88 [0.76 , 1.02] |
| Newsome 1988 (2) | -0.82098 | 0.544933 | 80 | 71 | 1.8% | 0.44 [0.15 , 1.28] |
| **Total (95% CI)** | | | **1872** | **1919** | **100.0%** | **0.87 [0.75 , 1.00]** |

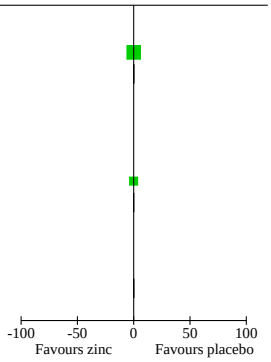
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable




**Footnotes**
(1) By person (event in at least one eye): ETDRS chart over an average of 6.3 years
(2) Study eye: ETDRS chart over 24 months

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

| Study or Subgroup | Zinc Mean [logMAR] | Zinc SD [logMAR] | Zinc Total | Placebo Mean [logMAR] | Placebo SD [logMAR] | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI [logMAR] |
|---|---|---|---|---|---|---|---|---|
| **4.5.1 Mean visual acuity at end of study** | | | | | | | | |
| Stur 1996 (1) | 0.046 | 0.12 | 37 | 0.027 | 0.14 | 41 | 66.0% | 0.02 [-0.04 , 0.08] |
| **Subtotal (95% CI)** | | | **37** | | | **41** | **66.0%** | **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 (2) | 0.082 | 0.124 | 40 | 0.142 | 0.219 | 37 | 34.0% | -0.06 [-0.14 , 0.02] |
| **Subtotal (95% CI)** | | | **40** | | | **37** | **34.0%** | **-0.06 [-0.14 , 0.02]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.46 (P = 0.14) | | | | | | | | |
| **Total (95% CI)** | | | **77** | | | **78** | **100.0%** | **-0.01 [-0.05 , 0.04]** |
| Heterogeneity: Chi² = 2.45, df = 1 (P = 0.12); I² = 59% | | | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.45, df = 1 (P = 0.12), I² = 59.2% | | | | | | | | |




**Footnotes**
(1) Study eye: LogMAR score (Bailey-Lovie chart) at 24 months
(2) Study eye: logMAR score calculated from change in no. of letters (EDTRS) 19 to 24 months

## ADDITIONAL TABLES

### Table 1. AMD clinical classification (Beckman Initiative for Macular Research Classification Committee)

| Classification of AMD | Definition (lesions assessed within 2 disc diameters of fovea in either eye) | Comparison with AREDS categories |
|---|---|---|
| Terminology | Small drusen < 63 µm | Small drusen < 63 µm |
| | Medium drusen ≥ 63 µm and < 125 µm | Intermediate drusen ≥ 63 µm and < 125 µm |
| | Large drusen ≥ 125 µm | Large drusen ≥ 125 µm |
| No apparent aging changes | No drusen and | AMD Category 1 |
| | no AMD pigmentary abnormalities* | No or small drusen |
| | | No pigment abnormalities |


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**Table 1. AMD clinical classification (Beckman Initiative for Macular Research Classification Committee)** *(Continued)*

| | | |
|---|---|---|
| Normal aging changes | Only small drusen and<br>no AMD pigmentary abnormalities* | AMD Category 1<br>No or small drusen<br>No pigment abnormalities |
| Early AMD | Medium drusen<br>No AMD pigmentary abnormalities* | AMD category 2<br>Intermediate drusen<br>Pigment abnormalities may be absent or present<br>Also includes small drusen if cover more than 1/150 disc areas |
| Intermediate AMD | Large drusen and/or<br>any AMD pigmentary abnormalities* | AMD category 3<br>Broader category including intermediate, large drusen, and noncentral geographic atrophy |
| Late AMD | Neovascular AMD and/or<br>any geographic atrophy | AMD category 4<br>Neovascular AMD or geographic atrophy<br>Also includes visual acuity worse than 6/9 due to AMD |

From: Ferris 2013
AMD: age-related macular degeneration; AREDS: Age-related Eye Disease Study
*AMD pigmentary abnormalities: any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities

**Table 2. Dietary reference values for adults for antioxidant vitamins and minerals from the Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine in the USA and the European Food Safety Authority**

| Antioxidant vitamin / mineral | Recommended daily intake | | Tolerable daily upper intake levels*** | | Example of 'high dose' in eye supplement |
|---|---|---|---|---|---|
| | USA: RDA* | European: PRI** | USA | European | |
| Vitamin C<br>mg | 90 (men)<br>75 (women) | 110 (men)<br>95 (women) | 2000 | Not defined | 500 (AREDS) |
| Vitamin E<br>mg (international units, IU) | 15 mg (28 IU) | AI****<br>13 (men)<br>11 (women) | 1000 (1465 IU) | 300 | 400 IU (AREDS) |
| Carotenoids<br>(none set) | | | | | |
| Selenium µg | 55 | 70 | 400 | 300 | 200 (Ocupower) |
| Zinc<br>mg | 11 (men)<br>8 (women) | *****<br>11 (men)<br>8.9 (women) | 40 | 25 | 80 (AREDS) |


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Data sources: Institute of Medicine 2000; Institute of Medicine 2001; European Food Safety Authority 2023.
* US standards: the recommended daily allowance (RDA) is the average daily level of intake sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
** European standards: the population reference intake (PRI) is the intake of a nutrient that is likely to meet the needs of almost all healthy people in a population.
*** The tolerable upper intake level is the maximum chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.
****Adequate intake: an adequate intake (AI) is used when there isn't enough data to calculate an average requirement. An AI is the average nutrient level, based on observations or experiments, that is assumed to be adequate for the population's needs.
***** Different recommendations according to phytate in diet. This is for 900 mg/day phytate in the diet.

**Table 3. Results of searches for previous versions of this review**

| Date review published | Date searches up to date | Newly included studies | Total number of studies included in the review | Total number of excluded studies | Studies awaiting assessment | Ongoing studies |
|---|---|---|---|---|---|---|
| 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 2017 update) | - |
| February 2002 | November 2001 | AREDS 2001; Holz 1993; VECAT 2002 | 7 | 1 | 0 | - |
| February 2006 | January 2006 | LAST 2004 | 8 | 1 | Wang 2004 (included November 2007) | - |
| November 2007 | August 2007 | Wang 2004 | 9 | 25 | 0 | - |
| October 2012 | August 2012 | Bartlett 2007; CARMIS 2011; LISA 2011; Newsome 2008 | 13 | 41 | CARMA 2013 (included 2017 update)<br>LUTEGA 2013 and Falsini 2010 (both excluded 2017 update) | AREDS2 2013 and NCT91948476 (Ma 2012) (both included 2017 update): NCT00879671 (this is the same trial as LISA 2011 included in October 2012)<br>NCT00893724 (excluded 2017 update) |
| June 2017 | March 2017 | AREDS2 2013; Berrow 2013; CARMA 2013; CLEAR 2013; France 1998*; Ma 2012 | 19 | 56** | 0 | NCT01694680; NCT02625376 |
| Current Update (2023) | November 2022 | Azar 2017; Garcia-Layana 2021; Li 2017; Li 2018; LUTEGA 2013***; Parravano 2019; Piatti 2020 | 24 | 59 | Chiosi 2020 | NCT01694680; NCT02625376; NCT03845582 |


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* 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 included this study in the June 2017 update.
** In the 2017 review, the following studies were listed separately as excluded studies, but we note they are the same study and have combined them in one record for the current update.

- Cangemi 2007 and ISRCTN57556290
- Rosenthal 2006, Khachik 2006 and NCT00006202
- Scalinci 2002 and Scorolli 2002
- Wolf-Schnurrbusch 2015 and NCT00563979

*** LUTEGA 2013 excluded in 2017 version of this review.


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**Table 4. Characteristics of included studies**

| | Study | Type of AMD | Treatment (dose/day) | Treatment duration | Follow-up | Data on eyes or people | Visual acuity | Progression AMD | Notes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | AMDSG 1996 | Early AMD | Ocuguard:<br>Beta-carotene 20,000 IU<br>Vitamin E 200 IU<br>Vitamin C 750 mg<br>Citrus bioflavonoid complex 125 mg<br>Quercitin (bioflavonoid) 50 mg<br>Bilberry extract (bioflavonoid) 5 mg<br>Rutin (bioflavonoid) 50 mg<br>Zinc picolinate 12.5 mg<br>Selenium 50 µg<br>Taurine 100 mg<br>N-acetyl cysteine 100 mg<br>L-glutathione 5 mg<br>Vitamin B2 25 mg<br>Chromium 100 µg | 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 | - |
| 2 | AREDS 2001 | AMD and VA 20/32 or better in 1 eye<br>956/3640 had AMD | Antioxidants:<br>Vitamin C 500 mg<br>Vitamin E 400 IU<br>Beta-carotene 15 mg<br>Zinc (zinc oxide) 80 mg<br>Cupric oxide 2 mg<br>Factorial design | 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, | - |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Antioxidants x zinc | | | | | haemorrhage under the retina, subretinal fibrosis.<br><br>Colour fundus photography | |
| 3 | 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)<br><br>Almost all participants in both intervention and comparator groups took AREDS supplement and multivitamin with the study medication.<br><br>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 | Control group had AREDS formula |
| 4 | Azar 2017 | People with stage 4 exudative AMD in only one eye (AREDS criteria) | Lutein (5 mg), zeaxanthin (1 mg), omega-3 fatty acids (DHA 560 mg and GLA 420 mg), vitamin C (80 mg), vitamin E (10 mg), vitamin B6 (2 mg), vitamin B9 (200 micrograms), vitamin B12 (1 microgram), zinc (10 mg) | 2 years | 2 years | Trial eye - eye with non-exudative AMD | Unclear how measured, not reported | Not reported, probably not measured | - |
| 5 | Bartlett 2007 | Soft or hard drusen, and areas of increased or decreased pigment associated with these drusen | Lutein esters 6 mg<br>Retinol 750 mg<br>Vitamin C 250 mg<br>Vitamin E 34 mg<br>Zinc 10 mg<br>Copper 0.5 mg | 9 months | 9 months | Trial eye selected (initial visit only); if both eyes were eligible for inclusion, the right eye was used | Change in logMAR acuity measured using ETDRS chart | Fundus photographs graded using AREDS classification system (4 categories). Mean (standard devia- | - |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | tion) grade was reported | |
| 6 | 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 | 3m ETDRS (logMAR) 750 lux retro-illuminated chart (Sussex Vision) | Not reported | - |
| 7 | 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 | - |
| 8 | 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<br>Vitamin E 30 mg<br>Zinc 22.5 mg<br>Copper 1 mg<br>Lutein 10 mg<br>Zeaxanthin 1 mg<br>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 | - |
| 9 | CLEAR 2013 | AMD grade 0 to 4 in one eye (Rotterdam | Lutein 10 mg | 12 months | 12 months | One eye per participant | Early Treatment | Not reported | - |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | grading) and visual acuity 0.5 or better | | | | | Diabetic Retinopathy Study (ETDRS) logMAR chart at 4 m | | |
| 10 | France 1998 | Neovascular AMD in one eye and drusen in the other | Zinc 30 mg | Unknown | Unknown | One eye per person | Unknown | - | - |
| 11 | Garcia-Layana 2021 | Neovascular AMD in one eye | Retilut® (Laboratorios Thea, Barcelona, Spain) vitamin C 160 mg; vitamin E 24 mg; zinc 20 mg, copper 2 mg, lutein 10 mg, zeaxanthin 2.6 mg, DHA 400 mg, resveratrol 30 mg, hydroxytryosol 3 mg | 12 months | 12 months | One eye per person | EDTRS letters | Development of CNV | Comparator group: Theavit® (Laboratorios Mayoli Spindler, Barcelona, Spain) vitamin C 120 mg, vitamin E 20 mg, zinc 15 mg, beta-carotene 800 mg, vitamin A 800 mg, manganese 2 mg, selenium 50 microgram |
| 12 | 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' | - |
| 13 | Kaiser 1995 | Nonserous AMD | Visaline:<br><br>Buphenine HCL 1.5 mg | 6 months | 6 months | Study eye identified | Decimal acuity measured using | Not reported | - |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Beta-carotene 10 mg<br>Tocopherol acetate 10 mg<br>Vitamin C 50 mg | | | | a Snellen chart | | |
| 14 | LAST 2004 | Atrophic AMD and reduced vision | Lutein 10 mg<br><br>Ocupower:<br><br>Natural beta-carotene (Betatenem) 15,000 IU<br><br>Vitamin C 1500 mg (as calcium ascorbate-Ester<br><br>CB)<br><br>Vitamin D3 400 IU<br><br>Vitamin E 500 IU (d-alpha tocopherol succinate)<br><br>Vitamin B1 50 mg<br><br>Vitamin B2 10 mg<br><br>Vitamin B3 70 mg<br><br>Vitamin B5 50 mg<br><br>Vitamin B6 50 mg<br><br>Vitamin B12 500 µg<br><br>Folic acid 800 µg<br><br>Biotin 300 µg<br><br>Calcium 500 mg<br><br>Magnesium 300 mg<br><br>Iodine 75 µg<br><br>Zinc 25 mg (as zinc L-methionine-L-OptiZincB)<br><br>Copper 1 mg<br><br>Manganese 2 mg | 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 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Selenium 200 µg<br>Chromium 200 µg<br>Molybdenum 75 µg<br>Lycopene 600 µg<br>Bilberry extract 160 mg (standardised to 25% anthocyanosides)<br>Alpha lipoic acid 150 mg<br>N-acetyl cysteine 200 mg<br>Quercetin 100 mg<br>Rutin 100 mg<br>Citrus bioflavonoids 250 mg<br>Plant enzymes 50 mg<br>Black pepper extract 5 mg (BioperineB)<br>Malic acid 325 mg<br>Taurine 900 mg<br>L-glycine 100 mg<br>L-glutathione 10 mg<br>Boron 2 mg | | | | | | |
| 15 | Li 2017 | Early-stage AMD | Lutein 20mg/day | 48 weeks | 48 weeks | Unclear how eyes reported | Unclear how measured | Not reported, probably not measured | - |
| 16 | Li 2018 | Clinical diagnosis of early AMD, which was defined as the presence of soft distinct drusen and/or soft indistinct drusen | Goji berries (wolfberry) | 90 days | 90 days | Unclear how eyes reported | Measured on a logMAR scale, not reported which chart | Not reported, probably not measured | - |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | and/or reticular drusen and/or pigmentary abnormalities. | | | | | | | |
| 17 | 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 | - |
| 18 | LUTEGA 2013 | Non-exudative AMD | Lutein 10 mg, zeaxanthin 1 mg, concentrated fish oil 255 mg, DHA 100 mg, EPA 30 mg, vitamin C 60 mg, vitamin E 20 mg, zinc 10 mg, copper 0.25 mg.<br><br>1 group 1 capsule per day; 1 group 2 capsules per day | 12 months | 12 months | Study eye: unclear how selected | Measured using an ETDRS chart | Not reported | - |
| 19 | Ma 2012 | Early AMD (drusen, pigmentary abnormalities) | Lutein 10 mg<br><br>Lutein 20 mg<br><br>Lutein 10 mg and zeaxanthin 10 mg | 12 months | 12 months | Unclear how many eyes included | Unclear how measured but reported in logMAR | Not reported | - |
| 20 | 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 | - |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 21 | 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 | - |
| 22 | Parravano 2019 | AREDS category 3 features (intermediate AMD) | MacuPrev (Farmaplus Italia s.r.l., Italy) lutein 20 mg, zeaxanthin 4 mg, N-acetylcysteine 140 mg, bromelain 2500GDU 80 mg, vitamin D3 800 IU, vitamin B12 18 mg, alpha-lipoic acid 140 mg, rutin 157 mg, vitamin C 160 mg, zinc oxide 16 mg, *Vaccinium myrtillus* 36% Anthocyanosides 90 mg, *Ganoderma lucidum* 600 mg, zinc-monocysteine 50 mg | 6 months | 6 months | One eye per person: Quote: "When both eyes fulfilled the inclusion criteria, the eye with the best VA was selected; when both eyes had the same VA, the right eye was chosen for analysis" | Unclear how measured, not reported | Not reported, probably not measured | - |
| 23 | Piatti 2020 | Intermediate AMD (AREDS) | Lutein 10 mg, astaxanthin 4 mg, zeaxanthin 2 mg, vitamin C 90 mg, vitamin E 30 mg, zinc 22.5 mg plus copper 1 mg, omega-3 fatty acids (fish oil 500 mg, containing EPA 185 mg and DHA 140 mg) | 24 months | 24 months | Study eye: eye with the best visual acuity was selected for the study; if both eyes had the same VA, the right eye was chosen. | Measured using ETDRS chart | Quote: "retinography" | - |
| 24 | 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 log-MAR score measured using Bailey-Lovie chart<br><br>Note: participants with | Incidence of neovascular lesion in study eye | Original trial of N = 500 terminated by sponsor (Astra) because statistical evalua- |


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**Table 4. Characteristics of included studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | neovascular event excluded from this outcome | | tion of first 40 participants at 24 months follow-up "did not show any treatment benefit" |
| 25 | VECAT 2002 | Early AMD (18%)<br><br>Late AMD (0.5%)<br><br>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 | - |
| 26 | Wang 2004 | Early (38%) or late (62%) AMD | Zinc oxide 80 mg, vitamin C, vitamin E | 24 to 32 months | Every 6 months from 24 to 32 months | Worse eye | Unclear how measured | Unclear how measured | - |

AMD: age-related macular degeneration
CNV: choroidal neovascularisation
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
ETDRS: Early Treatment Diabetic Retinopathy Study
GA: geographic atrophy
GLA: gamma-Linolenic acid
logMAR: logarithm of the minimum angle of resolution
RPE: retinal pigment epithelium
VA: visual acuity


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**Table 5. Multivitamin supplements**

| | Study (brand name) | Vitamin A | Vitamin C | Vitamin E | Be-ta-carotene | Lutein | Zeaxan-thin | Zinc | Selenium | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | AMDSG 1996 (OcuGuard, Twin Lab Inc, Ronkonkoma, NY) | | 750 mg | 200 IU | 20,000 IU | | - | 12.5 mg as zinc picoli-nate | 50 µg | Citrus bioflavonoid com-plex 125 mg quercitin (bioflavonoid) 50 mg bilberry extract (bioflavonoid) 5 mg rutin (bioflavonoid) 50 mg taurine 100 mg N-acetyl cysteine 100 mg L-glu-tathione 5 mg vitamin B2 25 mg chromium 100 µg |
| 2 | AREDS 2001 | | 500 mg | 400 IU | 15 mg | | | 80 mg as zinc oxide with cupric oxide 2 mg | | |
| 3 | Berrow 2013, (Ocuvite Duo, Bausch and Lomb, Berlin) | | 150 mg | 15 mg | | 12 mg | 0.6 mg | 25 mg as zinc oxide with cupric oxide 0.4 mg | | omega-3 fatty acids: EPA 240 mg and DHA 840 mg |
| 4 | Bartlett 2007 | Retinol 750 mg | 250 mg | 34 mg | | 6 mg | - | 10 mg with copper 0.5 mg | | - |
| 5 | CARMA 2013 (Ocuvite, Bausch and Lomb, Berlin) | | 150 mg | 15 mg | | 12 mg | 0.6 mg | 20 mg as zinc oxide with copper gluconate 0.4 mg | | |
| 6 | CARMIS 2011 | | 180 mg | 30 mg | | 10 mg | 1 mg plus astaxan-thin 4 mg | zinc 22.5 mg copper 1 mg | | |
| 7 | Garcia-Layana 2021 (Retilut) | | 120 mg | 24 mg | | 10 mg | 2.6 mg | 20 mg, copper 2 mg | | DHA 400 mg, resveratrol 30 mg, hydroxytryosol 3 mg |
| 8 | Kaiser 1995 (Visaline, Novopharma Cham, Switzer-land) | | 100 mg | 10 mg | 10 mg | | | | | 1.5 mg buphenine HCl |


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**Table 5. Multivitamin supplements** *(Continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 9 | LAST 2004 (OcuPower, Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida, FloraGlo (Kemin Foods International, Des Moines, Iowa) | 2500 IU | 1500 mg vitamin C (as calcium ascorbate) | 500 IU natural vitamin E (d-alpha tocopherol succinate) | 15,000 IU natural beta carotene (Betatenem) | 10 mg | - | 25 mg as zinc L-methionine-L-OptiZincB 1 mg copper | 200 µg | 400 IU vitamin D3 50 mg vitamin B1 10 mg vitamin B2 70 mg vitamin B3 50 mg vitamin B 550 mg vitamin B6 500 µg vitamin B12 800 µg folic acid 300 µg biotin 500 mg calcium 75 µg iodine 300 mg magnesium 2 mg manganese 200 µg chromium 75 µg molybdenum 600 µg lycopene 160 mg bilberry extract (standardised 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 10 mg L-glutathione 2 mg boron |
| 10 | LUTEGA 2013 | | 60 mg | 20 mg | | 10 mg | 1 mg | zinc 10 mg, copper 0.25 mg | | concentrated fish oil 255 mg (DHA 100 mg, EPA 30 mg) |
| 11 | Parravano 2019 (Macuprev, Farmaplus Italia s.r.l., Italy) | | 160 mg | | | 20 mg | 4 mg | 16 mg as zinc oxide | | N-acetylcysteine 140 mg, bromelain 2500GDU 80 mg, vitamin D3 800 IU, vitamin B12 18 mg, alpha-lipoic acid 140 mg, rutin 157 mg, Vaccinium myrtillus 36% anthocyanosides 90 mg, Ganoderma lucidum 600 mg |
| 12 | Piatti 2020 (Azyr Mega, SIFI S.p.A, Italy) | | 90 mg | 30 mg | | 10 mg | astaxanthin 4 mg zeaxanthin 2 mg | 22.5 mg plus copper 1 mg | | fish oil 500 mg, containing EPA 185 mg and DHA 140 mg |


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**Table 5. Multivitamin supplements** *(Continued)*

| | | | | |
|---|---|---|---|---|
| 13 | Wang 2004 | Dose not specified | Dose not specified | - |




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**Table 6. 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 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).<br><br>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 (plus AREDs formula) | 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)". Quote: "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". Quote: "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". Quote: "More lung cancers were noted in the beta carotene vs no beta carotene group (23 [2.0%] vs 11 [0.9%], nominal P=.04), mostly in former smokers." |
| 4 | Azar 2017 | Lutein and zeaxanthin with multivitamins | Quote: "No serious adverse events related to the supplements occurred across treatment" |
| 5 | Bartlett 2007 | Multivitamin | Quote: "There were no reported adverse effects from any of the study participants." |
| 6 | Berrow 2013 | Multivitamin (Ocuvite) | Did not report adverse effects |
| 7 | CARMA 2013 | Multivitamin (Ocuvite) | Did not report adverse effects |
| 8 | CARMIS 2011 | Multivitamin | Quote: "There were no significant systemic or ocular adverse events related to the nutritional supplementation." |
| 9 | 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. |


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**Table 6. Adverse effects in the included studies** *(Continued)*

| | | | |
|---|---|---|---|
| 10 | France 1998 | Zinc | Unpublished study, no data available |
| 11 | Garcia-Layana 2021 | Multivitamin (Retilut and Theavit) | 21/109 adverse events in people receiving multivitamins, including 6 cases of cataract and 5 cases of exudative AMD. |
| 12 | Holz 1993 | Zinc | Quote: "the zinc therapy was well-tolerated". |
| 13 | Kaiser 1995 | Multivitamin | Did not report adverse effects |
| 14 | LAST 2004 | Multivitamin (OcuPower) and lutein (FloraGlo) | The number of adverse effects were tabulated, but the study was underpowered to detect any differences. |
| 15 | Li 2017 | Lutein | Did not report adverse effects |
| 16 | Li 2018 | Goji berries (wolfberry) | Quote in Discussion: "... without causing any detectable adverse effects" |
| 17 | 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." |
| 18 | LUTEGA 2013 | Multivitamin | Quote: "No adverse or other unintended effects were noted in any of the observed groups in the present study" |
| 19 | Ma 2012 | Lutein and zeaxanthin | Quote: "No adverse events were observed or reported." Quote: "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)." |
| 20 | Newsome 1988 | Zinc | Quote: "In the zinc-treated group, one subject stopped study participation due to the feeling that the study tablet aggravated preexisting peptic ulcer symptoms. Another subject taking zinc complained of gastrointestinal tract upset, which was relieved by taking the study tablet with food." |
| 21 | Newsome 2008 | Zinc mono-cysteine | Quote: "ZMC (zinc mono-cysteine) appeared to be well tolerated"; 1/40 had gastrointestinal symptoms attributable to treatment. |
| 22 | Parravano 2019 | Multivitamin (Macuprev) | Did not report adverse effects |
| 23 | Piatti 2020 | Multivitamin (Azyr Mega) | Quote: "During the entire study, no significant adverse events were recorded." |
| 24 | Stur 1996 | Zinc | 4/56 in the zinc-treated group and 2/56 in the placebo group withdrew because of gastrointestinal symptoms. |
| 25 | 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. |
| 26 | Wang 2004 | Multivitamin and zinc | Did not report adverse effects. |


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AMD: age-related macular degeneration
AREDS: Age-Related Eye Disease Study
CNV: choroidal neovascularisation
HR: hazard ratio

## APPENDICES

### Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Degeneration
#2 MeSH descriptor Retinal Degeneration
#3 MeSH descriptor Retinal Neovascularization
#4 MeSH descriptor Choroidal Neovascularization
#5 MeSH descriptor Macula Lutea
#6 macula* near lutea*
#7 ((macul* OR retina* OR choroid*:TI) AND (degener* OR neovasc*:TI))
#8 ((macul* OR retina* OR choroid*:AB) AND (degener* OR neovasc*:AB))
#9 maculopath*
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Vitamins
#12 vitamin*
#13 MeSH descriptor Vitamin A
#14 retinol*
#15 MeSH descriptor beta Carotene
#16 caroten*
#17 MeSH descriptor Ascorbic Acid
#18 ascorbic next acid
#19 MeSH descriptor Vitamin E
#20 MeSH descriptor alpha-Tocopherol
#21 alpha tocopherol*
#22 MeSH descriptor Vitamin B 12
#23 cobalamin*
#24 MeSH descriptor Antioxidants
#25 antioxidant* or anti oxidant*
#26 MeSH descriptor Carotenoids
#27 carotenoid*
#28 MeSH descriptor Zinc
#29 zinc*
#30 MeSH descriptor Riboflavin
#31 riboflavin*
#32 MeSH descriptor Selenium
#33 selenium*
#34 MeSH descriptor Lutein
#35 lutein*
#36 MeSH descriptor Xanthophylls
#37 xanthophyll*
#38 zeaxanthin*
#39 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#40 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#41 (#39 OR #40)
#42 (#10 AND #41)

### Appendix 2. MEDLINE 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.


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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. retinal degeneration/
15. retinal neovascularization/
16. 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. beta carotene/
29. (caroten$ or betacaroten$).tw.
30. exp ascorbic acid/
31. ascorbic acid$.tw.
32. vitamin C.tw.
33. exp Vitamin E/
34. 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. selenium/
50. selenium$.tw.
51. lutein/
52. lutein$.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


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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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp macula degeneration/
34. retina degeneration/
35. retina neovascularization/
36. subretinal neovascularization/
37. (AMD or ARMD or CNV).tw.
38. ((macul$ 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. Retinol/
46. vitamin A.tw.
47. retinol$.tw.
48. beta carotene/
49. (caroten$ or betacaroten$).tw.
50. ascorbic acid/
51. ascorbic acid$.tw.
52. vitamin C.tw.
53. alpha tocopherol/
54. alpha?tocopherol$.tw.
55. alpha tocopherol$.tw.
56. vitamin E.tw.
57. vitamin B12.tw.
58. cyanocobalamin/
59. cobalamin$.tw.
60. antioxidant/
61. ((antioxidant$ or anti) adj1 oxidant$).tw.
62. carotenoid/
63. zinc/
64. zinc$.tw.
65. riboflavin/
66. riboflavin$.tw.
67. selenium/
68. selenium$.tw.


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69. 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

### Appendix 5. ISRCTN search strategy

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

### Appendix 6. ClinicalTrials.gov search strategy

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

### Appendix 7. ICTRP search strategy

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

### Appendix 8. 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.


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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 |
|---|---|---|
| 13 September 2023 | New citation required and conclusions have changed | Six new studies included in update; 1 previously excluded study reassessed and included in this update. 790 participants in these 7 studies. |
| 13 September 2023 | New search has been performed | Searches updated |

## HISTORY

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

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


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| Date | Event | Description |
|---|---|---|
| | | 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, 2017, and 2023 updates, both authors searched for new studies, conducted 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

JE and JGL: none known

## SOURCES OF SUPPORT

### Internal sources

- City University of London, UK

  John Lawrenson acknowledges the in-kind support of their institution for the undertaking of this review update.

### External sources

- Guide Dogs for the Blind Association, UK
- National Institute for Health Research (NIHR), UK

  Up to March 2021, this review update was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.
- Public Health Agency, UK

  As of April 2021, the completion of this review update was supported by the Health and Social Care (HSC) Research and Development (R&D) Division of the Public Health Agency which funds the Cochrane Eyes and Vision editorial base (including Jennifer Evans) at Queen's University Belfast, Northern Ireland.
- Queen's University Belfast, UK

  Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision's work is funded by the Centre for Public Health, Queen's University Belfast, Northern Ireland.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

Previous versions of this review have included the comparison: 'Any multivitamin or single component antioxidant supplement versus placebo'. We dropped this comparison from the current review because most 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 the National Institute for Health and Care Excellence (NICE 2018). We also applied the default minimum important difference interval for dichotomous outcomes of 0.8 to 1.25 for downgrading for imprecision.

The table below presents a comparison of outcome measures used in the 2017 and 2023 versions of the review with outcome measures in the 2012 version.


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| 2017 and 2023 review updates* | 2012 version of the review |
|---|---|
| Progression to late AMD (neovascular AMD, geographic atrophy, or both)<br>Progression to neovascular AMD<br>Progression to geographic atrophy | Progression of the disease (secondary)<br>• As defined by study investigators |
| Progression to visual loss<br>• Loss of 3 or more lines<br>• Continuous | Visual acuity (primary)<br>• Loss of 3 or more lines<br>• Continuous |
| Quality of life | Quality of life (secondary) |
| Resource use and costs | |
| Adverse effects | Adverse effects |

* In the current and 2017 versions of the 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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