E.2.2 Strategies to slow the progression of age-related macular degeneration (AMD)

RQ7: What is the effectiveness of strategies to reduce the risk of developing AMD in the unaffected eye or slow the progression of AMD?

The evidence tables in this section were produced by the Cochrane Eyes and Vision group, as part of a collaboration with the NICE Internal Clinical Guidelines Team.

Statin for age-related macular degeneration

Bibliographic reference	Guymer RH, Baird PN, Varsamidis M, Busija L, Dimitrov PN, Aung KZ, et al. Proof of concept, randomized, placebo-controlled study of the effect of simvastatin on the course of age-related macular degeneration. PloS One 2013;8 (12):e83759.
Methods	**Study design:** randomized controlled trial **Number randomized:** 114 total; 57 simvastatin; 57 placebo **Exclusions after randomization:** none **Number analysed: at 36 months:** 114 total; 57 simvastatin; 57 placebo **Unit of analysis:** individuals **Losses to follow up:** 34 participants total; 20 simvastatin; 14 placebo **How was missing data handled?:** last-observation-carried-forward method used for 34 participants; 11 participants with baseline data only and 23 participants who missed the 3-year follow-up visit **Power calculation:** 58 participants in each arm for power of 80% at alpha 0.05 to detect a 50% reduction in progression of disease
Participants	**Country:** Australia **Mean age:** 74.6 years overall; 74.8 years for simvastatin group; 74.4 years for placebo group

	Gender: 77/114 (68%) women 37/114 (32%) men total39/57 (68%) women 18/57 (32%) men in the simvastatin group 38/57 (67%) women 19/57 (33%) men in the placebo group **Inclusion criteria:** 1) males and females aged 50 years and older; 2) able to assess the macula in at least one eye; 3) visual acuity = 20/60 in study eye; 4) high risk drusen in both eyes: one or more large soft drusen, > 10 intermediate drusen, or late AMD in one eye and any drusen or pigment change in study eye; 5) normal cholesterol levels; and 6) not currently on cholesterol-lowering medications **Exclusion criteria:** 1) bilateral end-stage AMD; 2) medical or ophthalmic conditions which could potentially affect visual function, such as cataract, diabetes, glaucoma; 3) use of medications that may affect visual function, such as plaquenil, chloroquine, major tranquillizers; 4) currently on cholesterol-lowering medication; 5) use of statins is contraindicated; 6) alanine aminotransferase (ALT) two times the upper limit of normal; and 7) previous severe adverse or allergic reactions to statins **Equivalence of baseline characteristics:** no; more participants in simvastatin group had unilateral advanced AMD as compared with placebo; less smokers in placebo group than simvastatin group
Interventions	**Intervention 1:** two tablets of simvastatin (40 mg daily) for three years **Intervention 2:** placebo with an identical appearance for three years **Length of follow-up:** Planned: three years Actual: three years
Outcomes	**Primary outcome, as defined in study reports:** "Primary outcome was progression of non-advanced AMD to either advanced AMD or higher severity scores of non-advanced AMD", evaluated every 6 months. "Advanced AMD was defined as presence of either CNV or geographic atrophy (GA). CNV was confirmed on angiography and GA was defined as an area of hypopigmentation 175 mm with a choroidal vessel in its base on colour photography."

	Secondary outcomes, as defined in study reports: (1) change in visual function over time; (2) genotype as an effect modifier of the association between statins and progression of AMD **Adverse events reported**: yes **Intervals at which outcomes assessed:** 1, 6, 12, 18, 24, 30, and 36 months
Notes	**Funding sources**: Ian Potter Foundation, John Reid Charitable Trust and Royal Victorian Eye and Ear Hospital; National Health and Medical Research Council (NHMRC) supported the study through a Centre for Clinical Research Excellence award to CERA (#529923), a Practitioner Fellowship (#529905) and a Senior Research Fellowship (#1028444); Wagstaff Fellowship; Victorian Government **Disclosures of interest:** co-author Paul Baird is a PLOS ONE Editorial Board member **Study period:** 3 years; 2003 to 2006 **Reported subgroup analyses:** yes Trial investigators provided information on loss to follow-up by intervention at three-year follow-up (email communication) Trial reported at ARVO (abstract); trial registration number: ACTRN12605000320651 (registered at WHO International Clinical Trials Registry Platform)

Risk of bias	**Bias Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was performed by a biostatistician using permuted blocks of randomly varying size.
Allocation concealment (selection bias)	Low risk	The hospital pharmacist packed the medication into identical containers according to the randomization code. The sequentially numbered containers were allocated to the

		participants by the study coordinator in order of enrolment." "The allocation list was stored at a remote site."
Masking (performance bias and detection bias)	Low risk	"The study staff, the participants, and data analysts were masked to treatment allocation until the analysis was finalised."
Incomplete outcome data (attrition bias) All outcomes	High risk	Data missing for 34/114 (30%) participants at 3 years follow-up: 20/57 (35%) in the simvastatin group and 14/57 (25%) in the placebo group. Reasons for missing the 3-year visit were: personal, poor health, unable to contact, adverse reaction to study medication, reached late AMD, sick at 3-year follow-up, deceased, or developed macular hole. The study investigators imputed missing data using the last-observation-carried-forward method.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported in the 2013 results paper matched the protocol published in 2008.
Other bias	Unclear risk	"Analysis was done 'by person' and used the data from the eye showing greatest progression. If one eye of a person worsened and the other eye showed improvement, the person was classified as having progressed", but AMD progression by eye also was reported; at baseline, "the number of participants with unilateral advanced AMD was twice as large in the simvastatin group compared to the placebo group (x2 = 9.2, P = 0.002). Smoking also was less prevalent in the placebo group; the difference was marginally significant (x2 = 3.5, P = 0.06)."

Omega 3 fatty acids for preventing or slowing the progression of age-relate macular degeneration

Bibliographic reference	**Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)**
Study details	**Country/ies:** Switzerland

<table>
<tr><td>Bibliographic reference</td><td>Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)</td></tr>
<tr><td></td><td>Study type: open label RCT</td></tr>
<tr><td></td><td>Aim of the study: To investigate the effects of lutein/zeaxanthin supplementation as well as supplementation with lutein/zeaxanthin in a fixed combination with polyunsaturated fatty acid (PUFA).</td></tr>
<tr><td></td><td>Study dates: study recruitment between July 2007 and June2008</td></tr>
<tr><td></td><td>Sources of funding: supported by Novartis, the Swiss National Science Foundation and Velux Foundation Zurich</td></tr>
<tr><td>Participants</td><td>Sample size:

Lutein (n=40); Lutein +Omega (n=39)</td></tr>
<tr><td></td><td>Inclusion Criteria: people were age over 50 years with early or intermediate AMD. Only one eye of each patient was included in the study. If both eyes were eligible for the study, the eye with more advanced AMD changes was included.</td></tr>
<tr><td></td><td>Exclusion Criteria: People were with other eye disease in the study eye and opacities of optical media precluding fundus photography.</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><th></th><th>Lutein (n=40)</th><th>Lutein + Omega (n=39)</th><th>P values</th></tr>
<tr><td>Mean age, year (range)</td><td>75.2 (54, 88)</td><td>72.5 (54, 88)</td><td>>0.05</td></tr>
<tr><td>% of female (n)</td><td>55 (22)</td><td>61 (26)</td><td></td></tr>
<tr><td>Mean BM (range)</td><td>25 (16, 36)</td><td>25 (18,32)</td><td>>0.005</td></tr>
<tr><td>No. of early AMD</td><td>22</td><td>18</td><td></td></tr>
</table></td></tr>
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Bibliographic reference	**Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)**
	No. of intermediate AMD: 18 / 21 Mean visual acuity, ETDRs letter (SD): 79.7 (7.4) / 78.6 (10.5) / >0.05 Lutein serum, µg/ml (SD): 0.147 (0.076) / 0.163 (0.117) / >0.05 Zeaxanthin serum, µg/ml (SD): 0.025 (0.011) / 0.025 (0.012) / >0.05
Methods	**Study visits and procedures:** All patients received supplementation for a period of 6 months and were followed for a total of 12 months. Examinations were scheduled at baseline, month 1, and months 3,6,7,8,9, and 12. At each visit a comprehensive ocular examination with best-corrected visual acuity using ETDRs charts. At each visit the empty blisters from the study medication were collected and a pill count was performed to ensure compliance with the study medication.
	Intervention: Lutein and other vitamins (VitaluxPlus)
	Comparator: Lutein, omega-3, and other vitamins (VitaluxOmega)
	Outcomes: primary outcome: the effect of supplementation on contract sensitivity (CS) and macular pigment optical density (MPOD) after 6 months; secondary outcome: the change of CS, MPOD, BCVA and serum concentrations of lutein and zeaxanthin over the time period of 12 months.
	Analyses: Analysis of variance; paired t-test
	Length of follow up: 12 months

Bibliographic reference	Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)		
Results	**Lutein (n=40)**	**Lutein + Omega (n=39)**	**Effect (95%CI)**
	Macular pigment optical density		
	baseline (SD) 0.54 (0.19)	0.56 (0.21)	-0.02 (-0.11 to 0.07)
	6 months 0.66 (0.18)	0.60 (0.22)	0.06 (-0.03 to 0.15)
	Contrast sensitivity		
	baseline 1.29 (0.25)	1.23 (0.27)	0.06 (-0.05 to 0.17)
	6 months 1.69 (0.22)	1.30 (0.25)	0.39 (0.29 to 0.49)
	Best-corrected visual acuity		
	Baseline 80 (7)	79 (11)	1.00 (-3.08 to 5.08)
	6 months 79 (7)	80 (11)	-1.00

Bibliographic reference	**Ute E. K. WolfSchnurrbusch; Martin S. Zinkernagel; Marion R. Munk; Andreas Ebneter; Sebastian Wolf. Oral lutein supplementation enhances macular pigment density and contrast sensitivity but not in combination with polyunsaturated fatty acids. Investigative ophthalmology & visual science 2015; 56 (13)**
	12 months 81 (5) 80 (10) 1.00 (-5.08 to 3.08) (-2.50 to 4.50)
	Missing data handling/loss to follow up: none reported
Comments	**Was allocation adequately concealed?** Open label
	Was knowledge of the allocated intervention adequately prevented during the study? No description was found in the article
	Was the allocation sequence adequately generated? No description was found in the article
	Was the study apparently free of other problems that could put it at a high risk of bias? No
	Were incomplete outcome data adequately addressed? No description was found in the article
	Are reports of the study free of suggestion of selective outcome reporting? Primary and secondary outcomes reported

Bibliographic reference	**AREDS2** **Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309(19):2005-15.**
Methods	Parallel group RCT, 2 x 2 factorial design

	Both eyes included in the trial, both eyes received same treatment, adjustment made for within person correlation
Participants	**Country**: USA **Setting**: community **Number of participants**: 2080, 55% women **Average age**: 74 years **Age range**: 50 to 85 years **Inclusion criteria**: • bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye • consent to follow-up of at least 5 years • took at least 75% of the run-in supplements and agreed to stop the use of other supplements containing lutein, zeaxanthin, DHA, EPA, vitamin C, vitamin E, beta-carotene, zinc, or copper **Exclusion criteria**: • other ocular diseases such as high myopia, glaucoma, clinically significant diabetic retinopathy (10 or more microaneurysms or retinal haemorrhages), and other diseases that might confound the assessment of the ocular outcome measurements • eyes that had undergone intraocular (apart from cataract) surgeries • systemic diseases, including oxalate kidney stones, Wilson disease, haemochromatosis, lung cancer, or other diseases associated with poor 5-year survival Approximately 90% of participants were taking an additional multivitamin supplement
Interventions	• Omega 3 fatty acids (n = 1068 people, 1753 eyes) • Placebo (n = 1012 people, 1695 eyes) Omega 3 fatty acids were DHA (350 mg per day) and EPA (650 mg per day). Composition of placebo not specified

	All participants were asked to take the original AREDS formulation (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg, zinc oxide 80 mg, cupric oxide 2 mg). Those who agreed to take AREDS and consented to a second randomisation were assigned as follows • Original AREDS formula: omega 3 fatty acids group n = 147 (13.8%); placebo group n = 168 (16.6%) • No beta-carotene: omega 3 fatty acids group n = 231 (21.6%); placebo group n = 201 (19.9%) • Low-dose zinc (25 mg): omega 3 fatty acids group n = 179 (16.8%); placebo group n = 184 (18.2%) • No beta-carotene and low-dose zinc: omega 3 fatty acids group n = 201 (18.8%); placebo group n = 190 (18.8%) The participants who did not agree to a secondary randomisation largely took the AREDS formula: omega 3 fatty acids group n = 305 (28.6%); placebo group n = 265 (26.2%) Participants who were current smokers or former smokers who had stopped smoking within the year before enrolment were randomly assigned to 1 of the 2 arms without beta-carotene Duration: 5 years
Outcomes	**Primary outcome**: • Development of advanced AMD, defined as central geographic atrophy or retinal features of choroidal neovascularization detected on central grading of the stereoscopic fundus photographs or a history of treatment for advanced AMD after study enrolment **Secondary outcomes**: • Progression to moderate vision loss (3 lines) from baseline or treatment for choroidal neovascularisation • Serious adverse events • Mortality **Follow-up**: annually
Dates participants recruited	10/2006 to 09/2008
Declaration of interest	Yes - reported in paper. Including patent for AREDS formula

Sources of funding	This study was supported by the intramural program funds and contracts from the National Eye Institute (NEI), National Institutes of Health (NIH), Department of Health and Human Services, Bethesda, Maryland (contract HHS-N-260-2005-00007-C; ADB contract N01-EY-5-0007). Funds were contributed by the following NIH institutes: Office of Dietary Supplements; National Center for Complementary and Alternative Medicine; National Institute on Aging; National Heart, Lung, and Blood Institute; and National Institute of Neurological Disorders and Stroke. The study medications and raw materials were provided by Alcon, Bausch & Lomb, DSM, and Pfizer
Notes	In the primary randomisation 84% of participants took 75% of the study medications http://clinicaltrials.gov/show/NCT00345176

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A random block design was implemented using the AREDS2 Advantage Electronic Data Capture system by the AREDS2 Coordinating Centre (The EMMES Corporation, Rockville, MD) and stratified by clinical centre and AMD status (large drusen both eyes or large drusen in 1 eye and advanced AMD in the fellow eye) to ensure approximate balance across centres over time." Page 2285 of protocol paper
Allocation concealment (selection bias)	Low risk	Placebo-controlled study "Participants and study personnel were masked to treatment assignment in both randomizations. Page E2 of main study report
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Participants and study personnel were masked to treatment assignment in both randomizations. Page E2 of main study report

Blinding of participants and personnel (performance bias) Progression of AMD	Low risk	"Participants and study personnel were masked to treatment assignment in both randomizations." Page E2 of main study report
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Placebo-controlled study "Participants and study personnel were masked to treatment assignment in both randomizations." Page E2 of main study report
Blinding of outcome assessment (detection bias) Progression of AMD	Low risk	Placebo-controlled study "Participants and study personnel were masked to treatment assignment in both randomizations." Page E2 of main study report CNV was determined by masked readers from stereoscopic fundus photographs
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was high and balanced across groups DHA/EPA: 1062/1068 (99.4%) Placebo: 1007/1012 (99.5%)
Selective reporting (reporting bias)	Low risk	Not detected

Bibliographic reference	**NAT2**

	Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. Ophthalmology 2013;120(8):1619-31.
Methods	Parallel-group RCT One eye only included, study eye was selected on the basis of early AMD with neovascular AMD (CNV) in the fellow eye
Participants	**Country**: France **Setting**: community **Number of participants**: 300, 65% women **Average age**: 74 years **Age range**: 55 to 85 years **Inclusion criteria**: • bilateral large drusen or large drusen in 1 eye and CNV in the fellow eye (grading performed using a validated classification grid http://www.ncbi.nlm.nih.gov/pubmed/16988630) • visual acuity better than 0.4 logarithm of minimum angle of resolution units in the study eye • patients likely to attend follow-up visits during the study period and consent to follow-up of at least 5 years **Exclusion criteria**: • CNV in both eyes or no CNV in either eye • wide central subfoveal atrophy of the study eye • progressive ocular diseases (severe glaucoma or other severe retinopathy) • major corneal or lens opacities precluding retinal evaluation • serious systemic disease (cancer, stroke, etc.) preventing long-term participation • known allergy to the substances used in the study (fish oil, fluorescein, indocyanine green)

	• anticoagulant therapy (prohibited medication) or bleeding tendency • current or recent treatment (< 6 months) with nutritional supplements (oral supplement containing long-chain omega 3 fatty acids or alpha tocopherol acetate) • any concomitant nutritional supplement • participation in a clinical trial within the previous 30 days • history of drug use or excessive use of medication • patients likely to be lost to follow-up or unlikely to comply with the study protocol • monocular patients for reasons other than AMD • patients not covered by the French National Health system or wards of the court
Interventions	Omega 3 fatty acid (n = 150 people) Placebo (n = 150 people) Omega 3 fatty acids were 3 fish oil capsules, each capsule contained: DHA (280 mg), EPA (90 mg) and vitamin E (2 mg) (Reti-Nat, provided by Bausch & Lomb, Montpellier, France) Placebo contained 602 mg of olive oil Duration: 3 years
Outcomes	**Primary outcome**: • time to occurrence of CNV in the study eye **Secondary outcome**: • percentage of patients in whom CNV developed • changes in visual acuity from baseline (logMAR) • visual acuity decrease of 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart • drusen burden and progression, based on automatic detection of their number, size, and area on fundus photography • changes in red blood cell membrane (RBCM) EPA plus DHA levels • lens opacity • blood lipids including fasting plasma lipoprotein profile • signs of intolerance related to fish oil consumption

	• occurrence of systemic adverse events **Follow-up**: annually
Dates participants recruited	12/2003 to 10/2005
Declaration of interest	Eric H Souied: Consultant and lecturer—Laboratoire Bausch & Lomb Chauvin Pascale Benlian: Financial support and lecturer—Laboratoire Bausch & Lomb Chauvin Cécile Delcourt: Consultant and financial support—Laboratoire Bausch & Lomb Chauvin; Consultant and financial support—Laboratoires Théa; Consultant—Novartis
Sources of funding	Sponsored by Laboratoire Bausch & Lomb Chauvin, Montpellier
Notes	http://www.controlled-trials.com/ISRCTN98246501

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	QL-Ranclin software (Qualilab, Olivet, France) was used to generate the randomization list before enrolment. Souied et al 2013 p3
Allocation concealment (selection bias)	Low risk	The patients and the study personnel both were blinded to the treatment assignment. Souied et al 2013 p3
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personnel), however it is likely that they remained masked as to the allocation

Blinding of participants and personnel (performance bias) Progression of AMD	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personal), however it is likely that they remained masked as to the allocation
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personal), however it is likely that they remained masked as to the allocation
Blinding of outcome assessment (detection bias) Progression of AMD	Low risk	Not well reported. However, Qualilab provides an independent trial auditing service (not clear if this was the case here). No information provided regarding the outcome assessors (?study personal), however it is likely that they remained masked as to the allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used a per protocol analysis. Main reason for protocol deviation was premature withdrawal which occurred at a similar rate in DHA and placebo groups. Other protocol deviations included 'non-compliance with study medication or use of non-permitted medication'; 263 of the original 300 patients randomised were included in the analysis
Selective reporting (reporting bias)	Low risk	All pre-specified primary outcomes reported. All secondary outcomes (with the exception of mERG listed in trial protocol) were reported

Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Bibliographic reference	**CAPT (Complications of Age-Related Macular Degeneration)**

	Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: the complications of age-related macular degeneration prevention trial. Ophthalmology 2006;113(11):1974–86.
Methods	**Method of allocation**: treatment assignments were generated using a randomly permuted block method, stratified by clinical centre and using a randomly chosen block size. A member of the CAPT Co-ordinating Centre reviewed an eligibility checklist with the local ophthalmologist and clinic co-ordinator during a teleconference before disclosing which of the 2 eyes was assigned to laser treatment **Masking**: masked VA examiners. Unclear if participants and care providers were masked. Not reported if anatomic outcomes assessors were masked (i.e. Photograph Reading Centre), but masking was unlikely to be achieved since photocoagulation generates visible scars **Exclusions after randomisation**: none reported **Losses to follow-up**: during 5 years of follow-up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time **Unusual study design**: bilateral or paired study, i.e. 1 eye randomised to treatment or control and the fellow eye to the other study arm
Participants	**Country**: US **Number randomised**: 1052 participants **Enrolment period**: May 1999 to March 2001 **Age**: mean 71 years **Sex**: 637 women (60.6%) **Inclusion criteria**: at least 10 drusen of size = 125 µm within 3000 µm of FAZ centre; BCVA: 20/40 or more; aged = 50 years

	Exclusion criteria: CNV or serous retinal PED in either eyes; geographic atrophy within 500 µm of FAZ centre; any ocular disease that might affect VA
Interventions	**Treatment**: 60 burns in a grid pattern using a 100-µm spot size, 0.1-second duration and power to achieve a barely visible lesion. The burns were applied within an annulus between 1500 and 2500 µm from the FAZ centre **Control**: observation
Outcomes	Primary: loss of >= 15 letters Secondary: change in VA; change in contrast sensitivity; change in critical print size; incidence of late AMD (CNV, serous PED, geographic atrophy)
Notes	Since 2001, the participants were informed of the AREDS results and were left free to consume antioxidants Supported by the National Eye Institute, Bethesda, Maryland (grant no: EY012211, EY012261, EY012279) COI declaration: the Manuscript Writing Team had no COI with regard to the material presented in the article

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly permuted block method used, stratified by clinical centre and using a randomly chosen block size
Allocation concealment (selection bias)	Low risk	Eligibility assessed before randomisation and central allocation by telephone
Blinding (performance bias and detection bias)	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased

Development of CNV/geographic atrophy		
Blinding (performance bias and detection bias) Measurement of vision	Low risk	Masked VA examiners, unclear if care providers were masked. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Appendix 8. Throughout 5 years of follow-up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time. In the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

Bibliographic reference	**CNVPT** Choroidal neovascularization in the Choroidal Neovascularization Prevention Trial. The Choroidal Neovascularization Prevention Trial Research Group. Ophthalmology 1998;105(8):1364–72.
Methods	**BILATERAL**: method of allocation: right eye randomly assigned to either laser treatment or observation. Left eye assigned to alternate treatment **UNILATERAL**: random allocation to laser treatment or observation Stratified by clinical centre and study (bilateral/unilateral) and blocked using a randomly selected block size. Issued over telephone from central location **Masking**: participant: no; provider: unclear; outcome: no for fundus features; yes for VA

	Exclusions after randomisation: not reported **Losses to follow-up**: among participants alive at 12 months, 57/57 were examined in the laser group and 58/61 in the observation group. At 2 years, 46/57 (80.7%) treated eyes compared to 47/58 (81%) control eyes were still followed. However, causes of loss to follow-up other than death were not reported
Participants	**Country**: US in 15 clinical centres **Enrolment period**: October 1994 to December 1996 **BILATERAL**: number randomised: 156 participants (312 eyes). Age: mean 71 years. Sex: 61% women **UNILATERAL**: number randomised: 120 participants. Age: mean 73 years. Sex: 63% women in treatment group; 59% women in control group **Inclusion criteria**: aged = 50 years with colour stereo photographs and a fluorescein angiogram of both eyes taken within 14 days of enrolment, free of any condition that would preclude 2 years' follow-up. No exudative AMD. Study eye: > 10 large drusen (> 63 µm) within 3000 µm of the FAZ with VA of 20/40 or better and no evidence of current or past CNV **BILATERAL**: no exudative AMD in both eyes **UNILATERAL**: no evidence of current or past CNV. Exudative AM in fellow (non-study) eye **Exclusion criteria**: evidence of serous PED = 1 MPS disc area, geographic atrophy within 500 µm of the centre of the FAZ, myopia (= 8 dioptres spherical equivalent), previous laser treatment to the retina, severe non-proliferative or proliferative diabetic retinopathy or diabetic macular oedema, progressive ocular disease
Interventions	**Treatment**: low-intensity laser treatment. 3 different laser treatment protocols: 1. Laser 20: 20 laser burns, 100 µm in diameter, in a pattern of 3 rows placed between the 12 and 6 o'clock positions beyond the temporal perimeter of the FAZ. The desired intensity of the burns was a grey-white lesion. Direct application of laser burns to drusen to be avoided. Whenever the area of drusen had not been reduced by = 50% at 6 months of enrolment, a second treatment was applied nasal to the fovea in a mirror image of the first treatment. During the last 6 months of enrolment, a second laser treatment protocol was adopted that specified 24 laser burns, 100 µm in diameter in a circular pattern of 2 rows surrounding the macular drusen

	Control: observation of fellow eyes
Outcomes	VA (EDTRS); contrast threshold (Pelli Robson); reading ability (MN Read charts) Development of CNV, development of geographic atrophy, disappearance of drusen (stereoscopic colour photographs of the macular and disc of each eye and fluorescein angiogram)
Notes	Enrolment in these pilot studies was suspended after recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrolment in laser-treated eyes than in observed eyes, predominantly in the Fellow Eye Study Furthermore, data from the bilateral study arm were reported at 12 months but not thereafter Supported by an unrestricted gift from Research to Prevent Blindness, New York, NY, to the University of Pennsylvania; gifts to the Macular Degeneration Research Fund, Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA; grants from the Macula Foundation, New York, NY; Research Foundation of the University of Pennsylvania, Philadelphia, PA; and Mackall Trust, New York, NY; and grant R21 EY11275 from the National Eye Institute, National Institutes of Health, Bethesda, MD COI declaration: none of the authors have a proprietary interest in this study

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified by clinical centre and study (bilateral/unilateral) and blocked using a randomly selected block size

Allocation concealment (selection bias)	Low risk	Issued over the telephone from central location
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Participant and outcome assessors were not masked, unclear if care providers were masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8, Figure 3. UNILATERAL: 81% followed at 2 years in both study arms; loss to follow-up was balanced but causes of loss were not reported
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	High risk	Enrolment in these pilot studies was suspended under recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrolment in laser-treated eyes than in observed eyes, predominantly in the Fellow Eye Study

Bibliographic reference	**DLS** Owens SL, Bunce C, Brannon AJ, Wormald R, Bird AC, Drusen Laser Study Group. Prophylactic laser treatment appears to promote choroidal neovascularisation in high risk ARM: results of an interim analysis. Eye 2003;17(5): 623–7.

	Owens SL, Bunce C, Brannon AJ, Xing W, Chisholm IH, Gross M, et al. Prophylactic laser treatment hastens choroidal neovascularization in unilateral age-related maculopathy: final results of the drusen laser study. American Journal of Ophthalmology 2006;141(2):276–81.
Methods	**Method of allocation**: randomisation was conducted with a computerised weighted coin method in the Research and Development office. The randomisation assignment was provided by telephone, and the clinic co-ordinator printed the randomisation assignment on the participant's baseline form. The clinical investigator was then informed of the randomisation allocation. All study eyes of eligible participants in the UNILATERAL group were randomised. The study eye was randomised to laser treatment or no laser treatment. All right eyes of eligible participants in the BILATERAL group were randomised to laser treatment or no laser treatment; the fellow eye received the alternate treatment **Masking**: participant: unclear; provider: unclear; outcome assessor: masked VA examiner **Exclusions after randomisation**: none reported **Losses to follow-up**: UNILATERAL: at 3 years, VA was obtained in 73/92 (80.7%) laser-treated eyes vs. 66/85 (77.6%) control eyes. Development of CNV was recorded in 91/92 treated eyes and 85/85 control eyes. BILATERAL: VA obtained in 72/105 participants at 3 years, and CNV development assessed in 103/105 eyes at 3 years **Unusual study design**: some participants had both eyes randomised (BILATERAL group) and within-person correlation was taken into account
Participants	**Country**: UK **BILATERAL**: number randomised: 105 participants (210 eyes). Age: 70.1 years (range: 52 to 100). Sex: 31 men/74 women **UNILATERAL**: number randomised: 177 participants. Age: 72 years (range: 54 to 87). Sex: 80 men/97 women **Inclusion criteria**: drusen with/without focal RPE hyperpigmentation in the study eye and CNV in the fellow eye; BCVA at least 6/12 (20/40); aged at least 50 years

	Exclusion criteria: geographic atrophy in either eye; any other eye disease able to influence VA; allergy to fluorescein
Interventions	**Treatment**: argon green/yellow dye laser with 200-µm spot size, 0.2 second duration and the lowest energy to produce a very faint burn; overall 12 burns: 4 burns placed 750 µm from FAZ centre (12, 3, 6, 9 o'clock), and 8 burns 1500 µm from FAZ centre (12, 1.30, 3, 4.30, 6, 7.30, 9. 10.30, 12 o'clock); drusen treated directly if they were coincident with protocol treatment allocation **Control**: observation
Outcomes	Proportion of participants who developed CNV; VA
Notes	Protocol of treatment revised after 23 months: 12 burns (0.2 seconds to 200-µm spot size) placed in circular pattern at 1000 µm from FAZ centre Supported in part by Deutsche Forschungsgemeinschaft (DFG GR 1007/3-1 and Ho 1926/1-2) and the Deutsche Akademischer Austauschdienst ARC IX-95/32 (MG) COI declaration: not reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated method
Allocation concealment (selection bias)	Low risk	The clinical investigator was informed of the randomisation allocation by the co-ordinator by telephone after eligibility was assessed
Blinding (performance bias and detection bias)	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased

Development of CNV/geographic atrophy		
Blinding (performance bias and detection bias) Measurement of vision	Low risk	Masked VA examiners. Participants cannot be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8. Losses to follow-up were balanced but causes were not reported; no risk of bias given the paired study design for the BILATERAL study arm
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	High risk	The trial was stopped early after an interim analysis suggested that laser treatment induced CNV in treated eyes of participants in the unilateral group

Bibliographic reference	**Figueroa 1994** Figueroa MS, Regueras A, Bertrand J. Laser photocoagulation to treat macular soft drusen in age-related macular degeneration. Retina 1994;14(5):391-6.
Methods	**Method of allocation**: not reported. 1 eye of participants with bilateral drusen was assigned to treatment and the fellow eye to control **Masking**: not reported if participants and providers, but participants could not be masked since there was no sham procedure. VA examiners were masked **Exclusions after randomisation**: none reported

	Losses to follow-up: since they reported on results at last examination (mean follow-up 3 years), assessing the impact of loss to follow-up was difficult **Unusual study design**: paired or bilateral study; authors also reported on a parallel case series of people with CNV in 1 eye who were all treated in the fellow eye
Participants	**Country**: Spain **Number randomised**: 30 participants (60 eyes) **Age**: 69 years (range: 62 to 74) **Inclusion criteria**: AMD with large confluent soft drusen involving the fovea **Exclusion criteria**: not specified
Interventions	**Treatment**: green argon laser; 0.1 mW, 0.1 seconds, 100-µm spot; laser spot on drusen in the temporal fovea, or grid pattern if drusen > 300 µm **Control**: observation **Duration**: mean 3 years (range: 1.5 to 5)
Outcomes	Occurrence of CNV, reduction of drusen, VA
Notes	Drusen resolution possible also for drusen located far from the laser application Supported in part by National Institutes of Health grant NEI EY12769 and 5 P30 EY 01583, the Vivian Simkins Lasko Research Fund, the Nina C. Mackall Trust, and an unrestricted grant from Research to Prevent Blindness, New York, NY COI declaration: not reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Low risk	Masked visual examiner
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8 . Data at mean follow-up were reported. Since 12/30 participants were followed for < 3 years, it was difficult to assess the impact of this type of reporting. However, in the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Unclear risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

Bibliographic reference	**Frennesson 1995**

	Frennesson IC, Nilsson SE. Effects of argon (green) laser treatment of soft drusen in early age-related maculopathy: a 6 month prospective study. British Journal of Ophthalmology 1995;79(10):905-9.
Methods	**Method of allocation**: not reported; in 5 participants with both eyes eligible the eye with better VA was randomised **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: none reported **Losses to follow-up**: 2/19 participants in the treated group vs. 0/19 in the control group lost to follow-up at 3 years Unusual study design
Participants	**Country**: Sweden **Number randomised**: 38 participants **Age**: 71.6 years (SD 6.5) treated participants; 68.5 years (SD 6.2) control participants **Inclusion criteria**: soft drusen; VA at least 0.8 **Exclusion criteria**: CNV, PED, pigmentary clumping, macular atrophy, haemorrhage, any other eye disorder that could affect VA
Interventions	**Treatment**: argon green laser with 200-µm spot size, 0.05 seconds' duration, power to produce a barely visible lesion. Treatment with a temporal horse shoe-shaped area extending to the vascular arcades, with direct treatment of the drusen **Control**: observation **Duration**: 3-8 years
Outcomes	Anatomic: mean drusen area, development of CNV. Functional: Snellen VA; colour vision (Farnsworth panel D-15); central visual field (Humphrey 10-2)
Notes	The study was supported by grants from the Swedish Medical Research Council (Project No 12X-734), from the Research Committee of the County of Östergötland and from Synfrämjandet's Research Foundation COI declaration: not reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Unclear risk	Not reported. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8. 2/19 (11%) participants in the treated group vs. 0/19 in the control group lost to follow-up at 3 years; causes of loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

Bibliographic reference	**Frennesson 2009**

	Frennesson CI, Bek T, Jaakkola A, Nilsson SE. Prophylactic Laser Treatment Study Group. Prophylactic laser treatment of soft drusen maculopathy: a prospective, randomized Nordic study. Acta Ophthalmologica 2009;87(7):720-4.
Methods	**Method of allocation**: randomisation generated as a permuted block design; the randomisation was delivered from Linkoping University Hospital. Enrolling doctors were not masked to treatment allocation (personal communication) **Masking**: participant: yes; provider: no; outcome: no (personal communication) **Outcome**: incidence of CNV, VA **Follow up**: mean 3.7 years (range 1-7.5 years) **Exclusions after randomisation**: none reported **Losses to follow-up**: two-thirds of participants were followed up to 4 years, with losses balanced across groups **Unusual study design**: nothing reported
Participants	**Country**: Sweden, Denmark, Finland **Number randomised**: 135 participants **Age**: mean 70.4 years **Inclusion criteria**: people with soft drusen with or without mild pigmentary changes; VA = 0.8 (20/25) in the study eye, aged = 50 years **Exclusion criteria**: including pigmentary clumping, PED, CNV, haemorrhage or macular atrophy, and any other ophthalmological disease in the study eye that might possibly influence the outcome
Interventions	**Treatment**: laser treatment (subthreshold or barely visible laser spots). About 100 mild argon green laser spots with a size of 200 µm and a duration of 0.05 seconds **Unspecified control**, possibly observation only

Outcomes	VA, occurrence of CNV
Notes	The study was supported by grants from the Health Research Council in the South-East Region of Sweden, Crown Princess Margareta's Foundation for the Visually Handicapped and Synframjandet's Research Foundation COI information: not reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, permuted block design
Allocation concealment (selection bias)	High risk	Randomisation was delivered from Linkoping University Hospital. Enrolling doctors were not masked to treatment allocation
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Participants masked and doctors unmasked, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Care providers were unmasked. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Mean follow-up time was about 3.5 years and two-thirds of participants were followed up to 4 years, with losses balanced across groups. Study authors reported causes of missingness were death or illness in 5 of 6 cases at 2 years
Selective reporting (reporting bias)	Low risk	Main relevant outcome measure were reported

Other bias	Unclear risk	Unclear

Bibliographic reference	**Laser to Drusen Study 1995** Bressler SB, Vitale S, Hawkins BS, Alexander J, Orr PR, Schachat AP, et al. Laser to Drusen Trial: an assessment of short term safety within randomized, prospective, controlled clinical trial. Investigative Ophthalmology and Visual Science 1995;36:ARVO E-abstract 1028.
Methods	**Method of allocation**: computer-generated randomisation list with randomly selected block sizes. **Allocation groups**: observation vs. laser (1 : 1), laser further divided (1 : 1) in temporal vs. nasal and temporal treatment **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: none reported **Losses to follow-up**: 7/47 (15%) of treatment group and 10/52 (19%) of control group seen at 2 years
Participants	**Country**: US **Number randomised**: 99 participants **Age**: mean 74 years (SD 6.6), range 55 to 84 years **Sex**: 69.7% women **Inclusion criteria:** large drusen (> 63 µm in diameter) and focal hyperpigmentation, and no neovascular AMD in 1 eye only (study eye) evidence of neovascular AMD (CNV, disciform scar, laser scar for CNV) in 1 eye only (fellow eye) VA 20/40 or better in study eye (other information says 20/50 or better) no significant co-existing ocular disorder in study eye aged = 50 years

	Exclusion criteria: history of laser surgery or vitreous surgery in study eye low probability of completing 2-year follow-up schedule (poor health, live far from clinical centre, unwilling to return) geographic atrophy within 3000 µm of foveal centre other conditions associated with CNV, including pathological myopia (spherical equivalent exceeding -8.00 dioptres or clinical evidence of lacquer cracks), angioid streaks, histo spots, pattern dystrophies of RPE, etc. in study eye severe non-proliferative or worse diabetic retinopathy or diabetic macular oedema in study eye other progressive ocular disease that could impair VA such as glaucoma in the study eye lensectomy or intraocular lens implantation within 3 months
Interventions	Laser wavelength: dye yellow laser (577 nm) or infrared diode (very early - was discontinued). Number of burns: various, 2 scatter patterns described below; spot size: 50 µm; duration: 0.1 seconds; intensity: very light grey burn (just visible); no treatment within 500 µm of foveal centre and beyond 3000 µm from foveal centre; scatter burns approximately 2-3 burn widths apart, trying to avoid placing burns directly over focal clumps of hyperpigmentation. Do not have to place directly on drusen, but in placing scatter, small placement changes (< 50 µm) should be done to centre spot on drusen Pattern 1: (temporal = 180 degree) - not placed in nasal portion of macula (vertical line intersects foveal centre) Pattern 2: (temporal and nasal = 360 degree) - burns placed in scatter both nasal and temporal portion of macula (exclusive of central macula within 500 µm of foveal centre and not beyond 3000 µm of foveal centre)
Outcomes	Development of CNV; VA; information on other outcomes not available

Notes	Randomisation changed - originally 1 : 1 (laser vs. observation), then laser group randomised 1 : 1 (infrared diode vs. yellow dye) - each colour laser was randomised 1:1 (temporal vs. temporal and nasal) The red diode laser arm was stopped early (probably December 1995) Pilot study nature - so some clinical centres did not do all tests (reading, contrast) - not all clinical photographs graded Funding source unknown

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated. Randomly selected block size (Marta M Gilson, personal communication)
Allocation concealment (selection bias)	Low risk	Serially numbered sealed opaque envelopes. Co-ordinator had to fill out checklist - document eligibility - then open sequentially numbered envelope, record date opened, time opened, participant number, name code and sign the form (2 copies - keep 1, and fax other to co-ordinating centre within 24 hours of opening). Faxed forms were later mailed to co-ordinating centre (Marta M Gilson personal communication)
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Participants: unclear; care providers: ophthalmologists (applying laser) were not masked; care providers - co-ordinators: unclear; outcome assessors: Photograph Reading Centre graders were to be masked, but it was possible that some of the laser scars may have unmasked the graders (Marta M Gilson, personal communication)
Blinding (performance bias and detection bias) Measurement of vision	Unclear risk	VA examiners: unclear

Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Figure 3. 7/47 (15%) of treatment group and 10/52 (19%) of control group lost at 2 years. No information on reasons for loss to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes selected by review author
Other bias	Unclear risk	Unclear

Bibliographic reference	**Little 1995** Little HL, Showman J. A pilot randomized, controlled study on the effect of laser photocoagulation of confluent soft macular drusen. American Academy of Ophthalmology 1995:120.
Methods	**Method of allocation**: after participants eligibility was ascertained and participant consent was obtained, 1 eye was randomised to photocoagulation treatment; the right eye was assigned to treatment if participant's birth date was an odd month, the left if it was an even month **Masking**: participant: unclear; provider: unclear; outcome assessor: unclear **Exclusions after randomisation**: none reported **Losses to follow-up**: a minimum 1-year follow-up was obtained (mean 3.2 years) **Unusual study design**: paired study
Participants	**Country**: US **Number randomised**: 27 participants (54 eyes) **Age**: mean 69.7 years **Sex**: 9 men/18 women

	Inclusion criteria: symmetrical drusen; minimum drusen size 100 µm; at least 20 drusen or 10 drusen + 2 drusen at least 500 µm in diameter; drusen within 500 µm from foveola; VA at least 20/60 **Exclusion criteria**: PED; atrophy; subretinal fluid, haemorrhage, exudate; any other eye disorder which could affect VA
Interventions	**Treatment**: 577- to 620-nm wavelength laser with 100-200 µm spot size, 0.05-0.1 seconds' duration, 100-200 power. Direct treatment of the drusen **Control**: observation **Duration:** 1- to 6-year follow-up
Outcomes	Snellen VA; colour vision (Farnsworth panel D-15 colour-test); central visual field with Humphrey 10-2
Notes	No COI for any author

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	After participants eligibility was ascertained and participant consent was obtained, 1 eye was randomised to photocoagulation treatment; the right eye was assigned to treatment if person's birth date was an odd month, the left if it was an even month
Allocation concealment (selection bias)	High risk	See above, the enrolling researcher could have foreseen which eye would have been treated. Nonetheless, this can be irrelevant since both eyes of each participant were included, i.e. there was no risk of confounding
Blinding (performance bias and detection bias)	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased

Development of CNV/geographic atrophy		
Blinding (performance bias and detection bias) Measurement of vision	High risk	Not reported. Participants could not be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Unclear: only last visit data reported, thus being impossible to reconstruct the pattern of missing data; 4/27 participants were followed for = 1 year but < 2 years. However, in the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

Bibliographic reference	**Olk 1999** Olk RJ, Friberg TR, Stickney KL, Akduman L, Wong KL, Chen MC, et al. Therapeutic benefits of infrared (810-nm) diode laser macular grid photocoagulation in prophylactic treatment of nonexudative age-related macular degeneration: two-year results of a randomized pilot study. Ophthalmology 1999;106 (11):2082-90.
Methods	**Method of allocation**: not reported; BILATERAL: 1 eye was assigned to treatment and 1 eye to observation. UNILATERAL: 1 eye eligible that eye was assigned to either treatment or observation. BILATERAL/UNILATERAL: eyes assigned to treatment were further randomised to either 'visible' or 'subthreshold' treatment **Masking**: participant: unclear; provider: unclear; outcome: unclear

	Exclusions after randomisation: 25/152 participants (35 eyes) were enrolled initially in the pilot study but subsequently determined to be ineligible for various reasons, mainly violation of inclusion criteria **Losses to follow-up**: at 24 months, 33 eyes had missed visits: 9 eyes (4 observation, 2 visible, 3 subthreshold) were in deceased participants, 14 eyes were in the observation group, and 10 eyes were in the treatment group (5 eyes, visible; 5 eyes, subthreshold) **Unusual study design**: some eyes
Participants	**Country**: US **Number randomised**: BILATERAL: 77 participants (154 eyes) with both eyes eligible. UNILATERAL: 75 participants (75 eyes) with 1 eye eligible (unilateral study arm), that eye was assigned to either treatment or observation **Enrolment period**: July 1994 to June 1996 **Sex**: 152 participants enrolled; 57 men, 95 women **Age**: mean 74.5 years, range 54-88 years **Inclusion criteria**: aged > 50 years; diagnosis of AMD with = 5 large (= 63 µm), soft drusen within 2250 µm of the centre of the FAZ in both eyes (bilateral study arm) or in 1 eye (unilateral study arm) if the fellow eye had evidence of exudative AMD; and VA of = 20/63 on the ETDRS chart in all eligible eyes **Exclusion criteria**: exudative macular degeneration in either eye for bilateral participants and in both eyes for unilateral participants; other ocular diseases
Interventions	Eyes were treated with a slit-lamp integrated diode photocoagulator using 810-nm wavelength (IRIS Medical OcuLight SLx; IRIDEX Corp., Mt. View, CA). 48 diode laser lesions of 125 mm were applied in 4 concentric circles outside the FAZ in a scatter or grid pattern between 750 and 2250 mm from the centre of the fovea. Test spot laser lesions were applied to the retina nasal to the optic nerve using 200-millisecond duration, and the power was increased to produce a mild grey lesion (visible burn). For eyes assigned to visible treatment, this intensity was then applied in a grid pattern as described above. For eyes assigned to subthreshold treatment, the energy needed for the visible test burn was kept constant, but the duration was halved to 100 milliseconds and treatment then carried out. Only 1 laser treatment was applied to each eye throughout the duration of the study

Outcomes	Anatomic: reduction of drusen, development of CNV. Functional: VA
Notes	Within-person correlation of outcomes in the bilateral arm not analysed and reported Supported in part by grants from IRIS Medical, Mountain View, CA (producer of the laser used in the study), and The University of Pittsburgh Eye and Ear Foundation, Pittsburgh, PA COI declaration: not reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	High risk	Not reported. Participants could not be masked since no sham procedure was mentioned

Incomplete outcome data (attrition bias) All outcomes	Low risk	See Results, Appendix 8 and Figure 3. Losses to follow-up: at 24 months, 33 eyes had missed visits: 9 eyes (4 observation, 2 visible, 3 subthreshold) were in deceased participants, 14 eyes were in the observation group, and 10 eyes were in the treatment group (5 eyes, visible; 5 eyes, subthreshold). Causes of loss to follow-up other than death were not reported. In the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed. Thus, only losses in unilateral arm was considered
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

Bibliographic reference	**PTAMD bilateral 2009** Friberg TR, Brennen PM, Freeman WR, Musch DC, PTAMD Study Group. Prophylactic treatment of age-related macular degeneration report number 2: 810-nanometer laser to eyes with drusen: bilaterally eligible patients. Ophthalmic Surgery, Lasers and Imaging 2009;40 (6):530-8.
Methods	**Method of allocation**: study eyes were assigned randomly to either treatment or observation by a computer-generated, centre-specific, variable block size randomisation at a 1: 1 ratio. These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent **Masking**: participant: unclear; provider: unclear; outcome: unclear **Participant**: 1278 eyes of 639 participants **Outcome**: development of CNV and change in best-corrected VA **Exclusions after randomisation**: none reported **Losses to follow-up**: 374/639 (54.3%) participants followed to 2 years

	Unusual study design: paired study
Participants	**Country**: US **Number randomised**: 1278 eyes of 639 participants **Enrolment period**: April 1996 to March 2000 **Mean age**: 73.0 years (SD 2.5) **Inclusion criteria:** aged = 50 years. Eligible eye must have had BCVA of = 20/63 on the ETDRS chart in both eyes; AMD with = 5 drusen that were = 63 µm in diameter and were located within 2250 µm of the centre of the fovea; unilateral participants must have had 1 eye ineligible due to vision loss that was attributed to advanced AMD **Exclusion criteria**: other ocular disease causing visual loss
Interventions	Eyes randomised to treatment received a single-session treatment of a grid of 48 diode laser lesions of 125 µm in diameter. Laser treatment was applied in an annular grid that extended from 0.5 (750 µm) to 2.0 (3000 µm) disc diameters from the centre of the FAZ. A slit lamp-based diode laser photocoagulation system (IRIS Medical, Mountain View, CA) emitting energy at 810 nm was used to deliver the laser treatment. Laser lesions were placed in a subthreshold manner by first delivering test spot(s) of 200-millisecond duration placed outside of the macula at a low power (e.g. 200 mW) and then incrementally increasing the power in small (50 mW) increments until a faint grey (threshold) lesion could be detected visually through the treatment lens. While the power setting was left unchanged, the pulse duration was reduced to a 100-millisecond interval to achieve an invisible subthreshold lesion. Laser lesions were then scattered within the annular grid as defined above, beginning by placing 12 spots in a given quadrant and then proceeding to adjacent quadrants to complete the treatment pattern. The drusen were not targeted specifically or preferentially. If a visible lesion was produced while the annular grid treatment was performed, the power setting was reduced to achieve subthreshold lesions with the remainder
Outcomes	Anatomic: drusen reduction, development of CNV. Functional: VA

Notes	Supported by IRIDEX Corporation, Mountain View, CA (the producer of the laser used in the study); the Eye and Ear Foundation of Pittsburgh, Pittsburgh, PA; Research to Prevent Blindness, Inc., New York, NY and unrestricted funds from several participating centres COI declaration: the authors had no financial or proprietary interest in the materials presented

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, centre-specific, variable block size randomisation at a 1 : 1 ratio
Allocation concealment (selection bias)	Low risk	These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent
Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Unclear risk	Not reported, masking of care providers and photograph graders might be achieved since subthreshold photocoagulation should not generate visible scars. Participants cannot be masked since no sham procedure was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Large proportion of participants lost to follow-up, but this was unlikely to bias effect estimates since this was a paired study. In the updated version of this review, we considered missing data as no risk of bias in bilateral studies because a participant with paired treatment and control eyes is missed
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 lines of VA were well defined and relevant outcomes

Other bias	Unclear risk	Unclear

Bibliographic reference	PTAMD unilateral 2002 Friberg TR, Musch DC, Lim JI, Morse L, Freeman W, Sinclair S, et al. Prophylactic treatment of age-related macular degeneration. Report number 1: 810-nanometer laser to eyes with drusen. Unilaterally eligible patients. Ophthalmology 2006;113(4):612-22.
Methods	**Method of allocation**: study eyes were assigned randomly to either treatment or observation by a computer-generated, centre-specific, variable block size randomisation at a 1 : 1 ratio. These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent **Masking**: participant: unclear; provider: unclear; outcome: unclear **Exclusions after randomisation**: not reported **Losses to follow-up**: at 1 year, 184/244 (75%) participants followed (5 deaths), 92 treated eyes and 99 control eyes followed. At 3 years, 124/244 (51%) participants followed (20 deaths), 64 treated eyes and 55 control eyes followed **Unusual study design**: another arm of the study included participants with both eyes eligible, but this report deals with unilateral participants only
Participants	**Country:** US **Number randomised**: 244 participants **Age**: mean 75.4 years for treated participants, 75.1 years for observed participants **Gender** (% women): 59.3 treated participants, 61.5 observed participants **Inclusion criteria**: aged = 50 years. Eligible eye must have had BCVA of = 20/63 on the ETDRS chart; AMD with = 5 drusen that were 63 µm in diameter and were located within 2250 µm of the centre of the fovea; unilateral participants must have had 1 eye ineligible due to vision loss that was attributed to advanced AMD

	Exclusion criteria: other ocular disease causing visual loss
Interventions	Eyes randomised to treatment received a single-session treatment of a grid of 48 diode laser lesions of 125 µm in diameter. Laser treatment was applied in an annular grid that extended from 0.5 (750 µm) to 2.0 (3000 µm) disc diameters from the centre of the FAZ. A slit lamp-based diode laser photocoagulation system (IRIS Medical, Mountain View, CA) emitting energy at 810 nm was used to deliver the laser treatment. Laser lesions were placed in a subthreshold manner by first delivering test spot(s) of 200-millisecond duration placed outside of the macula at a low power (e.g. 200 mW) and then incrementally increasing the power in small (50 mW) increments until a faint grey (threshold) lesion could be detected visually through the treatment lens. While the power setting was left unchanged, the pulse duration was reduced to a 100-millisecond interval to achieve an invisible subthreshold lesion. Laser lesions were then scattered within the annular grid as defined above, beginning by placing 12 spots in a given quadrant and then proceeding to adjacent quadrants to complete the treatment pattern. The drusen were not targeted specifically or preferentially. If a visible lesion was produced while the annular grid treatment was performed, the power setting was reduced to achieve subthreshold lesions with the remainder
Outcomes	Anatomic: drusen reduction, development of CNV. Functional: VA
Notes	Supported by IRIDEX Corporation, Mountain View, CA (the producer of the laser used in the study); the Eye and Ear Foundation of Pittsburgh, Pittsburgh, PA; Research to Prevent Blindness, Inc., New York, NY and unrestricted funds from several participating centres COI declaration: the authors had no financial or proprietary interest in the materials presented

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, centre-specific, variable block size randomisation
Allocation concealment (selection bias)	Low risk	Random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible person who gave consent

Blinding (performance bias and detection bias) Development of CNV/geographic atrophy	Low risk	Unmasked study, but CNV occurrence was sufficiently objective as a diagnosis to be considered unbiased
Blinding (performance bias and detection bias) Measurement of vision	Unclear risk	Not reported, masking of care providers and photograph graders might be achieved since subthreshold photocoagulation should not generate visible scars. Participants could not be masked since no sham procedure was mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	See Results, Appendix 8, Figure 3. Survival analysis used. Losses to follow-up: at 1 year, 184/244 (75%) participants followed (5 deaths), 92 treated eyes and 99 control eyes followed. At 3 years, 124/244 (51%) participants followed (20 deaths), 64 treated eyes and 55 control eyes followed. Causes of loss other than death were not reported
Selective reporting (reporting bias)	Low risk	Development of CNV and atrophy, as well as loss of = 3 or more lines of VA were well defined and relevant outcomes
Other bias	Unclear risk	Unclear

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

Multivitamin supplements

Bibliographic reference	**AMDSG 1996** Richer S. Multicenter ophthalmic and nutritional age-related macular degeneration study-part 2: antioxidant intervention and conclusions. Journal of the American Optometry Association 1996;67(1):30-49.

Methods	Parallel group RCT **Method of allocation**: sponsor prepared coded tablets **Masking**: participant - not clear; provider - yes; outcome - yes **Losses to follow-up**: 4 died (2 treatment, 2 control); 1 adverse effect withdrawn (treatment); 7 lost to follow-up (1 treatment, 6 control)
Participants	**Country**: USA **Number of people randomised**: 71 (NR eyes) **Number (%) of people followed-up**: 59 (83%) (NR eyes) **Average age (range):** 72 years (NR) **Percentage women**: 7% **Ethnic group**: NR **Baseline visual acuity**: NR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria**: people with a monocular one line drop in Snellen visual acuity not attributable to cataract, amblyopia, systemic or ophthalmic disease AMD clinically observable drusen, RPE disruption and loss of macular reflex **Exclusion criteria:** greater than 1 year use of vitamin sex-prisoners of war chronic alcoholics with tobacco/nutritional amblyopia gastrointestinal absorption disorders
Interventions	**Intervention**: Ocuguard (Twin Lab Inc, Ronkonkoma, NY) broad-spectrum antioxidant: beta-carotene 20,000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercitin (bioflavonoid) 50 mg, bilberry extract (bioflavonoid) 5

	mg, rutin (bioflavonoid) 50 mg, zinc picolinate 12.5 mg, selenium 50 µg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 µg (daily)NR people randomised (NR eyes)39 (NR%) people followed-up (NR eyes) **Comparator**: placebo, starch NR people randomised (NR eyes)32 (NR%) people followed-up (NR eyes) Duration: 18 months
	Similarity between intervention and comparator: Treatment and placebo may not have been identical
Outcomes	**Primary:** not specified **Secondary**: not specified Outcomes reported in the paper: Snellen acuity with best refraction converted to logMAR units for analysisnear vision M units with dual sided Bailey-Lovie chart contrast sensitivity retinal grading score (adapted from Chesapeake Bay Study)subjective perception of vision; adverse gastrointestinal reactions **Follow-up:** **Eyes**: Reported right and left eyes separately
Notes	**Source of funding**: Twin Laboratories Inc, Ronkokoma NY; Stereo Optical Inc, Chicago, IL; Eye Communications Inc, Upland, CA; Illinois College of Optometry, Chicago, IL; Pacific University College of Optometry, Forest Grove, OR; Ezell Foundation, American Academy of Optometry, Rockville, MD Declaration of interest: NR Date study conducted: NR Trial registration number: NR

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

Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "Both the capsule for the placebo group (starch) and the capsule for the antioxidant group (Ocuguard) were formulated by Twin Laboratores Inc., Ronkonkoma, NY. An intermediary company, Eye Communications, Inc., Upland, CA. was responsible for assigning and maintaining the identity of codes, labeling and distribution of masked bottles of capsules to each DVA Medical Centre pharmacy service"Quote "Group one and group two patients were randomized between capsule number 1601 (starch placebo) and capsule number 1602 (Ocuguard) at each center by the optometrist co-investigator. Neither the optometrist nor the registered dietitian co-investigators nor the veteran subject knew the identify of the capsules."
Incomplete outcome data (attrition bias)	Unclear risk	17 patients withdrew from the study over 18 months. 4 patients died. 1 patient experienced an idiosyncratic reaction and was dropped. Attrition data were as follows: "71 patients at baseline, 67 patients at 6 m, 59 patients at 12 m, 59 patients at 18 m." Similar numbers of drop outs from groups 1 and 2 but the numbers were not clearly described.

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

Bibliographic reference	**AREDS 2001** Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report No. 8. Archives of Ophthalmology 2001;119(10):1417-36.
Methods	Parallel group RCT 2 x 2 factorial design. 67% participants took additional supplements to RDA levels (Centrum). In 1996 current smokers offered option of discontinuing supplementation; 2% of participants and 18% of smokers did so. A further 2.3% reassigned to no beta-carotene group. Intention-to-treat analysis maintained. **Method of allocation**: coded bottles **Masking**: participant - yes; provider - yes; outcome – yes **Losses to follow-up**: 2.4% balanced across study groups
Participants	**Country**: USA **Number of people randomised**: 3640 (NR eyes) **Number (%) of people followed-up**: 2.4% lost to follow up **Average age (range):** 69 years (55 to 80) **Percentage women**: 56% **Ethnic group**: 96% white **Baseline visual acuity**: NR

	Comorbidities affecting the eye: NR **Percentage current smokers**: 8% Inclusion criteria: • 20/32 or better in at least 1 eye • ocular media clear and therefore able to obtain adequate stereoscopic fundus photographs • at least 1 eye free from eye disease that could complicate assessment of AMD Exclusion criteria: • illness or disorders that would make long-term follow-up or compliance with study protocol unlikely or difficult
Interventions	**Intervention:** • antioxidants vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg (daily) • zinc 80mg as zinc oxide, copper 2mg as cupric oxide (daily) 2737 people randomised (NR eyes) (945 antioxidants only, 904 zinc only, 888 antioxidants plus zinc) 2.4% lost to follow-up but numbers by group not reported. Quote "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." **Comparator**: • placebo 903 people randomised (NR eyes) 2.4% lost to follow-up but numbers by group not reported. Quote "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." **Duration:** average follow-up 6.3 years **Similarity between intervention and comparator**: Quote "Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste.
Outcomes	**Primary:** • progression to advanced AMD (assessed using stereoscopic fundus colour photograph)

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

Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Simple randomization, stratified by clinical center and AMD category, was used to assign treatment. Participants in Categories 2, 3, and 4 were assigned with probability one quarter to each treatment group" Quote "Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant".

Allocation concealment (selection bias)	Low risk	Quote "Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant".
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "The 4 treatment interventions were double-masked..." Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code Quote "Four participants (0.1%) were reported to have been unmasked during the trial"
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "The 4 treatment interventions were double-masked..." Quote "Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code" Quote "Four participants (0.1%) were reported to have been unmasked during the trial"
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "Visual acuity was assessed by certified examiners using the ETDRS logMAR chart and a standardized refraction and visual acuity protocol (AREDS Manual of Operations; The EMMES Corporation, Rockville, Md)"
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "Stereoscopic fundus photographs of the macula were taken at baseline and annually beginning 2 years after randomization and graded centrally using standardized grading procedures."

Incomplete outcome data (attrition bias)	Low risk	Quote "Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups." Quote "Only 2.4% of AREDS participants were lost to follow-up (missed at least their last 2 consecutive visits). Losses to follow-up were balanced across treatment groups" Quote "Of almost 50000 possible follow-up visits, 10% were missed. The frequency of missed visits and mean follow-up time (6.3 years) did not differ by treatment group. Most participants (90%) had at least 5 years of follow-up."
Selective reporting (report 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."

Bibliographic reference	**Bartlett 2007** Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. European Journal of Clinical Nutrition 2007;61(9):1121-7
Methods	**Parallel group RCT** **Method of allocation**: sponsor prepared coded tablets **Masking**: participant - yes; provider - yes; outcome - yes **Losses to follow-up**: 5 (2 treatment, 3 control)
Participants	**Country**: UK **Number of people randomised**: 30 (30 eyes) **Number (%) of people followed-up**: 25 (83%) (25 eyes) **Average age (range):** 69 years (55 to 82)

	Percentage women: 53% **Ethnic group**: 100% white **Baseline visual acuity**: average visual acuity in intervention group was 0.20 logMAR and in control group as 0.08 logMAR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria**: • provide written informed consent • be available to attend one of the research centres • present with no ocular pathology in at least 1 eye, or no ocular pathology other than soft or hard drusen, and areas of increased or decreased pigment associated with drusen. Fundus examination was used to determine the presence of AMD. **Exclusion criteria:** • type I and II diabetes • prescribed antiplatelet or anticoagulant medication • concurrent use of nutritional supplements • advanced AMD in 1 or both eyes
Interventions	**Intervention:** • lutein esters 6 mg, retinol 750 mg, vitamin C 250 mg, vitamin E 34 mg, zinc 10 mg, copper 0.5 mg (daily) 17 people randomised (17 eyes) 15 (88%) people followed-up (15 eyes) **Comparator:** • placebo tablets containing cellulose (daily) 13 people randomised (13 eyes) 10 (77%) people followed-up (10 eyes)

	Duration: 9 months **Similarity between intervention and comparator**: Quote "The study formulation and placebo tablets were produced by Quest Vitamins Ltd, and were identical in external and internal appearance, and taste."
Outcomes	**Primary**: NR **Secondary**: NR Outcome measures specified on trial registration entry • Distance and near Visual Acuity (VA) measured using Bailey-Lovie logMAR charts • Contrast sensitivity (CS) measured using a Pelli-Robson chart • Colour vision measured using the PV-16 quantitative colour vision test • Macular Mapping (MM) test • Eger Macular Stressometer (EMS) used to assess glare recovery • Fundus photographs of the macular will be assessed using colour and edge analysis software Trial publication provided data on contrast sensitivity at 9 months follow-up. Protocol listed more outcomes (see below under selective reporting) and specified 9 and 18 months follow-up. Follow-up: 9 months (reported) and 18 months (not reported) Eyes: Trial eye selected (initial visit only). If both eyes were eligible for inclusion, the right eye was used
Notes	Sample size calculations reported in trial report: "A group size of nine was calculated to be sufficient to provide 80% power at the 5% significance level for CS based on an effect size of 0.3 log units, and mean and standard deviation (s.d.) values taken from a sample of 50 ARM and atrophic AMD patients of the University optometry clinic (1.3970.22 log CS)." Sample size calculations reported in protocol paper "From initial data collection we have calculated the treatment group sizes required in order to have 80% power at the 5% significance level for VA, CS, MM test, and the EMS. These values suggest that a total of 63 normal, and 96 age-related macular disease participants are required."

	Source of funding: Quote "The project was sponsored by the UK College of Optometrists. Intervention and placebo tablets were provided by Quest Vitamins Ltd UK." Declaration of interest: NR Date study conducted: March 2003 and December 2004 Trial registration number: ISRCTN78467674 (registered retrospectively)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random number generator function in Microsoft Excel is being used to allocate participants to μ and λ groups. Odd numbers allocate to the μ group Bartlett 2003 (protocol report) page 3 Only one investigator (HB) was involved in the randomization process, which employed the random number generator in Microsoft Excel for Windows XP. Odd and even numbers were used to identify group. Bartlett 2007, page 1122
Allocation concealment (selection bias)	Low risk	Enrolment was carried out by HB, who, along with FE, was masked to group assignment. Bartlett 2007, page 1121 Only one investigator (HB) was involved in the randomization process, which employed the random number generator in Microsoft Excel for Windows XP. Odd and even numbers were used to identify group. Bartlett 2007, page 1122 Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation. Bartlett 2003 (protocol report) page 3

Blinding of participants and personnel (performance bias) Visual acuity	Low risk	The study formulation and placebo tablets have been produced by Quest Vitamins Ltd, Aston Science Park, Birmingham, B7 4AP, and are identical in external and internal appearance, and taste. The manufacturer has allocated distinguishing symbols, μ and λ. The tablets are packaged in identical, sealed, white containers; the only difference being the symbol on the label. Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation. Bartlett 2003 (protocol report) page 3
Blinding of participants and personnel (performance bias) Progression AMD	Low risk	Not reported
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	The study formulation and placebo tablets have been produced by Quest Vitamins Ltd, Aston Science Park, Birmingham, B7 4AP, and are identical in external and internal appearance, and taste. The manufacturer has allocated distinguishing symbols, μ and λ. The tablets are packaged in identical, sealed, white containers; the only difference being the symbol on the label. Investigators and participants do not know which symbol represents the placebo tablets, and which represents the active formulation. Bartlett 2003 (protocol report) page 3 End of trial assessment using questionnaires indicated masking success. Out of those participants taking the placebo tablet, 10% correctly guessed which tablet they were taking, and 10% incorrectly guessed. Out of those taking nutritional supplement, 13% guessed correctly which tablet they were taking, and 7% incorrectly guessed. The remaining participants did not know which group they were randomized to.
Blinding of outcome assessment (detection bias) Progression AMD	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Statistical analysis was carried out on a per protocol basis.

Selective reporting (reporting bias)	High risk	Protocol report: following outcomes listed: visual acuity, contrast sensitivity, colour vision, macular mapping test, glare recovery, fundus photographs analysed by colour and edge analysis software. Trial report only contrast sensitivity (CS) reported: 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."

Bibliographic reference	**Berrow 2013** Berrow EJ, Bartlett HE, Eperjesi F, Gibson JM. The effects of a lutein-based supplement on objective and subjective measures of retinal and visual function in eyes with age-related maculopathy -- a randomised controlled trial. British Journal of Nutrition 2013;109(11):2008-14.
Methods	**Parallel group RCT** **Method of allocation**: unclear **Masking:** participant - no; provider - no; outcome - yes **Loss to follow-up**: unclear, either no loss to follow-up or 2/16 (12.5%) loss to follow-up
Participants	**Country**: UK **Number of people randomised**: 14 (14 eyes) **Number (%) of people followed-up**: 14 (100%) (14 eyes) **Average age (range):** 68 years (56 to 83) **Percentage women**: NR

	Ethnic group: Caucasian **Baseline visual acuity**: NR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR but average 7 pack-years in antioxidant group and 13.5 pack-years in the placebo group **Inclusion criteria:** • best-corrected distance VA of 0·2 LogMAR or better (for good mfERG central fixation) • clear optical media, as determined by a clear view of the fundus • no signs of other retinal or optic nerve disease other than ARM (as determined by fundal photography and questionnaire) in the study eye • good general health (as determined by health questionnaire) • no prescribed medication that could affect the retina (as determined by health questionnaire) **Exclusion criteria:** • moderate-to-dense lens opacities • intraocular lens • corneal opacities • glaucoma or ocular hypertension • previous history of intraocular inflammation • previous history of retinal detachment • retinal disease (other than ARM) • previous retinal laser • diabetes • systemic hypertension • history of ocular trauma • neurological disease • age-related macular degeneration (AMD) in the study eye • drugs causing retinal toxicity • previous ocular surgery • epilepsy

Interventions	**Intervention:** • Ocuvite Duo (Bausch and Lomb) vitamin C 150mg, cupric oxide 400µg, vitamin E 15mg, zinc oxide 20mg, lutein 12mg, zeaxanthin 0.6mg, EPA 240mg, DHA 840mg 8 people randomised (8 eyes) 8 (100%) people followed-up (8 eyes) **Comparator:** • no treatment 6 people randomised (6 eyes) 6 (100%) people followed-up (6 eyes) **Duration**: 40 weeks **Similarity between intervention and comparator**: different because no placebo group
Outcomes	from clinical trial registry entry Primary: • multifocal electroretinogram amplitudes and latencies, assessed every 20 weeks for a period of 80 weeks Secondary: • macular pigment optical density, assessed every 20 weeks for a period of 80 weeks No numeric data on outcomes reported. Quote "All participants undertook VA and CS assessment at all three visits. There were no significant changes between the treated and non-treated groups over 40 weeks for these measures." Follow-up: 40 weeks and 60 weeks Eyes: Quote "Only one eye from each participant was studied.[...] The eye with the best-corrected distance VA was determined at the participant's first visit and this eye was assessed for subsequent visits. If one eye had ARM, this eye was used. If both eyes had ARM, the eye with the best-corrected distance VA was used to ensure good mfERG fixation."

Notes	**Source of funding**: Quote "The authors would like to thank Bausch and Lomb, Kingston-Upon-Thames, Surrey, UK for funding the research position and supplying the Ocuvite Duo nutritional supplement." Declaration of interest: Quote "The authors declare no competing financial interests" Date study conducted: January 2009 to December 2011 Trial registration number: ISRCTN17842302 (retrospectively registered)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A total of fourteen participants with ARM were randomly allocated, using Microsoft Excel random number generator, to either receive a lutein-based oral supplement (treated group) or no supplement (non-treated group) at visit one."
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Not clearly reported.
Blinding of participants and personnel (performance bias)Visual acuity	High risk	Judgement Comment: No placebo - control group did not receive any intervention.
Blinding of participants and personnel (performance bias)Progression AMD	High risk	Judgement Comment: No placebo - control group did not receive any intervention.
Blinding of outcome assessment (detection bias)Visual acuity	Unclear risk	Judgement Comment: No placebo - control group did not receive any intervention but study was described as "single masked" so outcome assessors were not aware of group assignment up to 40 weeks when unmasking occurred. However, measurement of visual acuity may be influenced by participants knowledge of intervention.

Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Judgement Comment: No placebo - control group did not receive any intervention but study was described as "single masked" so outcome assessors were not aware of group assignment up to 40 weeks when unmasking occurred.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "A total of fourteen participants with ARM were randomly allocated, using Microsoft Excel random number generator, to either receive a lutein-based oral supplement (treated group) or no supplement (non-treated group) at visit one. These were from an original cohort of sixteen participants, two of which withdrew without giving reason. Only one eye from each" Judgement Comment: Unclear to which group the 2 participants who withdrew had been randomly allocated.
Selective reporting (reporting bias)	High risk	Judgement Comment: Trial was registered retrospectively so not possible to check this. Follow-up at 80 weeks was not reported.

Bibliographic reference	**CARMA 2013** Beatty S, Chakravarthy U, Nolan JM, Muldrew KA, Woodside JV , Denny F, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. Ophthalmology 2013;120(3):600-6.
Methods	**Parallel group RCT** **Method of allocation**: labelled containers **Masking**: participant - yes; provider - yes; outcome - yes **Loss to follow-up**: high attrition after 12 months - 9% follow-up at 3 years
Participants	**Country**: Ireland

	Number of people randomised: 433 (614 eyes) **Number (%) of people followed-up**: at 12 months 493 eyes (80%) ; at 24 months 260 eyes (42%) and at 36 months 58 eyes (9%) **Average age (range):** 74 years (NR) **Percentage women**: 57% **Ethnic group**: NR **Baseline visual acuity**: average 80 letters on logMAR chart **Comorbidities affecting the eye**: NR **Percentage current smokers**: 14% **Inclusion criteria:** • 50 years and older • any severity of early AMD in one eye and late AMD (neovascular AMD or central GA) in the fellow eye. The study eye was the eye free of late-stage AMD. • features of early AMD in at least 1 eye when both eyes were free of late-stage AMD. The minimum severity level was 20 soft distinct or indistinct drusen in the central macular field; if there were fewer than 20 drusen, focal hyperpigmentation was required to be present. Both eyes could be study eyes. • visual acuity of 0.3 logMAR units or better (70 letters or better on the ETDRS chart equivalent to Snellen 20/40) in the eye selected to be study eye **Exclusion criteria:** not explicitly stated
Interventions	**Intervention:** • Ocuvite (Bausch and Lomb, Berlin, Germany) lutein 12mg, zeaxanthin 0.6mg, vitamin E 15mg, vitamin C 150mg, zinc oxide 20 mg, copper 0.4mg (daily dose) one tablet twice daily 216 people randomised (304 eyes) NR (NR%) people followed-up (243 eyes) at 12 months

	Comparator: • Placebo (cellulose microcrystalline, lactose and magnesium stearate) (twice daily) 217 people randomised (310 eyes) NR (NR%) people followed-up (250 eyes) at 12 months **Duration**: Total study duration 3 years but high attrition after 12 months **Similarity between intervention and comparator:** Quote "The placebo consisted of cellulose, lactose, and magnesium stearate and was manufactured to be indistinguishable from the active preparation in size, colour, smell, and taste."
Outcomes	**Primary:** • distance visual acuity Secondary: • retinal visual acuity • morphological progression of AMD (grading of stereoscopic colour fundus photographs) • macular pigment levels and serum levels of antioxidants Follow-up: every 6 months for 3 years but high attrition after 12 months Eyes: mixture of one or two eyes per person (see above for details). Analysed by eye but eyes were not considered independent.
Notes	Source of funding: Quote "Supported by a grant from Bausch and Lomb, Dr. Mann Pharma, Berlin, Germany. The data set was managed and analysed by the independent statistician (MRS) and his team. The senior corresponding author (UC) had full access to the data outputs. The funders had no access to the data, were not involved in the data analysis, and had no role in the construction of the manuscript, except in the approval of the final draft." Declaration of interest: Quote "The author(s) have no proprietary or commercial interest in any materials discussed in this article." Date study conducted: June 2004 to April 2008

	Trial registration number: ISRCTN94557601 (retrospectively registered)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Each participant enrolled in the CARMA Study is allocated a unique number, which determines treatment allocation according to the computerized randomization database." " Quote "A block randomization design was used with stratification by center and by group status, and separate block randomized 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." 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 labeled with pre-assigned numbers at the site of manufacturing, and then shipped to both clinical centers for distribution. A single pharmacist involved with manufacturing of the study preparation holds the key to randomization of the CARMA supplements."
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote "The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other." and "Participants and study staff were masked to treatment assignments"
Blinding of participants and personnel (performance bias)	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

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

Bibliographic reference	**CARMIS 2011** Piermarocchi S, Saviano S, Parisi V, Tedeschi M, Panozzo G, Scarpa G, et al. Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. European Journal of Ophthalmology 2011;22(2):216-25.
Methods	**Parallel group RCT** **Method of allocation**: random list, unclear how delivered **Masking**: participant - no; provider - no; outcome – unclear **Losses to follow-up**: 18% in supplement group, 38% in no supplement group

Participants	**Country**: Italy **Number of people randomised**: 145 (145 eyes) **Number (%) of people followed-up**: 84 (58%) (84 eyes) **Average age (range)**: 73 years (NR) **Percentage women**: 59% **Ethnic group**: NR **Baseline visual acuity**: average 82 letters (ETDRS chart) **Comorbidities affecting the eye**: 30% of intervention group had had cataract surgery but none of the control group **Percentage current smokers**: 17% **Inclusion criteria:** • age 55 to 80 • diagnosis of nonexudative (dry) age-related macular degeneration (AMD) in at least one eye having extensive (as measured by drusen area) intermediate (>= 63 mm, <125 mm) drusen; and at least one large (>=125 mm) drusen or geographic atrophy not involving the center of the macula • best-corrected visual acuity in the trial eye >=20/32 (0.2 logarithm of the minimum angle of resolution [logMAR]), 74 letters of Early Treatment Diabetic Retinopathy Study [ETDRS] chart) • able to understand and comply with the requirements of the trial • no condition limiting view of the fundus (e.g., vitreous hemorrhage, cataracts, epiretinal membrane) • available for a minimum trial duration of approximately 6 months • agree to take only the nutritional supplement that is provided during this study Exclusion criteria: • ocular disease that causes irreversible reduction of visual acuity (amblyopia, uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant macular edema) • lens opacity and score 4+ (Lens Opacity Classification System II) • insufficient pupil dilation

	• previous laser treatment of the posterior pole for any other reason • macular changes not attributable to AMD • carotenoids intolerance • major chronic disease • life expectation lower than 6 months • withdrawal of informed consent • enrolment in another clinical study with experimental product within the last 4 weeks or during the current study
Interventions	**Intervention:** • vitamin C 180 mg, vitamin E 30 mg, zinc 22.5 mg, copper 1 mg, lutein 10 mg, zeaxanthin 1 mg and astaxanthin 4 mg (AZYR SIFI, Catania, Italy) (daily) 103 people randomised (103 eyes) 84 (82%) people followed-up (84 eyes) **Comparator:** • no dietary supplementation 42 people randomised (42 eyes) 26 (62%) people followed-up (26 eyes) Duration: 24 months Similarity between intervention and comparator: different, no placebo group
Outcomes	reported in methods section of paper Primary: • change in BCVA (the number of letters read on the logMAR chart) Secondary: • changes in macular function by CS using a Pelli-Robson chart (Clement Clarke International, Harlow Essex, UK) scored per lines • changes in visual function via the Italian-validated version of the 25-item NEI VFQ-25

	reported in results section • multi-focal electroretinograms (ERG) at 6 and 12 months Follow-up: 6, 12 and 24 months Eyes: One eye per person. Quote "When patients fulfilled the inclusion criteria (Tab. I), the eye with the best VA was selected. When both eyes had the same VA, the right eye was chosen for final analysis."
Notes	Source of funding: NR Declaration of interest: Quote "The authors report no proprietary interest or financial support". Date study conducted: December 2003 to September 2006 Trial registration number: NR

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 randomized study... " Quote "The study coordinator allocated study numbers sequentially, as participants were enrolled. Participants were then randomly allocated to the treatment or no treatment group. A permuted blocks allocation scheme was used to perform this random allocation. The allocation list was stored at a remote site." Quote "Study drug was administered by an unmasked physician who had no other role in the study." No mention was made of allocation ratios but 103 people recruited to treatment group and 42 to no treatment group

Blinding of participants and personnel (performance bias)Visual acuity	High risk	Quote "A 24-month prospective open-label randomized study... "
Blinding of participants and personnel (performance bias)Progression AMD	High risk	Quote "A 24-month prospective open-label randomized study... "
Blinding of outcome assessment (detection bias)Visual acuity	High risk	Quote "A 24-month prospective open-label randomized study... " Quote "In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator." However, as patients were not masked this could have affected the measurement of visual acuity
Blinding of outcome assessment (detection bias)Progression AMD	Unclear risk	Quote "A 24-month prospective open-label randomized study... " Quote "In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator."
Incomplete outcome data (attrition bias)	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 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.

Lutein

Bibliographic reference	**AREDS2 2013**

	Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL 3rd, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA Ophthalmology 2014;132(2):142-9.
Methods	**Parallel group RCT** **Method of allocation**: coded tablets **Masking**: participant - yes; provider - yes; outcome - yes Loss to follow-up: Quote "Of the 4203 randomized 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.
Participants	**Country**: USA **Number of people randomised**: 4203 (6916 eyes) **Number (%) of people followed-up**: 4176 (99%) using LOCF (6891 eyes) **Average age (range)**: 74 years (68 to 79) **Percentage women**: 56% **Ethnic group**: 97% white **Baseline visual acuity**: average 78 letters on EDTRS chart **Comorbidities affecting the eye**: 25% bilateral pseudophakic, 13% with diabetes **Percentage current smokers**: 7% **Inclusion criteria**:

	• high risk of progression to advanced AMD with either bilateral large drusen or non-foveal geographic atrophy (no advanced AMD) or large drusen or non-foveal geographic atrophy in one eye and advanced AMD in the fellow eye (AREDS Simple Scale Score of 2, 3 or 4) • age 50 to 85 years • took at least 75% of study medication during the run-in phase • able and willing to consent to both the qualification and the randomisation/follow-up phases of the study • likely, willing and able to undergo yearly examinations for at least five years • agreed to stop current use of supplements containing lutein, zeaxanthin, omega-3 LCPUFAs (specifically DHA+EPA), vitamin C, vitamin E, beta-carotene, zinc or copper, other than those supplied by AREDS2 • fundus photographs of adequate quality as assessed with a standardized protocol by the Reading Center (University of Wisconsin Fundus Photograph Reading Center) • randomized 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 2mg or more of lutein and/or 500 mg or more of omega-3 LCPUFAs for a period of 1 year or more prior to the date of randomization (A participant was eligible for the study if he/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 • hemochromatosis • Wilson's disease • recent diagnosis of oxalate kidney stones • any condition that would make adherence or follow-up difficult or unlikely • current participation in other studies that might affect adherence to the AREDS2 follow-up schedule

	• use of systemic anti-angiogenic therapy for treatment of choroidal neovascularization or cancer
Interventions	**Intervention**: • lutein 10mg and zeaxanthin 2mg (1 tablet/day) 2123 people randomised (3468 eyes) 2107 (99%) people followed-up (3451 eyes) **Comparator**: • placebo (1 tablet/day) 2080 people randomised (3448 eyes) 2069 (99%) people followed-up (3440 eyes) Almost all participants in both intervention and comparator groups took AREDS supplement and multivitamin with the study medication. **Duration**: 5 years (median) **Similarity between intervention and comparator**: The placebo was composed from free flowing corn starch-coated matrix of bead lets formed into a tablet of identical shape, size, and coating/internal colour (using the same quantity of colouring agents) as that containing lutein+zeaxanthin. **Other study arm**: There was another study arm looking at docosahexaenoic acid (DHA) 350mg and eicosapentaenoic acid (EPA) 650mg (2 soft-gel capsules/day) not included in this review
Outcomes	**Primary**: • progression to advanced AMD in people at moderate to high risk for progression **Secondary**: • progression to moderate vision loss • adverse events • progression of lens opacity or incidence of cataract surgery

	• effect of study supplements on cognitive function • effect of DHA/EPA on cardiovascular morbidity and mortality **Follow-up**: annual follow-up for 5 years **Eyes**: Quote "The unit of analysis for ophthalmic outcomes was by eye. The primary efficacy outcome, time to progression to advanced AMD, was assessed using a Cox proportional hazards model incorporating the method of Wei et al for obtaining robust variance estimates that allows for dependence among multiple event times (1 or 2 study eyes)."
Notes	Source of funding: Quote "This study is supported by the intramural program funds and contracts from the National Eye Institute/National Institutes of Health (NEI/NIH), Department of Health and Human Services, Bethesda, MD. Contract No. HHS-N-260-2005-00007-C. ADB Contract No. N01-EY-5-0007. Funds were generously contributed to these contracts by the following NIH institutes: Office of Dietary Supplements (ODS), National Center for Complementary and Alternative Medicine (NCCAM), National Institute on Aging (NIA), National Heart, Lung and Blood Institute (NHLBI), and National Institute of Neurological Disorders and Stroke (NINDS)" Declaration of interest: Quote "A complete list of all AREDS2 investigator financial disclosures, which were collected for regulatory purposes, pursuant to US FDA regulations in 21 CFR Part 54, can be found at www.areds2.org. The member(s) of the writing committee have made the following disclosure(s): Frederick L. Ferris III; Bausch & Lomb (P) and the remainder had no conflicts of interest." Date study conducted: September 2006 to October 2012 (from clinical trials.gov entry) Trial registration number: NCT00345176

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 (Advantage EDC SM) by the AREDS2 Coordinating Centre (The EMMES Corporation, Rockville, Maryland) and stratified by clinical centre 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 centres over time."
Allocation concealment (selection bias)	Low risk	Judgement Comment: Central co-ordinating centre organised the random allocation and placebo controlled study
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Judgement Comment: Placebo controlled trial. Personnel measuring visual acuity unaware of allocation. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Judgement Comment: Placebo controlled trial. Fundus images graded by masked graders. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Judgement Comment: Placebo controlled trial. Personnel measuring visual acuity unaware of allocation. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Judgement Comment: Placebo controlled trial. Fundus images graded by masked graders. Quote "All 4 formulations are balanced on excipients and packaged in capsules of identical size, shape and colour."

Incomplete outcome data (attrition bias)	Low risk	Quote "Of the 4203 randomized 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 on clinical trials registry and in published protocol paper were reported

Bibliographic reference	**CLEAR 2013** Murray IJ, Makridaki M, van der Veen RL, Carden D, Parry NR, Berendschot TT. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. Investigative Ophthalmology and Visual Science 2013;54(3):1781-8.
Methods	**Parallel group RCT** **Method of allocation**: coded tablets prepared by manufacturer **Masking**: participant - yes; provider - yes; outcome - yes **Loss to follow-up**: 13%
Participants	**Country**: The Netherlands and the UK **Number of people randomised**: 84 (84 eyes) **Number (%) of people followed-up**: 73 (87%) (73 eyes) **Average age (range)**: 71 years (NR) **Percentage women**: 61% (56% in intervention group 67% in control group) **Ethnic group**: NR **Baseline visual acuity**: average 0.1 logMAR intervention group and 0.05 logMAR in control group respectively

	Comorbidities affecting the eye: NR **Percentage current smokers**: NR **Inclusion criteria:** • 50 to 80 years • AMD grade 0 to 4 in one eye (Rotterdam grading) • best corrected visual acuity (BCVA) of LogMAR 0.5 or better • minimal cataract. **Exclusion criteria:** • any ophthalmic disorder, such as diabetic retinopathy; optic atrophy; pigmentary abnormalities considered by the investigating ophthalmologist to be less typical of AMD than of some other condition (e.g., myopia); • history of glaucoma • any dietary supplements containing lutein, zeaxanthin or meso-zeaxanthin within 3 months of the start of the study. • unable to understand the study procedures or unable to give informed consent
Interventions	**Intervention:** • lutein 10mg (daily) 42 people randomised (42 eyes) 36 (86%) people followed-up (36 eyes) **Comparator:** • placebo soya bean oil (daily) 42 people randomised (42 eyes) 37 (88%) people followed-up (37 eyes) **Duration**: 12 months **Similarity between intervention and comparator**: Quote "The [..] capsules and their packaging were completely indistinguishable"
Outcomes	**Primary:**

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

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

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

Bibliographic reference	**Huang 2015** Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lu XR, et al. Changes following supplementation with lutein and zeaxanthin in retinal function in eyes with early age-related macular degeneration: a randomised, double-blind, placebo-controlled trial. British Journal of Ophthalmology 2015;99(3):371-5.
Methods	**Parallel group RCT** **Method of allocation**: unclear **Masking**: participant - yes; provider - yes; outcome - yes **Loss to follow-up**: unclearly reported
Participants	**Country**: China **Number of people randomised**: 112 (NR eyes) **Number (%) of people followed-up**: 108 (96%) (NR eyes) **Average age (range):** 69 years (NR) **Percentage women**: 57% **Ethnic group**: NR **Baseline visual acuity**: average 0.32 logMAR **Comorbidities affecting the eye**: 23% had early cataract **Percentage current smokers:** 7% **Inclusion criteria:** • clinical diagnosis of early AMD (defined as the presence of soft drusen, presence of retinal pigmentary abnormalities with no signs of late AMD, or both) according to the Age-Related Eye Disease Study System • clear ocular media

	• agreement to adhere to the study regimen
	Exclusion criteria: • ocular disorders • unstable systemic or chronic illness • consumed dietary supplements containing antioxidants or carotenoids within the previous 6 months
Interventions	**Intervention:** • lutein 10mg or lutein 20mg or lutein 10mg and zeaxanthin 10mg (3 groups) (daily) NR people randomised (NR eyes) 80 (%) people followed-up (NR eyes) **Comparator:** NR people randomised (NR eyes)28 (%) people followed-up (NR eyes) **Duration**: 24 months **Similarity between intervention and comparator**: Quote "All the supplements were packaged identically with the same labels." But unclear how the placebo was made
Outcomes	**Primary:** • VFQ (Chinese version) **Secondary:** • not specifically reported but reported contrast sensitivity, visual acuity, MPOD, **Follow-up:** 24 weeks, 48 weeks and 24 months **Eyes**: unclear
Notes	**Source of funding**: Quote "The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Grant no. 81273063)." Declaration of interest: NR

	Date study conducted: : NR Trial registration number: NCT10528605 (registered retrospectively)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "for randomization, the sequence was computer generated in a 1: 1: 1: 1 ratio within permuted blocks of size 8."
Allocation concealment (selection bias)	Low risk	Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote: "All the supplements were packaged identically with the same labels." Quote: "All subjects, examiners, and study staff were masked to treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 112 patients randomised. 4 excluded due to DNA. Remainder analysed
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No access to trial protocol and trial was registered retrospectively.

Bibliographic reference	**Veterans LAST study 2004** Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry 2004;75(4):216-30.
Methods	**Parallel group RCT** **Method of allocation**: coded bottles **Masking**: participant - yes; provider - yes; outcome – yes **Losses to follow-up**: 7 withdrew, 4 lost to follow-up, 3 died. Slightly lower % follow-up in group 2 (lutein/antioxidant) 80% compared with other 2 groups (lutein alone 86% placebo 87%).
Participants	**Country:** USA **Number of people randomised**: 90 (NR eyes) **Number of people followed-up**: 76 (84%) (NR eyes) **Average age (range)**: approximate 75 years **Percentage women**: 4% **Ethnic group**: NR **Baseline visual acuity**: average ranged from 0.279 to 0.445 logMAR by eye and treatment group **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria**: • atrophic AMD diagnosed by ophthalmoscopy

	• at least one visual abnormality reduced contrast sensitivity, photo-stress glare recovery deficit or deficit on Amsler grid • clear ocular media • free of any other ocular/systemic disease that could affect central or parafoveal macular visual function. **Exclusion criteria:** • cataract or retinal surgery within 6 months • photosensitising drugs • taken lutein supplements within the previous 6 months
Interventions	**Intervention**: • lutein 10 mg non-esterified lutein (FloraGlo from Kemin Foods International, Des Moines, Iowa) 29 people randomised (NR eyes) 25 (86%) people followed-up (NR eyes) • lutein plus additional antioxidants and nutrients (OcuPower, Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida) 30 people randomised (NR eyes) 24 (80%) people followed-up (NR eyes) **Comparator:** • placebo, maltodextrin 31 people randomised (NR eyes) 27 (87%) people followed-up (NR eyes) **Duration**: 12 months Ocupower had a range of nutrients including lutein, vitamin A, beta-carotene, vitamins C, D3, E, B1, B2, B3, B5, B6, B12, folic acid, biotin, calcium, magnesium, iodine, zinc copper, manganese, selenium, chromium, molybdenum, lycopene, bilberry extract, alpha lipoic acid, N-acetyl cysteine, quercetin, rutin, citrus bioflavonoids, plant enzymes, black pepper extract, malic acid, taurine, L-glycine, L-glutathione, boron **Similarity between intervention and comparator**: Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food"

Outcomes	Primary: • macular pigment optical density Secondary: not specified The following clinical measurements were made: lens opacity; retinal images; Macular Pigment Optical Density (MPOD); visual acuity (Snellen) distance and near; glare testing; glare recovery; contrast sensitivity; VFQ-14 (activities of daily living, night driving, glare recovery symptoms); Amsler grid; self reported vision It was difficult to extract data on outcomes of relevance to this review: i.e. visual acuity and progression of AMD. Follow-up: 12 month Eyes: reported right and left eyes separately
Notes	**Source of funding**: Quote "This material is based on work supported by the DVA Medical Center, North Chicago, Illinois and the Department of Veteran's Affairs, Hines, Illinois." Quote "Grant sponsors are Kemin Foods, Inc. (Des Moines, Iowa); L/itacost.com, with its subsidiary Nutraceutical Sciences Institute (NSI: Boynton Beach, Florida); and Great Smokies Diagnostic Laboratory (Asheville, North Carolina). FloraGloB non-esterified lutein is a product of Kemin Foods. The FloraGloB lutein antioxidant supplement evaluated is known as OcuPower@, U.S. Patent #6,103,756-Wayne Gorsek, inventor; L/itacost.com assignee." Declaration of interest: NR Date study conducted: August 1999 to May 2001 Trial registration number: NR

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" Page 217

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." Page 218 All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study
Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food.
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Blinding of outcome assessment (detection bias)Progression AMD	Low risk	Quote "All personnel at the DVA Medical Center were unaware of the masked allocation codes during the 12-month clinical study" Quote "Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food."
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: Loss to follow-up 14/90: Lutein 10 mg group n = 29 • 1 person lost to follow-up • 1 person died • 2 other withdrawals Lutein 10 mg and antioxidant group n = 30

		• 2 persons lost to follow-up • 4 other withdrawals Placebo group n = 31 • 1 persons lost to follow-up • 1 person died • 1 other withdrawals Members of placebo group removed from analysis due to the fact that they had taken lutein
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: Difficult to assess with the information available

Zinc supplements

Bibliographic reference	**Newsome 1988** Newsome DA, Swartz M, Leone NC, Elston RC, Miller E. Oral zinc in macular degeneration. Archives of Ophthalmology 1988;106(2):192-8.
Methods	**Parallel group RCT** **Method of allocation**: computer-generated table of random numbers **Masking**: participant - yes; provider - yes; outcome – yes **Losses to follow-up**: 23 (10 treatment, 13 placebo)
Participants	**Country**: USA **Number of people randomised**: 174 (NR eyes) **Number (%) of people followed-up**: 151 (87%) (258 eyes)

	Average age (range): NR (42 to 89 years) **Percentage women**: 65% **Baseline visual acuity**: NR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR **Inclusion criteria:** macular degeneration: clinically visible drusen with varying degrees of pigmentary change with visual acuity in 1 eye of 20/80 or better **Exclusion criteria:** cataract reducing vision more than one line; other known serious eye disease; diabetes mellitus; other known systematic/metabolic disease or congenital condition which might interfere with results
Interventions	**Intervention:** • zinc sulfate 200 mg (daily) 1 x 100mg twice daily 90 people randomised (NR eyes) 80 (89%) people followed-up (134 eyes) **Comparator:** • placebo 84 people randomised (NR eyes) 71 (85%) people followed-up (124 eyes) Duration: 1 to 2 years Similarity between intervention and comparator: Quote "Identical apprearing tablets containing lactose and fructose served as the placebo" Analyses were also stratified according to number of eyes per person.

Outcomes	Primary: not specified Secondary: not specified Outcomes reported in paper: • Pinhole corrected visual acuity using ETDRS charts • changes in visible pigment, drusen or atrophy from grading of macular photographs • adverse effects of zinc including copper deficiency anaemia Follow-up: 6, 12, 18 and 24 months Eyes: Some people had one eye enrolled in the study and some had two eyes Quote "To analyze the results of two eyes of the same participant, the individual eye data were averaged and that value was used"
Notes	**Source of funding**: Research Fund, Department of Veterinary Science, Utah State University, Logan; James L Shupe, DVM; Mary Katherine Peterson Foundation, Houston Declaration of interest: NR Date study conducted: NR Trial registration number: NR

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

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

Bibliographic reference	**Stur 1996** Stur M, Tittl M, Reitner A, Meisinger V. Oral zinc and the second eye in age-related macular degeneration. Investigative Ophthalmology and Visual Science 1996;37(7):1225-35.
Methods	**Parallel group RCT** **Method of allocation**: sponsor prepared coded bottles **Masking**: participant - yes; provider - yes; outcome - yes **Losses to follow-up**: 6 withdrawn due to adverse gastrointestinal effects (4 treatment, 2 control); 14 withdrawn when developed neovascularisation (9 treatment, 5 control); 14 lost to follow-up (6 treatment, 8 control)
Participants	**Country**: Austria **Number of people randomised**: 112 (112 eyes) **Number (%) of people followed-up**: 92 (82%) (92 eyes); 78 (70%) (78 eyes) included the analyses because eyes that developed CNV were excluded **Average age (range):** 71 years (50 to NR) **Percentage women**: 57% **Ethnic group**: NR **Baseline visual acuity:** average 0.075 logMAR **Comorbidities affecting the eye**: NR **Percentage current smokers**: 21% **Inclusion criteria:** • exudative AMD in 1 eye (defined as angiographic evidence of classic or occult choroidal neovascularisation or RPE detachment) and early ARM with visual acuity 20/40 or better in other eye (early ARM: macular drusen with no angiographic evidence of exudative lesion)

	Exclusion criteria: • dense senile cataract • any other eye disease which could produce significant and permanent loss of visual acuity during follow-up • physical status that could prevent follow-up; history of serious systemic or metabolic disease
Interventions	**Intervention:** • zinc sulfate 200 mg (daily) 1 tablet 56 people randomised (56 eyes) NR (%) people followed-up but 37 (37 eyes) included in the analyses excluding eyes that developed CNV **Comparator:** • placebo 1 tablet people randomised (x eyes) NR (%) people followed-up but 41 (41 eyes) included in the analyses excluding eyes that developed CNV Duration: 24 months Similarity between intervention and comparator: Intervention was lemon flavoured effervescent tablet made of citric acid containing saccharine and sorbitol and placebo was as for treatment but without the zinc sulfate
Outcomes	**Primary:** not specified **Secondary**: not specified Outcomes reported in paper: Best-corrected LogMAR visual acuity measured using Bailey-Lovie chart; contrast sensitivity; incidence of choroidal neovascularisation; progression of disease (Wisconsin Age-related Maculopathy Grading System); copper deficiency anaemia **Follow-up**: 6, 12, 18 and 24 months Eyes: One eye per person, CNV in one eye and not in the fellow eye. The fellow eye was the "study eye"

Notes	A priori sample size estimate was 500 patients but trial stopped early because interim analysis showed no detectable trend Funders: Astra, Linz, Austria; Austrian Foundation for the Propagation of Scientific Research Source of funding: Quote "Supported in part by the Austrian Foundation for the Propagation of Scientific Research (Ostetreichischer Fonds zur Forderung der xuissenschaftlichen Forschung), Project 7215-MED." Quote "The authors thank the staff at Astra GmbH, Linz, Austria, for providing the coded doses of zinc sulfate and placebo." Declaration of interest: Quote "Proprietary interest category: N" Date study conducted: March 1990 to June 1992 Trial registration number: NR

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

Blinding of participants and personnel (performance bias)Visual acuity	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
Blinding of participants and personnel (performance bias)Progression AMD	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
Blinding of outcome assessment (detection bias)Visual acuity	Low risk	Quote "Coded doses of zinc sulfate and placebo were prepared by the sponsor (Astra, Linz, Austria). All doses were lemon-flavored effervescent tablets made of citric acid that provided improved gastrointestinal absorption and contained saccharine and sorbitol. Treatment group doses contained an additional 200 mg of zinc sulfate. (This preparation is identical to a zinc sulfate preparation registered in Austria and other European countries under the name Solvezink; Astra, Wedel, Germany.) Tablets were bottled in identical containers."
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)	High risk	Quote "One hundred twelve patients were enrolled between March 1, 1990 and June 30, 1992. Six patients (four in the treatment group, two in the placebo group) could not tolerate the medication because of gastrointestinal side effects and had to be withdrawn from the study. Fourteen patients did not return for the scheduled follow-up visits or decided to withdraw from the study because of personal reasons. The withdrawal of these 14 patients was not connected to any side effects of the study medication. The rest of the recruited patients (92 patients) returned for all required visits." Quote "During the treatment period, a CNV developed in the study eye in 14 patients (nine in the treatment group, five in the placebo group). Ten of these patients underwent laser treatment and were withdrawn from the study."
Selective reporting (reporting bias)	Unclear risk	Difficult to assess with the information available

Bibliographic reference	**Wang 2004** Wang H, Li RX, Wang MF. Effects of zinc and antioxidant on visual function of patients with age-related macular degeneration. Zhongguo Linchuant Kangfu 2004;8:1290-1.
Methods	**Parallel group RCT** **Method of allocation**: unknown **Masking**: participant - unknown; provider - unknown; outcome – unknown **Losses to follow-up**: unknown
Participants	**Country**: China **Number of people randomised**: 400 (400 eyes) **Number of people followed-up**: NR **Average age (range):** 65 years (52 to 76)

	Percentage women: 53% **Ethnic group**: NR **Baseline visual acuity:** NR **Comorbidities affecting the eye**: NR **Percentage current smokers**: NR
Interventions	**Intervention:** • zinc oxide 80 mg daily, vitamin C, vitamin E NR people randomised (NR eyes) NR (%) people followed-up (NR eyes) **Comparator:** • placebo NR people randomised (NR eyes) NR (%) people followed-up (NR eyes) Duration: 24 to 32 months Similarity between intervention and comparator: NR
Outcomes	Primary: not specified Secondary: not specified Outcomes: visual acuity, early and late AMD Follow-up: every 6 months for 24 to 32 months Eyes: one eye per person, worse eye was selected
Notes	Limited information available on this trial. AMD patients were stratified into early and late-stage disease

	Source of funding: NR Declaration of interest: NR Date study conducted: NR Trial registration number: NR

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)Visual acuity	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)Progression AMD	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)Visual acuity	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)Progression AMD	Unclear risk	Not reported

Incomplete outcome data (attrition bias)	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Visual acuity was measured but not reported, possible because of non-significant results