HTA 15.09.10 Systematic review of treatment of dry age-related macular degeneration and Stargardt disease.

Supplementary file 5. Nutrient treatments for AMD

Carotenoids

Berrow et al

Study details	**Participant details**
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;109:2008-14. *Country:* UK *Design:* RCT *Number of centres:* one *Funding:* commercial funding *Trial ID:* ISRCTN 17842302	*Number of Participants*: 14 total; 8 lutein +; 6 controls *Number of eyes* 14 total; 8 lutein +; 6 controls (eye with the best-corrected distance visual acuity). *Sample attrition/dropout*: 2 (unclear which group). *Sample crossovers:* none *Inclusion criteria:* age-related maculopathy, best-corrected distance visual acuity (at least 0·2 LogMAR), clear optical media, no signs of other retinal or optic nerve disease other than age-related maculopathy in the study eye, good general health and no prescribed medication that can affect the retina. *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, other retinal disease, previous retinal laser, diabetes, systemic hypertension, history of ocular trauma, neurological disease, AMD in the studied eye, drugs causing retinal toxicity, previous ocular surgery, epilepsy.

Intervention details	**Outcomes**
Intervention *1.* Lutein based supplement *2.* no supplement (control) *Dose details:* vitamin C 150 mg, cupric oxide 400 µg, vitamin E 15 mg, lutein 12 mg, zeaxanthin 0.6 mg, zinc 20 mg, omega-3 fatty acids 1,080 mg per day *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 40 weeks	*Outcomes (state if primary)* Contrast sensitivity Visual acuity (logMAR) Multi-focal electroretinography measures (primary outcome, not extracted) Food diary (not extracted) Compliance *Length of follow-up:* 40 weeks (additional 20 weeks for the lutein supplement group)

Participant characteristics, %			
	Lutein +, n=8	**Control, n=6**	**P value**
Age, years mean (SD)	65.5 (9.27)	69.67 (7.52)	0.40
Sex, % male			
Ethnic origin *% White*	100	100	
Smoking history (pack-years)	7.04 (9.42)	13.5 (15.86)	0.36

Comments: reports dietary intake of vitamins and minerals (not extracted)			
Results			
	Lutein, n=8	**Control, n=6**	**P Value**
Visual acuity			
Comments: states there were no significant changes between the lutein group and the control group over 40 weeks.			
Contrast sensitivity			
Comments: states there were no significant changes between the lutein group and the control group over 40 weeks.			
Compliance			
States that mean compliance, measured as the percentage of tablets taken, was 81·1 (SD 13·0) %.			
Adverse events			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Used a random number generator
Allocation concealment (selection bias)	Unclear	No details of allocation concealment
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Says single masked, no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Says single masked, no further details, no discussion of blinding of outcome assessors
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	2 participants discontinued, unclear which group, analysis not ITT
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	High	No data presented for key outcomes
Other biases	Low	No other apparent bias

Murray et al

Study details	**Participant details**
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 & Visual Science 2013;54:1781-8. *Country:* UK and The Netherlands *Design:* RCT *Number of centres:* 2 *Funding:* commercial and non-commercial funding *Trial ID:* NCT01042860	*Number of Participants*: total 84; lutein 42; placebo 42 *Number of eyes* one eye was analysed *Sample attrition/dropout*: total 11; lutein 6 (did not receive intervention 3, discontinued for medical reasons 3); placebo 5 (did not receive intervention 2, discontinued for medical reasons 1, unknown 2). Numbers reported suggest 1 additional participant discontinued in the placebo group. *Sample crossovers:* none *Inclusion criteria:* aged 50-80 years, AMD grade 0 to 4 in one eye, BCVA (LogMAR) at least 0.5, minimal cataract *Exclusion criteria:* any ophthalmic disorder (e.g diabetic retinopathy, optic atrophy, pigmentary abnormalities considered to be less typical of AMD, glaucoma, any dietary supplements containing lutein, zeaxanthin or meso-zeaxanthin within 3 months of the start of the

	study.

Intervention details	**Outcomes**
Intervention *1.* Lutein *2.* Placebo *Dose details:* lutein 10mg capsules taken daily *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 12 months	*Outcomes (state if primary)* MPOD BCVA (ETDRS, logMAR) Compliance (lutein serum concentration) (Scanning laser ophthalmoscope (SLO), retinal reflectometry, dark adaptometry, optical coherence tomography, ocular scatter – states reported in separate report) *Length of follow-up:* 12 months

Participant characteristics, %			
	Lutein, n=36	**Placebo, n=36**	**P value**
Age, years mean (SD)	71.9 (8.7)	69.1 (8.6)	0.1708
Sex, % male	44.4	33.3	
Ethnic origin *% White*			
Classification			
Smoking history			
Mean (SD) visual acuity	0.10 (0.17)	0.05 (0.13)	0.1155
Mean (SD) MPOD	0.38 (0.19)	0.49 (0.20)	0.0124
lesion size			
previous treatments			
Key comorbidities			
Family history			
Comments:			
Results			
	Lutein, n=36	**Placebo, n=36[a]**	**P Value**
Mean (SD) MPOD at 12 months	0.53 (0.22)	0.49 (0.18)	NR
MPOD % change from baseline at 12 months	39.5	0	NR
Comments: similar patterns of change were seen at month 4 and month 8 (reducing in the lutein group, no change in the placebo group) [a]table for MPOD shows n=37 which concurs with figure 1, elsewhere reports n=36			
Mean (SD) visual acuity at 12 months	0.09 (0.14)	0.09 (0.13)	<0.05
Mean change in visual acuity	0.01	0.04	<0.05
Comments			
Compliance			
Comments States patients in the lutein group at both centres showed a highly significant increase in serum lutein concentration (details not extracted)			
Adverse events			
Comments			
Subgroups	**Lutein, n=19**	**Placebo, n=14**	
Visual acuity worse than 0.06 (post hoc) *Baseline* *12 months*	 0.23 (0.12) 0.16 (0.10)	 0.16 (0.11) 0.19 (0.12)	 0.1405 NR
Visual acuity worse than 0.06 (post hoc) *Change from baseline* *% change from baseline*	 0.07 (0.10) 30.4	 -0.03 (0.12) -18.75	 <0.05 NR

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States randomisation code was generated by the sample manufacturer, but doesn't say how.
Allocation concealment (selection bias)	Unclear	Treatment numbers were allocated consecutively. If a discontinued patient was replaced, the next available treatment number was used. No details of concealment of allocation numbers
Blinding participants and personnel (performance bias), Objective outcomes	Low	Lutein and placebo and their packaging were indistinguishable, the code remained with the manufacturer until the end of the trial and experimenters were unaware of treatment group.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No details of blinding of outcome assessors
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	Analysis was on those completing the intervention only, discontinuations similar between groups but inconsistency in the reporting of numbers analysed in the placebo group.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All stated outcomes (in trial record and publication) reported. States other outcomes to be reported separately.
Other biases	Unclear	No other apparent biases Not clearly stated but appears that the 2 centres were randomised separately

Weigert et al

Study details	**Participant details**
Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, Werkmeister RM, et al. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. Investigative Ophthalmology & Visual Science 2011;52:8174-8. *Country:* Austria *Design:* RCT *Number of centres:* one *Funding:* Commercial funding *Trial ID:* NCT00879671	*Number of Participants*: Total 126 (Lutein 84, placebo 42) *Number of eyes:* 126 (Lutein 84, placebo 42) *Sample attrition/dropout*: measurements could not be obtained in 1 patient, 9 dropped out after baseline visit (groups not reported), a further 16 withdrew (10 lutein, 6 placebo), the reason was a serious adverse event in 2 lutein and 1 placebo. *Sample crossovers:* not reported *Inclusion criteria:* AMD categories 2, 3, or 4, according to the AREDS criteria with no CNV in the study eye, aged 50 -90 years, clear nonlenticular ocular media, and a visual acuity > 0.4, naive to previous lutein and/or zeaxanthin administration. Only one eye was chosen for inclusion, if both eyes were eligible, one eye was selected randomly. *Exclusion criteria:* primary retinal pigment epithelium atrophy >125 µm, moderate or severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, participation

	in a clinical trial in the 3 weeks preceding the study, ocular surgery within the last 6 months, and a history of treatment with photosensitizing drugs

Intervention details	**Outcomes**
Intervention *1.* Lutein *2.* Placebo *Dose details:* months 1 to 3: 20 mg once daily, months 4 to 6: 10 mg once daily *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 6 months	*Outcomes (state if primary)* Macular pigment optical density (MPOD) (primary outcome) Visual acuity (ETDRS) Visual function: retinal sensitivity measured by mean differential light threshold (MDLT) Blood pressure and pulse rate (not extracted) Intraocular pressure (not extracted) Compliance Serious adverse effects leading to withdrawal *Length of follow-up:* 6 months

Participant characteristics, %			
	All patients, n=126		**P value**
Age, years mean (SD)	71.6 (8.6)		
Sex, % male	39.7		
Classification, n *AREDS staging, 2/3/4*	50/23/43[a]		
Smoking history			
visual acuity, %, mean (SD)	83.9 (6.0)		
MPOD, mean (SD)	0.35 (0.1)		
MDLT, dB, mean (SD)	71.6 (8.6)		
Comments [a]numbers do not add up, assume based on the 116 who continued after the baseline evaluation and were included in the analysis.			
Results			
	Lutein, n=84	**Placebo, n=42**	**P Value**
Percent change in MPOD, mean (SD) at 6 months	27.9 (2.9)	0.7 (3.9)	P<0.001
Comments			
Percent change in MDLT, mean (SD) at 6 months	7.3 (13.2)	0[a]	P=0.96
Comments			
Change in visual acuity, ETDRS letters, at 6 months mean (SD)	2.1 (0.4)	1[a]	P=0.07
Comments [a] Estimated from figure			
Compliance in 99 patients, the remaining tablets were within ±10% of the expected number. In the remaining 17 patients, the count was between ±10% and ±20% of the expected number.			
Adverse events, %			
Serious adverse events leading to study withdrawal	2.4 (myocardial infarction, CNV)	2.4 (CNV)	
Comments			
Subgroups			
States subgroup analysis revealed that the change in MPOD was equally seen in all AREDS subgroups (data presented in a figure, not extracted.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States ‘randomised’ only, details not reported

Allocation concealment (selection bias)	Unclear	Details not reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as double-masked but no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Described as double-masked but no further details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	High	For patients who did not complete the study according to the protocol a last-observation-carried-forward procedure was performed. Those patients who were lost after the baseline visit were not included in the study.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	High	low density lipoprotein and Plasma lutein concentrations stated on trial register, not reported
Other biases	Low	No other bias

Ma et al

Study details	**Participant details**
Ma L, Yan SF, Huang YM, Lu XR, Qian F, Pang HL, et al. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. Ophthalmology 2012;119:2290-7. Ma L, Dou HL, Huang YM, Lu XR, Xu XR, Qian F, et al. Improvement of retinal function in early age-related macular degeneration after lutein and zeaxanthin supplementation: a randomized, double-masked, placebo-controlled trial. American Journal of Ophthalmology 2012;154:625-34.e1 Possibly linked to 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;99:371-5. Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. BioMed Research International 2015;2015:564738. *Country:* China	*Number of Participants*: Total 108 1. Lutein 10 mg n=27 2. Lutein 20 mg n=27 3. Lutein and Zeaxanthin n=27 4. Placebo, n=27 *Number of eyes* Not reported *Sample attrition/dropout*: n=1 (lutein 10 mg group) *Sample crossovers:* one *Inclusion criteria:* 50-79 years, clinical diagnosis of early AMD (defined as the presence of soft drusen, presence of any retinal pigmentary abnormalities in the absence of signs of late AMD, or both), according to the Age-Related Eye Disease Study classification system. *Exclusion criteria:* late AMD or other macular or choroidal disorders (e.g., macular edema, macular holes, central serous chorioretinopathy, or macular epiretinal membrane); demonstrated presence of significant central lens opacities precluding fundus autofluorescence; implanted intraocular lens, glaucoma, or unstable chronic illness; history of intraocular inflammation, ocular trauma, laser treatment for retinal diseases, retina-vitreous surgery, or photodynamic therapy; currently taking medications affecting macular function (e.g., chloroquine or oxazepam); or consumed dietary supplements containing vitamins or carotenoids within prior 6 months.

Design: RCT *Number of centres:* One *Funding:* National Natural Science Foundation of China *Trial ID:* NCT01048476; NCT01528605	

Intervention details	**Outcomes**
Intervention *1.* Lutein 10 mg *2.* Lutein 20 mg *3.* Lutein 10 mg and Zeaxanthin 10 mg *4.* Placebo *Dose details:* As above, taken daily *Dose modifications:* None *Concurrent treatment:* None *Duration of treatment:* 48 weeks	*Outcomes (state if primary)* MPOD (primary outcome) Best-corrected visual acuity (BCVA) Contrast sensitivity Photorecovery time Amsler grid testing Compliance Adverse effects *Length of follow-up:* 48 weeks

Participant characteristics, %				
	Lutein 10 mg, n=26	**Lutein 20 mg, n=27**	**Lutein and Zeaxanthin, n=27**	**Placebo, n=27**
Age, years mean (SD)	69.9 (8.4)	69.0 (6.8)	68.6 (7.0)	68.9 (7.6)
Sex, % male	38.5	44.4	44.4	40.7
Smoking history				
- *Never*	88.5	88.9	85.2	88.9
- *Former*	7.7	7.4	3.7	3.7
- *Current*	3.8	3.7	11.1	7.4
BCVA, logMAR, mean (SD)	0.30 (0.23)	0.28 (0.23)	0.28 (0.24)	0.31 (0.19)
Early cataracts, %	23.1	18.5	29.6	22.2
MPOD, density unit, mean (SD)	0.31 (0.15)	0.31 (0.12)	0.31 (0.12)	0.32 (0.14)
Contrast sensitivity, log, mean (SD)				
- *3 cycles/degree*	1.27 (0.36)	1.30 (0.36)	1.26 (0.33)	1.29 (0.36)
- *6 cycles/degree*	1.41 (0.34)	1.46 (0.35)	1.43 (0.39)	1.43 (0.39)
- *12 cycles/degree*	1.03 (0.32)	1.03 (0.34)	1.05 (0.36)	1.05 (0.41)
- *18 cycles/degree*	0.60 (0.38)	0.57 (0.33)	0.58 (0.39)	0.58 (0.39)
Photorecovery time, sec	16.1 (14.1)	16.3 (11.5)	17.4 (12.2)	18.7 (17.1)
Amsler grid defects, %	23.1	15.4	22.2	11.1
lesion size				
previous treatments				
Key comorbidities				
Family history				
There were no significant differences between groups (p values reported)				
Results				

Change from baseline at 48 weeks (95% CI)	**Lutein 10 mg, n=26**	**Lutein 20 mg, n=27**	**Lutein and Zeaxanthin, n=27**	**Placebo, n=27**
MPOD[a]	0.07 (-0.01, 0.13)	0.08 (0.02, 0.12)	0.07 (0.00, 0.11)	0.00 (-0.05, 0.05)
[a]Data estimated from figure. States no significant differences in changes in MPOD were found among groups at any time point from the analysis of covariance.				
BCVA, logMAR, mean (95% CI), 48 weeks	-0.04 (-0.11, 0.03)	-0.02 (-0.11, 0.06)	-0.04 (-0.10, 0.01)	-0.00 (-0.06, 0.05)
P = ns for between-group difference in change from baseline derived from analysis of covariance analysis adjusting for baseline value. 24 week analysis showed similar pattern of results				
Contrast sensitivity, log, mean (95% CI), 48 weeks				
- *3 cycles/degree*	0.13 (0.03, 0.29)	0.18 (0.07, 0.28)[a]	0.18 (0.05, 0.32)	-0.03 (-0.19, 0.13)
- *6 cycles/degree*	0.18 (0.03, 0.34)	0.21 (0.10, 0.32)[a]	0.15 (0.04, 0.31)	-0.01 (-0.17, 0.16)
- *12 cycles/degree*	0.14 (0.02, 0.27)	0.15 (0.02, 0.28)	0.12 (-0.04, 0.28)	0.02 (-0.15, 0.19)
- *18 cycles/degree*	-0.01 (-0.18, 0.15)	0.10 (-0.06, 0.26)	0.09 (-0.11, 0.29)	-0.02 (-0.18, 0.13)
P = ns for between-group difference in change from baseline derived from analysis of covariance analysis adjusting for baseline value. [a]Lutein 20mg significantly different from placebo group ($p<0.05$) at 3 cycles/degree (between-group difference, 0.21; 95% CI, 0.01– 0.40, $P<0.05$) and 6 cycles/degree (between-group difference, 0.22; 95% CI, 0.03– 0.41; $P<0.01$) 24 week analysis showed similar pattern of results				
Photorecovery time, seconds, mean (95% CI), 48 weeks	-0.73 (-5.60, 4.14)	-1.85 (-6.90, 3.21)	0.44 (-4.83, 5.71)	0.85 (-4.55, 6.25)
P = ns for between-group difference in change from baseline derived from analysis of covariance analysis adjusting for baseline value. At 24 weeks the pattern of photorecovery time was different in the lutein 10mg group (was slower) and in the lutein and Zeaxanthin group (was faster), but there were no significant differences seen.				
Amsler grid defects, %	NR	NR	NR	NR
Data not reported, states no significant changes				
Pill compliance, defined as taking at least 90% of pills, was 96.2% in the 10-mg lutein group (96.2%) and 100% in the other groups.				
Adverse events	0	0	0	0
States no adverse event related to the study drug occurred during the study				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	low	randomization sequence with stratification by baseline macular pigment optical density (MPOD) was computer generated, using a permuted block design with block size of 8
Allocation concealment (selection bias)	unclear	Not reported
Blinding participants and personnel (performance bias), Objective outcomes	low	All participants, the study investigators, and data analysts were masked to treatment assignment. To protect the blinding, the different capsules were indistinguishable by size, weight, or colour
Blinding participants and personnel (performance bias), Subjective outcomes	n/a	n/a

Blinding outcome assessors (detection bias), Objective outcomes	low	All participants, the study investigators, and data analysts were masked to treatment assignment. To protect the blinding, the different capsules were indistinguishable by size, weight, or colour
Blinding outcome assessors (detection bias), Subjective outcomes	n/a	n/a
Incomplete outcome data (attrition bias), Objective outcomes	low	99% completed treatment
Incomplete outcome data (attrition bias), Subjective outcomes	n/a	n/a
Selective reporting (reporting bias)	Low	All outcomes reported, NCT record checked
Other biases	low	No other biases

Huang et al

Study details	**Participant details**
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;99:371-5. Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. BioMed Research International 2015;2015:564738. Possibly linked to Ma 2012 studies, see above for citation details *Country:* China *Design:* RCT *Number of centres:* one *Funding:* Non-commercial funding *Trial ID:* NCT01528605 (incorrectly reported in paper as NCT10528605)	*Number of Participants*: Total 112 (states 114 in the acknowledgements), 108 analysed *1.* Lutein 10 mg n=26 *2.* Lutein 20 mg n=27 3. Lutein 10 mg + zeaxanthin 10 mg n=27 4. Placebo n=28 *Number of eyes:* not reported *Sample attrition/dropout*: 4 excluded from analysis (failed to attend examinations) *Sample crossovers:* Not reported *Inclusion criteria:* Age > 50 years, clinical diagnosis of early AMD (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. *Exclusion criteria:* other ocular disorders or unstable systemic or chronic illness or consumed dietary supplements containing antioxidants or carotenoids within the previous 6 months.

Intervention details	**Outcomes**
Intervention *1.* Lutein 10 mg *2.* Lutein 20 mg 3. Lutein 10 mg + zeaxanthin 10 mg 4. Placebo *Dose details:* Not reported	*Outcomes (state if primary)* Macular pigment optical density (MPOD) (primary outcome), N1P1 response densities (amplitudes per unit retinal area in nV/deg2) (not extracted) Mean retinal sensitivity (the average sensitivity of the test loci at 1°, 3° and 5° eccentricities), BCVA (Early Treatment Diabetic Retinopathy Study (ETDRS) protocol) Contrast sensitivity

Dose modifications: Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 2 years	Flash recovery time Vision-related quality of life (VFQ-25) Adverse events *Length of follow-up:* 2 years

Participant characteristics, %					
	Lutein 10 mg, n=26	**Lutein 20 mg, n=27**	**lutein +zeaxanthin, n=27**	**Placebo, n=28**	**P value**
Age, years mean (SD)	69.7 (8.3)	69.3 (6.9)	68.5 (6.9)	69.0 (7.5)	
Sex, % male	34.6	51.9	44.4	39.3	
Smoking history % *Never* *Former* *Current*	 84.6 11.5 3.8	 88.9 7.4 3.7	 85.2 3.7 11.1	 89.3 3.6 7.1	
Early cataracts, %	23.0	18.5	29.6	21.4	
MPOD, density units, mean (SD)	0.307 (0.142)	0.315 (0.122)	0.320 (0.118)	0.315 (0.144)	
Contrast sensitivity, log, mean (SD) *3 cycles/degree* *6 cycles/degree* *12 cycles/degree* *18 cycles/degree*	 1.26 (0.36) 1.41 (0.34) 1.02 (0.33) 0.57 (0.39)	 1.24 (0.39) 1.40 (0.39) 1.00 (0.34) 0.49 (0.35)	 1.25 (0.32) 1.45 (0.38) 1.06 (0.36) 0.53 (0.37)	 1.22 (0.37) 1.40 (0.39) 0.97 (0.37) 0.50 (0.35)	
Best-corrected visual acuity, logMAR, mean (SD)	0.31 (0.21)	0.31 (0.21)	0.32 (0.25)	0.34 (0.19)	
Photorecovery time, sec, mean (SD)	16.68 (14.22)	15.86 (11.17)	17.38 (12.00)	18.57 (16.78)	
VFQ25 score, means (SD)	75.46 (14.60)	75.58 (15.35)	74.26 (14.46)	76.04 (18.09)	
lesion size					
previous treatments					
Key comorbidities					
Family history					
no significant between-group differences in any baseline demographic or clinical variable.					
Results					
	Lutein 10 mg, n=26	**Lutein 20 mg, n=27**	**lutein +zeaxanthin, n=27**	**Placebo, n=28**	**P value**
MPOD, density units, at 2 years, mean (SD)	0.442 (0.127)	0.441 (0.133)	0.383 (0.149)	0.324 (0.163)	
Repeated-measures analyses showed a significant time × treatment interaction of MPOD ($P = 0.046$). MPOD significantly increased during the supplementation ($P < 0.001$), whereas no statistical treatment effect was shown ($P = 0.072$).					
Mean retinal sensitivity at 2 years					
Total	13.8	13.4	12.6	11.8	
1° eccentricity	13.2[b]	12.4[a]	11.0	10.2	
3° eccentricity	14.2	14.0	13.8	13.0	
5° eccentricity	13.0	13.6	13.1	12.1	
Data estimated from figure. [a] versus placebo p<0.05, [b] versus placebo p<0.01, (repeated-measures analysis of variance with post hoc tests).					
Contrast sensitivity at 2 years, log, mean (SD)					
3 cycles/degree	1.47 (0.34)	1.32 (0.25)[a]	1.39 (0.39)	1.25 (0.32)	
6 cycles/degree	1.50 (0.33)	1.54 (0.36)[a]	1.50 (0.36)	1.25 (0.30)	
12 cycles/degree	1.10 (0.35)	1.05 (0.36)	1.09 (0.35)	0.87 (0.33)	

18 cycles/degree	0.59 (0.45)	0.65 (0.39)	0.74 (0.33)[a]	0.40 (0.34)	
Repeated-measures analyses of the above variables did not reveal any differential treatment effects, except a significant time effect observed for 3 cycles/degree ($P < 0.05$). [a] versus placebo p<0.05					
Best-corrected visual acuity, logMAR, at 2 years, mean (SD)	0.26 (0.15)	0.28 (0.16)	0.27 (0.24)	0.30 (0.25)	
Photorecovery time, sec, at 2 years, mean (SD)	15.00 (8.40)[a]	15.36 (12.75)[a]	15.67 (11.04)	24.41 (14.40)	
VFQ25 score, at 2 years, means (SD)	79.61 (13.52)	76.65 (16.32)	80.13 (11.73)	77.31 (17.05)	
[a] versus placebo p<0.05 Scores range from 0 to 100, where higher scores indicate better function					
Outcome 3					
No adverse events related to the study were observed or reported.					
Compliance					
97% (105/108) of participants took at least 93% (missing 2 days) of their supplements every month.					

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	randomisation sequence with stratification by baseline MPOD was computer generated using a permuted block design with block size of 8.
Allocation concealment (selection bias)	Unclear	Not reported
Blinding participants and personnel (performance bias), Objective outcomes	Low	All subjects, examiners and study staff were blinded to treatment assignment, and all capsules were identical in appearance.
Blinding participants and personnel (performance bias), Subjective outcomes	Low	All subjects, examiners and study staff were blinded to treatment assignment, and all capsules were identical in appearance.
Blinding outcome assessors (detection bias), Objective outcomes	Low	All subjects, examiners and study staff were blinded to treatment assignment, and all capsules were identical in appearance.
Blinding outcome assessors (detection bias), Subjective outcomes	Low	All subjects, examiners and study staff were blinded to treatment assignment, and all capsules were identical in appearance.
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Small proportion (3.6%) excluded from analysis, reason given but groups not reported
Incomplete outcome data (attrition bias), Subjective outcomes	Unclear	Small proportion (3.6%) excluded from analysis, reason given but groups not reported
Selective reporting (reporting bias)	Low	Outcomes reported as stated in trial register
Other biases	Low	No other biases

Kelly et al

Study details	**Participant details**
Kelly ER, Plat J, Haenen GR, Kijlstra A, Berendschot TT. The effect of modified eggs and an egg-yolk based beverage on serum lutein and zeaxanthin concentrations and macular pigment optical density: results from a randomized trial. PLoS ONE [Electronic Resource] 2014;9:e92659 *Country:* The Netherlands *Design:* RCT	*Number of Participants*: total 100 (beverage 20; lutein egg 20; zeaxanthin egg 20; normal egg 20; control 20) *Number of eyes* total 100 (beverage 20; lutein egg 20; zeaxanthin egg 20; normal egg 20; control 20) *Sample attrition/dropout*: total 3 (beverage 0; lutein egg 1 moved away; zeaxanthin egg 0; normal egg 1 moved away; control 1 lost contact) *Sample crossovers:* assume none

Number of centres: one *Funding:* commercial funding *Trial ID:* NCT00527553 Protocol available at: http://journals.plos.org/plosone/article/file?type=supplementary&id=info:doi/10.1371/journal.pone.0092659.s002	*Inclusion criteria:* Healthy individuals aged at least 18 years *Exclusion criteria:* diabetes, heart disease, lipid metabolic diseases, AMD in both eyes (at least the eye studied in the trial had to be healthy), ocular media opacity or other ocular diseases, smokers, those taking supplements containing lutein and/or zeaxanthin in the past 6 months, BMI >30 kg/m^2, those with a MPOD score below 0.55.

Intervention details	**Outcomes**
Intervention *1.* lutein egg yolk beverage *2.* lutein enriched egg *3.* zeaxanthin enriched egg *4.* normal egg *5.* control (no dietary modification) *Dose details:* eggs and beverage (equivalent of 1 egg yolk) taken once daily. Lutein beverage (970 µg lutein, 340µg zeaxanthin); Lutein egg (921.4 (SD 105) µg lutein and 137.3 (SD 14.0) µg per yolk); Zeaxanthin egg (174.3 (SD 14.5) µg lutein and 487.3 (SD 31.0) µg per yolk); normal egg (167.8 (SD 8.7) µg lutein and 85.0 (SD 1.7) µg per yolk). *Dose modifications:* not reported *Concurrent treatment:* asked not to make any other major modifications to diet *Duration of treatment:* assume 90 days	*Outcomes (state if primary)* Serum values of lutein and zeaxanthin (not data extracted) MPOD *Length of follow-up:* 90 days

Participant characteristics, %						
	Lutein beverage, n=20	**Lutein egg, n=20**	**Zeaxanthin egg, n=20**	**Normal egg, n=20**	**Control, n=20**	**P value**
Age, years mean (SD)	43 (16)	45 (19)	48 (17)	53 (12)	44 (16)	0.34
Sex, % male	40	40	45	45	45	0.99
MPOD, mean (SD)	0.38 (0.12)	0.32 (0.12)	0.35 (0.14)	0.31 (0.14)	0.34 (0.15)	0.60
Results						
	Lutein beverage, n=20	**Lutein egg, n=20**	**Zeaxanthin egg, n=20**	**Normal egg, n=20**	**Control, n=20**	**P value**
MPOD at 90 days	0.32 (0.16)	0.36 (0.16)	0.36 (0.21)	0.35 (0.22)	0.35 (0.17)	0.96

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Random allocation sequence was generated using proprietary software
Allocation concealment (selection bias)	unclear	No discussion of concealment of allocation in publication or supplementary protocol
Blinding participants and personnel	High	States the egg groups were double blinded but it

(performance bias), Objective outcomes		was not possible to blind the egg beverage group (or the control)
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	unclear	No blinding reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Low	Few drop outs, unlikely to bias results
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	High	Protocol states visual acuity and contrast sensitivity were outcomes, these were not reported.
Other biases	Low	No other apparent biases

Kelly et al

Study details	**Participant details**
Kelly D, Nolan JM, Howard AN, Stack J, Akuffo KO, Moran R, et al. Serum and macular response to carotenoid-enriched egg supplementation in human subjects: the Egg Xanthophyll Intervention clinical Trial (EXIT). British Journal of Nutrition 2017;117:108-23. *Country:* Ireland *Design:* CCT *Number of centres:* 2 *Funding:* commercial and non-commercial funding *Trial ID:* ISRCTN25867083	*Number of Participants*: total 50: carotenoid eggs 25; placebo eggs 25 *Number of eyes:* not reported *Sample attrition/dropout*: total 4: 2 carotenoid egg group (cholesterol exceeded upper threshold limit; personal reasons); 2 placebo egg group (cholesterol exceeded upper threshold limit; personal reasons). *Sample crossovers:* none *Inclusion criteria:* age 18-65, no known allergy to eggs, no history of CVD, no ocular pathology, cholesterol levels of ≤6·5 mmol/l. *Exclusion criteria:* current or recent history of supplementation with macular carotenoids and/or cholesterol-lowering statins.

Intervention details	**Outcomes**
Intervention *1.* carotenoid-enriched eggs (lutein and meso-zeaxanthin in a 1:1 ratio) *2.* standard (placebo) egg *Dose details:* two-eggs daily, five days per week, prepared as scrambled eggs by the study investigators *Dose modifications:* if a participant did not attend they were given two eggs to prepare at home, to ensure 100% compliance. *Concurrent treatment:* different side options served with the eggs (toast, croissants, muffins) *Duration of treatment:* 8 weeks	*Outcomes (state if primary)* Serum carotenoid concentrations (not extracted) Macular Pigment measurement (two methods, different eccentricities) BCVA (ETDRS charts, logMAR) Serum cholesterol levels (not extracted) Contrast sensitivity (25 outcomes, limited extraction, see below) Adverse events *Length of follow-up:* 8 weeks

Participant characteristics, %

	Carotenoid-enriched eggs, n=25	**Placebo eggs, n=25**	**P value**
Age, years mean (SD)	35 (8)	41 (10)	0.015
Sex, % male	84	40	0.001
Smoking history, % *Never* *Past* *Current*	 68 20 12	 64 16 20	 0.583
BCVA	106 (5.6)	105 (4.5)	0.579
Macular pigment, mean (SD) by densitometer at *0.25°* *0.5°* *1°*	 0.549 (0.19) 0.440 (0.19) 0.276 (0.14)	 0.527 (0.17) 0.413 (0.16) 0.283 (0.17)	 0.674 0.596 0.895
Macular pigment, mean (SD) by spectralis at *0.23°* *0.51°* *1.02°*	 0.521 (0.18) 0.414 (0.16) 0.272 (0.13)	 0.475 (0.13) 0.378 (0.11) 0.271 (0.08)	 0.319 0.369 0.981
Comments: some differences in third decimal place between table 1 and table 2 in the report.			
Results			
	Carotenoid-enriched eggs, n=25	**Placebo eggs, n=25**	**P Value**
BCVA mean (SD) final visit	107.7 (4.45)	105.4 (4.78)	P=0·035
Comments These analyses controlled for baseline age, triglyceride and sex			
Macular pigment	See below	See below	
Comments: there were no significant between-group differences in MP at any measured eccentricities, whether measured on the Densitometer (0·25°; P=0·840, 0·5°; P= 0·593, 1·0°; P= 0·579) or Spectralis (0·23°; P=0·706, 0·51°; P=0·663, 1·02°; P=0·345). Actual data not extracted as BCVA data is available			
Contrast sensitivity	See below	See below	
Comments: only one between group difference was seen for the letter CS at 15·15 cpd (P=0·046), which exhibited an improvement in the enriched egg group.			
Adverse events	0	0	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	Participants were divided in to two groups according to site at Institute, states not randomly assigned.
Allocation concealment (selection bias)	High	No concealment of allocation
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Single blind study, participants in group 1 were treated at one site and participants in group 2 at another site to preserve the masked nature of the trial because the enriched eggs had a more pronounced yellow colour. Eggs were marked so that investigators knew which were control and which were study eggs.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Clinical assessments by one researcher but no discussion of blinding.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition	Low	Numbers and reasons provided, balanced

bias), Objective outcomes		between groups, says none were excluded from the analysis
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Study outcomes in the trial record are reported.
Other biases	Low	No other apparent biases

Richer et al

Study details	**Participant details**
Richer SP, Stiles W, Graham-Hoffman K, Levin M, Ruskin D, Wrobel J, et al. Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78 *Country:* US *Design:* RCT *Number of centres:* one *Funding:* Chrysantis, Inc (manufacturer) primary sponsor. Secondary sponsors from industry. *Trial ID:* NCT00564902	*Number of Participants*: Total n= 60, *1.* 8 mg zeaxanthin, n=25 *2.* 8 mg zeaxanthin + 9 mg lutein, n=25 *3.* 9 mg lutein ('Faux placebo), n=10 *Number of eyes:* Not stated *Sample attrition/dropout*: n= 9, *1.* 8 mg zeaxanthin, n=4 *2.* 8 mg zeaxanthin + 9 mg lutein, n=4 *3.* 9 mg lutein ('Faux placebo), n=1 *Sample crossovers:* none. *Inclusion criteria:* Early and moderate AMD retinopathy. Patients had symptoms and measurable deficits on the contrast sensitivity chart or demonstrated glare disturbances, Amsler grid abnormalities, or subjective functional night driving or reading disturbances that they wished to improve. *Exclusion criteria:* high-risk retinal characteristics for advanced AMD or advanced AMD for which existing medical or surgical options were available. Retinal characteristics included presence of significant active exudative AMD pathology by fluorescein angiography or optical coherence tomography (OCT), a single large drusen, > 15 multiple intermediate drusen, parafoveal geographic atrophy, or loss of vision in 1 eye because of advanced AMD. Consumption of L (or Zx) beyond the minimal 250 µg/d within 6 months, active comorbidities, such as uncontrolled and severe diabetes, glaucoma, uveitis, or optic neuritis, Alzheimer's disease or non-Alzheimer's dementia or schizophrenia, use of retinotoxic medications.

Intervention details	**Outcomes**
Intervention *1.* zeaxanthin *2.* zeaxanthin + lutein *3.* lutein ('Faux placebo') *Dose details:* *1.* 8 mg zeaxanthin, 1 capsule per day with a meal. *2.* 8 mg zeaxanthin + 9 mg lutein, 1 capsule per day with a meal. *3.* 9 mg lutein, 1 capsule per day with a meal. *Dose modifications:* none reported.	*Outcomes (state if primary)* Estimated central foveal one degree macular pigment optical density (MPOD) (primary outcome) Colenbrander average eye near high-contrast visual acuity, Shape discrimination, Contrast sensitivity function (CSF), area under curve at 5 spacial frequencies, Glare recovery, Scotoma count (twenty-degree Kinetic Field Analyzer, data in figure only, not extracted) Blue-yellow increment threshold (not extracted) Subjective visual function questionnaire (VQF25)

Concurrent treatment: none stated. *Duration of treatment:* 12 months	Adverse events Compliance *Length of follow-up:* 12 months

Participant characteristics, %				
	Zeaxanthin, n=25	**Zeaxanthin + Lutein, n=25**	**Lutein (faux placebo), n=10**	**P value**
Age, years mean (SD)	74.4 (11)	75.8 (9)	73.9 (9)	ns
Sex, % male	96	96	90	
Smoking history (pack/d/5 y)	0.7 (0.2)	0.2 (0.7)	0.3 (0.5)	ns
Visual Function Questionnaire;	87.0 (10)	86.0 (13)	89.7 (8)	ns
ETDRS distance visual acuity	95.4 (7)	93.7 (9)	98.5 (5)	ns
100% and 10% Colenbrander near visual acuity	88.3 (10) 77.2 (12)	86.8 (12) 72.7 (16)	93.3 (8) 81 (10)	ns
Smith Kettlewell Institute Low Luminance	60.6 (14) 63.6 (13)	52.2 (20) 57.8 (17)	64.5 (10) 66.3 (12)	0.04
Estimated macula pigment, density units	0.36, SE 0.05	0.27, SE 0.03	0.37, SE 0.05	ns
Contrast sensitivity function photopic distance (mean)	201, SE 22	204, SE 30	212, SE 34	ns
Glare recovery	26.7, SE 5	35.6, SE 6	52.9, SE 16	ns
Shape discrimination	1.0, SE 0.2	0.7, SD 0.1	0.7, SE 0.2	ns
lesion size				
previous treatments				
Key comorbidities - *Type 2 diabetes*	0.2 (0.4)	0.2 (0.4)	0.3 (0.5)	ns
Family history				
BMI	28.6 (5)	29.4 (5)	29.8 (5)	ns
AMD duration, months	42.8 (47)	45.5 (41)	28.0 (26)	ns
AREDS report #18 retinal grade	1.78 (1.0)	1.1 (0.8)	0.9 (0.7)	0.007
Comments: values for estimate macula pigment density units differ slightly in the clinical trials record.				
Results				
At 12 months:	**Zeaxanthin, n=25**	**Zeaxanthin + Lutein, n=25**	**Lutein (faux placebo), n=10**	**P value**
Foveal (1degree) estimated macular pigment, density unit	Right: Baseline: 0.35; 12 mo: 0.48 Left: Baseline: 0.35; 12 mo: 0.48	Right: Baseline: 0.31; 12 mo: 0.51 Left: Baseline: 0.27; 12 mo: 0.52	Right: Baseline: 0.39; 12 mo: 0.57 Left: Baseline: 0.35; 12 mo: 0.51	P=0.47 (12 months)
Comments: By 12 months, foveal MP increased in all 3 groups from low-normal to normal density				
ETDSR Colenbrander average eye near high-contrast visual acuity (SE)	96.8 (8.35)	92.8 (5.9)	98.9 (5.7)	NR
SE from clinical trials register, possibly a SD				
Comments: Colenbrander average eye near high-contrast visual acuity improved at least 1 line in all 3 intervention groups. Statistical significance of between group differences not reported.				
Colenbrander average eye low-contrast near visual acuity	81.5	81.5	88.2	NR
Statistical significance of between group differences not reported.				
Contrast sensitivity function (CSF), area under curve at 5 spacial frequencies (SE)	254.7 (35.2)	247.1 (35)	310.5 (33.8)	NR

Statistical significance of between group differences not reported. SE from clinical trials register, possibly a SD given the baselines are reported to be SDs, and high values				
Shape discrimination, average eye (SD)	0.6 (0.46)	0.6 (0.25)	0.5 (0.24)	P=0.74
Statistical significance of between group differences not reported.				
Glare recovery, seconds (Right eye, left eye)	R: 18.40 L: 16.00	R: 17.20 L:14.10	R: 21.60 L:12.40	NR
Comments Reports statistical significance for change from baseline for each group only; Statistical significance of between group differences not reported.				
AREDS report #18 retinal grade	1.68	1.14	1.56	
Statistical significance of between group differences not reported.				
	Zeaxanthin, n=21	**Zeaxanthin + Lutein, n=21**	**Lutein (faux placebo), n=9**	**P value**
100% kinetic field [dB] (mean (SE))	Baseline: 2649 (750) 12 mo: 1129 (650)	Baseline: 1717 (765) 12 mo: 2207 (210)	Baseline: 5514 (2074) 12 mo: 2704 (1745)	
Statistical significance of between group differences not reported. SE from clinical trials register, possibly a SD given the baselines are reported to be SDs, and high values				
6.5º Tritan threshold [dB] (mean (SE))	Baseline: 6 (9) 12 mo: 3.45 (1.09)	Baseline: 8.6 (12) 12 mo: 8.37 (1.39)	Baseline: 4.9 (4) 12 months: 4.46 (1.08)	
Statistical significance of between group differences not reported. SE from clinical trials register, possibly a SD given the baselines are reported to be SDs, and high values				
Composite summed subjective VFQ25 questionnaire	NR	NR	NR	NR
VFQ25 questionnaire answers improved slightly (+2%) over 12 months, but were not statistically significant, with no summed category intergroup differences by ANOVA				
Adverse events				
Two deaths (unrelated to study intervention), 1 case of pneumonia. No other significant adverse events.				
Compliance: 90% at least 2 study visits; 96% pill intake compliance gauged.				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	'randomly generated number'
Allocation concealment (selection bias)	Unclear	'The manufacturer assigned a 4-digit randomly generated number to each of the 60 subjects, which in turn was simultaneously linked (internal to Chrysantis, Inc.) to 1 of 3 randomly assigned interventions. Capsule bottles were identified only by the first randomly generated numeric code and randomly dispensed by the Pharmacy Service of Department of Veteran Affars directly to the subjects who was unaware of the specific intervention group' Comment: although it is stated the linking was internal, it is unclear how allocation concealment was undertaken.

Blinding participants and personnel (performance bias), Objective outcomes	Low	'subject who was unaware of the specific intervention group' 'No individual at DVA Medical Center (including the principal investigator) knew the identity of the contents within the bottles with respect to intervention group.'
Blinding participants and personnel (performance bias), Subjective outcomes	Low	'subject who was unaware of the specific intervention group' 'No individual at DVA Medical Center (including the principal investigator) knew the identity of the contents within the bottles with respect to intervention group.'
Blinding outcome assessors (detection bias), Objective outcomes	Low	'Those administering and assessing the outcomes were blinded to group assignment, which was held offsite by the grant administrator.'
Blinding outcome assessors (detection bias), Subjective outcomes	Low	'Those administering and assessing the outcomes were blinded to group assignment, which was held offsite by the grant administrator.'
Incomplete outcome data (attrition bias), Objective outcomes	Low	Numbers and reasons reported, balanced between groups.
Incomplete outcome data (attrition bias), Subjective outcomes	Low	Numbers and reasons reported, balanced between groups.
Selective reporting (reporting bias)	Unclear	Measures of variance presented in figures only, between group differences not analysed, data not reported for Visual function questionnaire.
Other biases	Low	No other biases noted

Akuffo et al

Study details	**Participant details**
Akuffo KO, Nolan JM, Howard AN, Moran R, Stack J, Klein R, et al. Sustained supplementation and monitored response with differing carotenoid formulations in early age-related macular degeneration. Eye 2015;29:902-12. Sabour-Pickett S, Beatty S, Connolly E, Loughman J, Stack J, Howard A et al. Supplementation with three different macular carotenoid formulations in patients with early age-related macular degeneration. 2014 Retina 34:1757–1766, 2014 *Country:* Ireland *Design:* RCT *Number of centres:* one *Funding:* Non-commercial funding. Industrial Orgánica and Macuvision Europe provided the study supplements. *Trial ID:* ISRCTN60816411	*Number of Participants*: Total 67 enrolled. Baselines given for n=52 with 12-month follow-up: 1. Lutein 20 mg + zeaxanthin 2 mg n=17 *2.* Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg n=21 *3.* Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg n=14 3-year results for n=41 (study states 47 completed final study visit, numbers differ for each outcome reported, for primary outcome these were): 1. Lutein 20 mg + zeaxanthin 2 mg n=13 *2.* Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg n=16 *3.* Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg n=12 *Number of eyes:* 67 (47 at 3 year follow-up, one per participant) *Sample attrition/dropout*: n=20 (NB 15 were enrolled but not included in baselines). Drop out from total enrolled not reported per group. *Sample crossovers:* Not reported. *Inclusion criteria:* early AMD (one to eight on AREDS 11-step severity scale, presence of drusen and pigmentary changes) in at least 1 eye (the study eye); corrected distance visual acuity of ≥6/12 in the study eye, no other ocular pathology.

	Exclusion criteria: a recent history (within 3 months of baseline visit) of macular carotenoid supplementation; diabetes mellitus; any visually consequential ocular comorbidity

Intervention details	**Outcomes**
Intervention *1.* Lutein 20 mg + zeaxanthin 2 mg (0.86 mg stated in 3 year follow-up paper) *2.* Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg *3.* Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg *Dose details:* One tablet consumed daily with a meal. Discrepancies between label claim and measured values of the supplements used in this trial have been reported and in particular, Group 1 supplement contained small amounts of MZ (0.30 mg). *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 3 years	*Outcomes (state if primary)* Change in macular pigment ocular density (MPOD) as measured by customized heterochromatic flicker photometry (cHFP) (primary outcome) BCVA, letter contrast sensitivity (basis of power calculation along with MPOD), serum concentrations of macular carotenoids (not data extracted), grade of AMD. *Length of follow-up:* 3 years

Participant characteristics, %				
	Lutein 20 mg + zeaxanthin 2 mg, n=17	**Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg, n=21**	**Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg, n=14**	**P Value**
Age[a], years mean (SD)	65 (7)	64 (9)	70 (8)	0.117
Sex[a], % male	29	38	36	0.851
Smoking history[a] *Current* *Past* *Never*	 12 47 41	 10 33 57	 0 71 29	0.224
CDVA (corrected distance visual acuity)[a], mean (SD)	99 (7)	99 (8)	98 (6)	0.868
Letter contrast sensitivity[b], mean (SD)[c] *1.2 cpd* *2.4 cpd* *6.0 cpd* *9.6 cpd* *15.15 cpd*	n=12 1.87 (0.25) 1.76 (0.30) 1.42 (0.30) 1.14 (0.31) 0.75 (0.32)	n=15 1.71 (0.24) 1.68 (0.31) 1.37 (0.24) 1.06 (0.27) 0.70 (0.37)	n=13 1.75 (0.31) 1.63 (0.31) 1.23 (0.44) 0.94 (0.48) 0.61 (0.48)	
Macular pigment optical density[b], mean (SD) *0.25° eccentricity* *0.5° eccentricity* *1.0° eccentricity* *1.75° eccentricity*	n=13 0.51 (0.29) 0.41 (0.28) 0.30 (0.19) 0.17 (0.11)	n=16 0.50 (0.24) 0.45 (0.21) 0.29 (0.13) 0.15 (0.12)	n=12 0.51 (0.20) 0.39 (0.19) 0.26 (0.17) 0.12 (0.13)	
[a] N=52 with 12-month follow-up. [b]N=47 with 12 month follow-up but N's reported do not equal 47 [c] Letter CS reported at baseline and follow-up was of a different magnitude in the 2014 paper, the reasons for this are unclear.				
Results				
	Lutein 20 mg + zeaxanthin 2 mg, n=13	**Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg, n=16**	**Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg, n=12**	**P Value**

Macular pigment optical density at 36 months, mean (SD), % change from baseline,				
0.25° eccentricity	0.72 (0.24), 41	0.76 (0.23), 52	0.85 (0.25), 67, 0.000	NR
0.5° eccentricity	0.62 (0.26), 51	0.64 (0.20), 42	0.68 (0.20), 74, 0.000	NR
1.0° eccentricity	0.45 (0.19), 50	0.46 (0.15), 59	0.52 (0.16), 100, 0.000	NR
1.75° eccentricity	0.23 (0.19), 35	0.28 (0.11), 87	0.34 (0.14), 183, 0.000	NR
States that the effect on MP levels over time, at any eccentricity, does not differ significantly between supplement groups. P-values only provided for within participant changes Data also presented at 12 and 24 months and percentage change from 12-24 months, 24-36 months, results consistent with end of study results.				
Best-corrected visual acuity	NR	NR	NR	
States that the observed effects over time did not differ between intervention groups				
Letter contrast sensitivity at 36 months, mean (SD), % change from baseline	**Lutein 20 mg + zeaxanthin 2 mg, n=12**	**Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg, n=15**	**Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg, n=13**	**P Value**
1.2 cpd	1.89 (0.16), 1	1.86 (0.18), 9	1.82 (0.20), 4	
2.4 cpd	1.87 (0.17), 6	1.81 (0.21), 8	1.78 (0.21), 9	
6.0 cpd	1.60 (0.15), 13	1.52 (0.25), 11	1.52 (0.27), 24	
9.6 cpd	1.35 (0.16), 18	1.27 (0.34), 20	1.30 (0.22), 38	
15.15 cpd	1.02 (0.23), 36	0.91 (0.38), 30	0.97 (0.25), 59	
States that the observed effects over time did not differ between intervention groups. Data also presented at 12 and 24 months and percentage change from 12-24 months, 24-36 months, results consistent with end of study results.				
Change in grade of AMD, increase of 2 steps along AREDS 11-step scale	1/13	0/16	2/12	P=0.29
When grades were collapsed to 1–3 (representing eyes at low risk of progression to advanced AMD), and AREDS grades 4–8 (representing eyes at high risk of progression to advanced AMD), no study eye in any intervention group progressed from low risk to high risk of progression to advanced AMD over the course of the study period, and no study eye regressed from high risk to low risk of progression to advanced AMD in any intervention group, and no participant progressed to advanced AMD (AREDS grades 9–11). Findings were identical for all three intervention groups.				

Some data from secondary publication: Sabour-Pickett et al. 2014. Supplementation with three different macular carotenoid forumulations in patients with early age-related macular degeneration. Retina, 2014; 34; 1757-66

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Not reported, states 'randomly assigned' only
Allocation concealment (selection bias)	Unclear	Not reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as single-blind but not stated who was blinded. All study supplements were indistinguishable in terms of external appearance and packaged in identical containers, assume participants blinded.
Blinding participants and personnel (performance bias), Subjective outcomes	-	-
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Described as single-blind but not stated who was blinded. All study supplements were indistinguishable in terms of external

		appearance and packaged in identical containers, assume participants blinded.
Blinding outcome assessors (detection bias), Subjective outcomes	-	-
Incomplete outcome data (attrition bias), Objective outcomes	High	Only those participants who completed each study visit were included in analysis, reasons for dropouts between 12 and 36 months not given.
Incomplete outcome data (attrition bias), Subjective -outcomes	-	-
Selective reporting (reporting bias)	Low	Trial register checked
Other biases	Low	No other biases

Peng et al

Study details	**Participant details**
Peng ML, Chiu HF, Chou H, Liao HJ, Chen ST, Wong YC, et al. Influence/impact of lutein complex (marigold flower and wolfberry) on visual function with early age-related macular degeneration subjects: A randomized clinical trial. Journal of Functional Foods 2016;24:122-30. *Country:* Taiwan *Design:* Before and after study (one group) (not RCT as described in title) *Number of centres:* one *Funding:* Non-commercial funding. Lutein complex was provided by Standard Foods Corporation, Taipei *Trial ID:* Not reported	*Number of Participants*: Total 56 1. Lutein complex n=56 *Number of eyes* Not reported *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* Age 30-50 years, soft drusen, early stage AMD (AREDs classification stage-I) *Exclusion criteria:* chronic diseases (cardiovascular disease, cancer, diabetes mellitus), smoking, alcoholism, cataract, glaucoma or other disturbances at the anterior segment of the eyes

Intervention details	**Outcomes**
Intervention *1.* Lutein complex: lutein 12g + zeaxanthin 2 mg *Dose details:* Lutein and zeaxanthin were extracted from a commercially prepared (lyophilized) marigold flower (Tagetes erecta) and wolfberry (Lycium barbarum) to prepare lutein complex. Each serving (60 mL) contained 12 mg of lutein, 2 mg of zeaxanthin, 7 g of carbohydrate, 1 g of fat and 10 mg of sodium *Dose modifications:* Not reported *Concurrent treatment:* Not reported, a run-in period for 2-weeks unable to take any supplements *Duration of treatment:* 5 months	*Outcomes (state if primary)* BCVA Intraocular pressure Photostress recovery Ocular comfort index (questionnaires, assume unvalidated) Macular pigment optical density (MPOD) *Length of follow-up:* unclear as paper is contradictory; either 2 weeks or one month after end of intervention, i.e. 5.5 months or 6 months

BCVA: best corrected visual acuity

Participant characteristics, %			
	Lutein complex, n=56		**P value**
Age, years mean (SD)			

Sex, % male	37.5		
Frequency of eye usage, mean (SD)	12.76 (3.70)		
BCVA (LogMAR), mean (SD)	0.14 (0.09)		
Intraocular pressure	14.47 (1.75)		
Photostress Recovery, second, mean (SD)	41.36 (14.37)		
Ocular comfort Index, mean (SD)	43.28 (10.12)		
MPOD, density units, mean (SD)	0.61 (0.17)		
Results			
At follow-up (2 weeks after end of 5-month intervention)	**Lutein complex 1, n=56**		**P Value**
Frequency of eye usage, mean (SD)	12.38 (3.41)		
BCVA (LogMAR), mean (SD)	0.09 (0.08)[a]		
Intraocular pressure	13.44 (1.98) [a]		
Photostress Recovery, second, mean (SD)	24.98 (12.48) [a]		
Ocular comfort Index, mean (SD)	46.77 (8.32) [a]		
MPOD, density units, mean (SD)	0.65 (0.15)[a]		
[a] p<0.05 vs baseline. Study notes that improvements seen at 5 months (end of intervention) were sustained at 2-weeks follow-up (although some statistically significant differences between 5 month and follow-up apparent)			
Adverse events			
Assessed but not explicitly reported			
Compliance			
average percentage intake of LC beverage was 85.53% at the end of the study			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	y		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?	x		
5. Was the sample size sufficiently large to provide confidence in the findings?	x		
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	x		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	x		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials: JC Fair

Rater #2 initials: EL Fair
Final agreed: Good (upgraded following consistency review)
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Wu et al.

Study details	**Participant details**
Wu J, Cho E, Willett WC, Sastry SM, Schaumberg DA. Intakes of Lutein, Zeaxanthin, and Other Carotenoids and Age-Related Macular Degeneration During 2 Decades of Prospective Follow-up. JAMA Ophthalmology 2015;133:1415-24. *Country:* USA *Design:* prospective cohort study *Number of centres:* not applicable *Funding:* Not commercial funding *Trial ID:* Not reported	*Number of Participants*: Total 102,046 *Number of eyes:* unit of analysis = participant (worst eye used for classification) *Sample attrition/dropout*: Not applicable *Sample crossovers:* Not applicable *Inclusion criteria:* Participants in the prospective cohort studies: Nurses' Health Study (NHS) the Health Professionals Follow-up study (HPFS), age 50-90 years. Participants contributed person-time to the analysis from return of the baseline questionnaire or reaching age 50 years to the confirmed diagnosis of AMD, death, loss to follow-up, or the end of follow-up (May 31, 2010, for the NHS and January 31, 2010, for the HPFS), whichever occurred first. *Exclusion criteria:* participants who did not return the initial food frequency questionnaire (FFQ), left the entire vegetable sections blank or had >70 food items blank, reported implausible dietary intake, prevalent AMD, cancer (except nonmelanoma skin cancer), diabetes mellitus, or cardiovascular disease (disease exclusions: NHS, n = 8536; HPFS, n = 5709), participants who never reported an eye examination during follow-up (NHS, n = 3362; HPFS, n = 4763) and the person-time during any 2-year interval in which a participant did not report an eye examination. AMD case ascertainment: excluded cases with only small hard drusen (<63 μm in diameter)

Intervention details	**Outcomes**
Intervention *1.* Dietary intake of lutein, zeaxanthin and other carotenoids including any supplements of beta-carotene, multivitamins and lycopene – used to calculate an average predicted plasma score *Dose details:* Dietary intakes according to lutein/zeaxanthin quintile at middle of follow-up provided *Dose modifications:* Not applicable *Concurrent treatment:* Not applicable *Duration of treatment:* Not applicable	*Outcomes (state if primary)* Cases of intermediate AMD (includes intermediate drusen, pigment abnormalities, large drusen, noncentral geographic atrophy) and advanced AMD (includes neovascular AMD and central GA) *Length of follow-up:* 26 years (NHS) and 24 years (HPFS)

Participant characteristics, %			
	Intervention , n=102,046		**P value**
Age, years mean (SD)			
Sex, % male	37.8		
Ethnic origin *% White*	Approximately 97%		

Smoking history *Current smoker*	Approximately 8%		
Key comorbidities *Hypertension*	Approximately 37%		
Comments: from age-standardised characteristics in 1996 (mid follow-up)			
Results			
	Intervention , n=102,046		
Incident intermediate AMD, number of cases	1361		
Incident advanced AMD, number of cases	1118		
>96% of advanced cases were neovascular AMD			
Relative Risks of AMD According to Quintiles of Predicted Plasma Carotenoid Scores (comparing extreme quintiles 1 and 5), Multivariate RR (95% CI)[a]			**P value for trend**
Advanced AMD			
lutein/zeaxanthin	0.59 (0.48-0.73)		<0.001
β-Cryptoxanthin	0.73 (0.60-0.89)		0.002
Lycopene	0.93 (0.76-1.13)		0.17
α-carotene	0.69 (0.56-0.84)		<0.001
β-Carotene	0.82 (0.67-1.01)		0.03
food-sourced β-carotene	0.64 (0.52-0.79)		<0.001
Total carotene from food	0.64 (0.51-0.79)		<0.001
total carotenoid index[b]	0.65 (0.53-0.80)		<0.001
Intermediate AMD			
lutein/zeaxanthin	0.93 (0.78-1.12)		0.42
β-Cryptoxanthin	0.85 (0.72-1.02)		0.12
Lycopene	1.04 (0.87-1.23)		0.64
α-carotene	0.94 (0.79-1.12)		0.86
β-Carotene	1.03 (0.85-1.24)		0.92
food-sourced β-carotene	1.02 (0.84-1.24)		0.47
Total carotene from food	0.99 (0.82-1.19)		0.64
total carotenoid index[b]	0.92 (0.77-1.10)		0.80
Comparing extreme quintiles, an inverse association with advanced AMD for predicted plasma carotenoid scores of lutein/zeaxanthin, β-cryptoxanthin, α-carotene, food-sourced β-carotene, total carotene from food, and total carotenoid index was identified. Predicted plasma lutein/zeaxanthin score and total carotenoid index had a linear relationship with advanced AMD within the range of dietary intake. Carotenoids other than lycopene had a similar linear relation (all P for linearity < .05; all P for nonlinearity > .10; graphs not shown). There was no association for any predicted plasma scores for intermediate AMD. [a]Adjusted for age, body mass index, pack-years of smoking, physical activity, current aspirin use, history of hypertension, diabetes mellitus, and cardiovascular disease, dietary variables including alternative healthy eating index (excluding fruits and vegetables), alcohol intake, docosahexaenoic acid, and α-linolenic acid (all in quintiles). In the NHS, models were adjusted for postmenopausal status and menopausal hormone use; in the HPFS, adjustment was made for race. [b]quintile score of each carotenoid summed Calculated intakes followed a similar pattern for advanced AMD and intermediate AMD (not data extracted). Relative Risks of AMD according to primary carotenoid-containing foods (highest intake compared with almost never) also presented but in a figure only, not data extracted. These foods were generally inversely related to advanced AMD, although with variation for cooked/raw forms. For advanced AMD, the effect was statistically significant for total spinach, orange juice, tomato sauce, raw carrots and total carrots. For intermediate AMD, the effect was statistically significant for cooked spinach and orange juice.			
Adverse events			
Not reported			

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	X		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			CD
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?	x		
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Good

*CD, cannot determine; NA, not applicable; NR, not reported

Trieschmann et al., 2007{#592}

Study details	Participant details
Trieschmann M, Beatty S, Nolan JM, Hense HW, Heimes B, Austermann U, et al. Changes in macular pigment optical density and serum concentrations of its constituent carotenoids following supplemental lutein and zeaxanthin: the LUNA study. Experimental Eye Research 2007;84:718-28 *Country:* Germany *Design:* CCT *Number of centres:* assume one *Funding:* Commercial funding *Trial ID:* not reported	*Number of Participants*: total 136 (Lutein and Zeaxanthin 108, control 28) *Number of eyes* total 136 (Lutein and Zeaxanthin 108, control 28) *Sample attrition/dropout*: 13 excluded from analysis in total, 11 in the lutein / zeaxanthin group and 2 in the control group. Failed to attend last follow-up visits. *Sample crossovers:* assume none *Inclusion criteria:* age ≥50 years, no or minimal lens opacity, no history of lutein and/or zeaxanthin supplementation, or supplementation with co-antioxidants, good general health. One eye was selected for investigation, the eye with higher quality autofluorescence image was selected, if this was the same in both eyes the eye with better visual acuity was selected. If there was no difference in visual acuity the right eye was selected. *Exclusion criteria:* eyes with central atrophic spots as well as those with central RPE proliferation or choroidal neovascularisation.
Intervention details	**Outcomes**

Intervention *1.* Lutein and Zeaxanthin supplement *2.* no supplements (control) *Dose details:* 12 mg lutein and 1 mg zeaxanthin, both provided as ester, 120 mg vitamin C, 17.6 mg vitamin E, 10 mg zinc and 40 µg selenium. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 24 weeks	*Outcomes (state if primary)* Serum carotenoid levels (not extracted) Serum lipids and zinc concentration (not extracted) MPOD Compliance (supplement group) *Length of follow-up:* approximately 9 months

Participant characteristics, %			
	Lutein and Zeaxanthin, n=108	**Control, n=28**	**P value**
Age, years mean (SD)	71.5 (7.1)	71 (8.1)	0.77
Sex, % male	62.6	57	0.6
Classification *Features of AMD* *Drusen* *Non-central retinal pigment epithelium proliferation* *Atrophic changes* *Healthy maculae*	 92.6 60 33 7 7.4	 89.2 62 32 6 10.7	
Smoking history *Current*	 4.7	 NR	
MPOD at 0.5° eccentricity, optical density units, mean (SD)	0.504 (0.197)	0.525 (0.189)	0.6
lesion size			
Key comorbidities *Hypertension* *Diabetes mellitus* *Coronary heart disease* *Stroke*	 58.9 10.3 18.7 2.8	 NR NR NR NR	
Results			
	Lutein and Zeaxanthin, n=97	**Control, n=26**	**P Value**
MPOD at 0.5° eccentricity mean (SEM) difference at 9 months follow-up	0.1 (0.009)	0.03 (0.02)	<0.0008
Subgroups			
Comments: reports subgroup analysis on MPOD for females, current cigarette smoking and age, responders and non-responders and with respect to changes in serum lutein and zeaxanthin (data not extracted)			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	Not a randomised study
Allocation concealment (selection bias)	High	No details of allocation to groups
Blinding participants and personnel (performance bias), Objective outcomes	High	Control group did not receive a placebo
Blinding participants and personnel (performance bias),	N/A	

Subjective outcomes		
Blinding outcome assessors (detection bias), Objective outcomes	Low	Outcome assessors were masked
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Similar rates of drop out between group, no ITT analysis
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Although compliance results not reported this was not a specified outcome
Other biases	Low	No other apparent biases.

Arnold et al

Study details	**Participant details**
Arnold C, Winter L, Frohlich K, Jentsch S, Dawczynski J, Jahreis G, et al. Macular xanthophylls and omega-3 long-chain polyunsaturated fatty acids in age-related macular degeneration: a randomized trial. JAMA Ophthalmology 2013;131:564-72. *Country:* Germany *Design:* RCT *Number of centres:* one *Funding:* Commercial funding *Trial ID:* NCT00763659	*Number of Participants*: Total 172 (Supplement group 1 60, supplement group 2 66, placebo 46) *Number of eyes:* Total 172 (Supplement group 1 60, supplement group 2 66, placebo 46) *Sample attrition/dropout*: Total 27. Supplement group 1: 10, supplement group 2: 11, placebo: 6. Reasons: exudative AMD, reduced mobility after prolonged illness, hospitalization, lack of time *Sample crossovers:* assume none *Inclusion criteria:* nonexudative AMD classified according to AREDS. 1 eye of each patient was included. *Exclusion criteria:* central geographic atrophy, exudative forms of AMD, or pronounced opacity in the intended study eye

Intervention details	**Outcomes**
Intervention *1.* Supplement of lutein, zeaxanthin, and ω-3 long-chain polyunsaturated fatty acids (LCPUFAs) *2.* Supplement of lutein, zeaxanthin, and ω-3 long-chain polyunsaturated fatty acids (LCPUFAs), double dose *3.* Placebo *Dose details:* *1.* One capsule containing 10 mg of lutein, 1 mg of zeaxanthin, 100 mg of docosahexaenoic acid (DHA), and 30 mg of eicosapentaenoic acid (EPA) each day, and one placebo capsule, once per day *2.* Two capsules, each containing 10 mg of lutein, 1 mg of zeaxanthin, 100 mg of docosahexaenoic acid (DHA), and 30 mg of eicosapentaenoic acid (EPA) each day 3. Two placebo capsules *Dose modifications:* not reported	*Outcomes (state if primary)* Plasma xanthophyll concentrations and fatty acid profiles (not data extracted) Optical density of the macular pigment (MPOD, stated as primary outcome in trial report) Antioxidant capacity in plasma (not data extracted) *Length of follow-up:* 12 month

Concurrent treatment: Participants instructed to abstain from dietary supplements containing carotenoids and fish oil during the study period *Duration of treatment:* 12 months	

Participant characteristics, %			
	Supplement group 1, n=50	**Supplement group 2, n=54**	**Placebo, n=40**
Age, years mean (SD)	69 (11)	70 (9)	68 (9)
Sex, % male	42	48.1	47.5
Comments: baseline characteristics only reported on participants who remained in the study			
Results			
	Supplement group 1, n=50	**Supplement group 2, n=55**	**Placebo, n=40**
Macular pigment optical density units, degrees^2	0.22[a]	0.25[a]	-0.01[a]
Comments: [a] estimated from figure. States the optical density of the macular pigment increased significantly in group 1 and group 2, whereas the levels in the placebo group remained relatively constant. The double dose of the supplement (group 2) did not lead to a significantly higher optical density of the macular pigment compared with group 1, however the values in both treatment groups differed significantly from those in the placebo group at all measured times.			
Adverse events	NR	NR	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Random number generator
Allocation concealment (selection bias)	Low	States masking was done by an independent scientist who did not have contact with the study participants, sequential numbering used
Blinding participants and personnel (performance bias), Objective outcomes	Low	States participants, care providers, and those assessing outcomes were masked using sequential numbering. Placebo and supplement capsules not outwardly distinguishable
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Low	States participants, care providers, and those assessing outcomes were masked using sequential numbering
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	High	Withdrawals similar between groups, reasons reported, but no ITT analysis
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	Low	Outcomes reported as expected
Other biases	Low	No other bias

Robman et al

Study details	**Participant details**
Robman L, Vu H, Hodge A, Tikellis G, Dimitrov P, McCarty C, et al. Dietary lutein, zeaxanthin, and fats and the progression of age-related macular degeneration. Canadian	*Number of Participants*: Total 254 *Number of eyes* 254 (for progression definition 1; unclear for other outcomes)

Journal of Ophthalmology 2007;42:720-6. *Country:* Australia *Design: cohort study* *Number of centres: assume one* *Funding:* Non-commercial *Trial ID:* not reported	*Sample attrition/dropout*: 2 incomplete data on AMD grading and nutritional status *Sample crossovers:* Not applicable *Inclusion criteria:* early AMD (intermediate drusen, soft drusen and [or] retinal pigment epithelium abnormalities) in the absence of geographic atrophy or neovascular AMD in at least 1 eye. Participants were identified from 2 previous studies *Exclusion criteria:* None stated.

Intervention details	**Outcomes**
Intervention *1.* Dietary intake of lutein and zeaxanthin and fats *Dose details:* Not applicable (13 fruit and 25 vegetable items, each with 10 frequency options, were included in the food frequency questionnaire) *Dose modifications:* Not applicable *Concurrent treatment:* Not reported *Duration of treatment:* Not applicable	*Outcomes (state if primary)* Progression of AMD using 3 definitions: 1. an increase in AMD severity one or more levels in the worse affected eye 2. an increase in AMD severity one or more levels in either eye; or an increase in ≥ 2 steps in the grades of size, total number, area occupied by a lesion, and spread 3. Qualitative (better, worse, same) from macular photographs *Length of follow-up:* average 7 years

Participant characteristics, %			
	Intervention 1, n=252		**P value**
Age, mean (SD) years	N=254 74 (SD 7)		
Sex, % male	47		
Smoking history *Former or current*	 46		
Family history	5		
Comments States those whose AMD had progressed were about 3 years older (odds ratio [OR] for 1-year age increment 1.07, 95% CI 1.03–1.12), more likely to have a family history of AMD (OR 4.8, 95% CI 1.46–15.68), and more likely to be smokers (OR 2.06, 95% CI 1.14–3.71) than nonprogressors.			
Results			
	All participants, n=252		
Cases of progression, % *Definition 1* *Definition 2* *Definition 3*	 24[a] 32 33		
Comments States there was a high level of agreement between definition 2 and 3, with 3.5% cases of disparity [a]of these 15 participants progressed to the late stages of AMD			
	Definition of progression 1	Definition of progression 2	Definition of progression 3
Association between progression of AMD and intake of lutein and zeaxanthin (mg/d)[a]	OR 2.65 95% CI 1.13, 6.22 P=0.02	OR 1.72 95% CI 0.78, 3.78 P=0.18	OR 1.84 95% CI 0.84, 4.00 P=0.13
Association between progression of AMD and intake of energy-adjusted intake of ω-3 fatty acids (g)[a]	OR 1.82 95% CI 0.99, 3.37 P=0.06	OR 1.58 95% CI 0.88, 2.84 P=0.12	OR 1.65 95% CI 0.92, 2.96 P=0.09

[a] Intake as a continuous variable; quintile median of intake and quintiles of intake also reported; the association was significant for:
Definition 1 and Quintile median of lutein and zeaxanthin intake (µg/day) OR 2.89 (95% CI 1.01–8.25) p=0.05;
Definition 1 and Quintile 4 of lutein and zeaxanthin intake (880–1072µg/day) OR 3.30 (95% CI 1.18–9.22) p=0.02;
Definition 3 and Quintile median of ω -3 fatty acid intake (g/day) OR 2.56 (95% CI 1.11–5.91) p=0.03.
Other quintiles reported but not extracted. Multivariate analysis adjusted for age, smoking, AMD family history, source study, and duration of follow-up.
States that no association of AMD progression was observed with the intake of total fat, saturated, polyunsaturated, or monounsaturated fats; trans fatty acids; or ω-6 fatty acids (data not presented).

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	(masked for one outcome)
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Vishwanathan et al

Study details	Participant details
Vishwanathan R, Goodrow-Kotyla EF, Wooten BR, Wilson TA, Nicolosi RJ. Consumption of 2 and 4 egg yolks/d for 5 wk increases macular pigment concentrations in older adults with low macular pigment taking cholesterol-lowering statins. American Journal of Clinical Nutrition 2009;90:1272-9. *Country:* USA *Design:* before and after study	*Number of Participants*: 56 recruited; 52 completed study *Number of eyes* not reported *Sample attrition/dropout*: 4 unable to complete (2 unexpected vacation, 1 stopped taking cholesterol lowering medication, 1 gastrointestinal discomfort); only 37 had MPOD measurements, 3 of which were unable to undergo the measurements, remainder because the device was not calibrated. *Sample crossovers:* not applicable *Inclusion criteria:* over 60 years, taking cholesterol lowering

Number of centres: *Funding:* commercial and non-commercial support *Trial ID:* not reported	medication for at least 3 months, able to undergo blood collection and the willingness to consume foods containing the equivalent of 2 and 4 egg yolks per day for 5 weeks each. *Exclusion criteria:* not stated

Intervention details	**Outcomes**
Intervention *1.* Egg yolk consumption *Dose details:* 4 week lead in; daily foods containing 2 eggyolks for 5 weeks; 4 weeks egg-free period; daily food containing 4 egg yolks for 5 weeks. Food items were provided. Analysis of sample of eggs used (n=25) found lutein concentration was 243 (SE 24) µg and zeaxanthin 230 (SE 31) µg. *Dose modifications:* none *Concurrent treatment:* Those taking multivitamins containing lutein switched to multivitamins without lutein for 4 weeks before study initiation. No restriction of the consumption of lutein and zeaxanthin-containing vegetables or fruit. Instructed to refrain from eating eggs or egg yolk–rich products (other than study eggs or foods) during the entire study period; egg whites were allowed. *Duration of treatment:* 10 weeks (in a 14 week period)	*Outcomes (state if primary)* MPOD Serum lutein and zeaxanthin (not extracted) 7-day diet record (not extracted except for compliance aspect) Serum lipids and lipoprotein (not extracted) *Length of follow-up:* 18 weeks

Participant characteristics, %			
	Egg consumption, n=52		**P value**
Age, years mean (SE)	69 (0.8)		
Sex, % male	40		
Ethnic origin *% White*	 98		
Classification *AMD*	 15		
Smoking history *Never* *Past*[a]	 31 40		
visual acuity			
lesion size			
MPOD, mean (SE) *0.25°* *0.5°* *1°*	N=37 0.55 (0.04) 0.49 (0.04) 0.35 (0.03)		
Hypertension *Diabetes*	56 15		
[a]29% unaccounted for Also reports proportions taking statins and which type, not extracted.			
Results			
	Egg consumption n=37		**P Value**
MPOD, mean (SE) at week 5 (end of 2 egg period) *0.25°* *0.5°* *1°*	 0.55 (0.04) 0.52 (0.04) 0.37 (0.03)		
Comments: states not significant from baseline at any eccentricity			

MPOD, mean (SE) at week 14 (end of 4 egg period) *0.25°* *0.5°* *1°*	 0.60 (0.03) 0.54 (0.03) 0.39 (0.03)		
Comments: Not significant from baseline at any eccentricity. Also reports values for the 4-week wash out period.			
Subgroups			
Reports a post hoc analysis of MPOD for those high at baseline (>0.5 at 0.25°, >0.4 at 0.5°, and >0.35 at 1°) versus those low at baseline (≤0.5 at 0.25°, ≤0.4 at 0.5°, and ≤0.35 at 1°) but not extracted.			

1. Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?		x	
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?		x	
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?		x	
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

Quality Rating: Poor
Small sample, outcome measure in a subgroup only, no blinding of outcome assessor

*CD, cannot determine; NA, not applicable; NR, not reported

Olk et al

Study details	Participant details
Olk RJ, Peralta E, Gierhart DL, Brown GC, Brown MM. Triple combination therapy and zeaxanthin for the treatment of neovascular age-related macular degeneration: an interventional comparative study and cost-effectiveness analysis. Int J Retina Vitreous 2015;1:22. *Country:* USA *Design:* Cohort study	*Number of Participants*: Total 424 (triple therapy 210, triple therapy + zeaxanthin 214) *Number of eyes:* Total 543 (triple therapy 290, triple therapy + zeaxanthin 253) *Sample attrition/dropout*: Not reported *Sample crossovers:* assume none *Inclusion criteria:* classic, minimally classic, and/or occult subfoveal CNV. Only eyes with macular blood, subretinal fluid, and/or retinal

Number of centres: one *Funding:* Commercial *Trial ID:* Not reported	edema with characteristic CNV findings confirmed by fluorescein angiography, optical coherence tomography (OCT) or indocyanine green angiography were included. *Exclusion criteria:* Eyes with greater than 12 optic disc areas of CNV, eyes with less than 20/400 vision, presence of blood if covered greater than 12 disc areas.

Intervention details	**Outcomes**
Intervention *1.* Triple therapy *2.* Triple therapy + zeaxanthin *Dose details:* Triple therapy: i) Intravitreal injection of 1.25 mg of bevacizumab at the initial visit ii) 1000 micrograms of intravitreal dexamethasone within 1 week iii) reduced-fluence photodynamic therapy with verteporfin (PDT), usually within 2 weeks from baseline. Group 2 also received oral zeaxanthin, 20 mg, daily *Dose modifications:* Retreatment was based on the presence of any of the following: subretinal fluid/blood on clinical exam, intraretinal or subretinal fluid on OCT, decrease in vision, late leakage on fluorescein angiography, or occult plaque. Overall, mean number of treatment cycles triple therapy: 2.1 over 1 year and 2.8 over 2 years; triple therapy + zeaxanthin: 1.6 at 1 year and 2.1 over 2 years. *Concurrent treatment:* All patients were taking a multi-vitamin and an AREDS I antioxidant regimen. *Duration of treatment:* 2 years	*Outcomes (state if primary)* Cost utility Visual acuity in study (CNV) eye (not data extracted) Reduction in retinal thickness in study eye (not data extracted) Development of CNV in fellow eye *Length of follow-up:* 12 (90%-94%) to 24 (71%-72%) months

Participant characteristics, %			
	Triple therapy, n=210	**Triple therapy + zeaxanthin, n=214**	**P value**
Age, years mean (range)	82 (50-99)	80 (53-97)	
Sex, % male	27.6	40.7	
Classification *Bilateral CNV* *Unilateral CNV*	 38.1 61.9		
CNV in first eye and drusen in fellow eye, %	76	37.4	
Smoking history			
visual acuity, mean LogMAR	1.12 (20/250)	1.00 (20/200)	
Comments: states that over 90% of fellow eyes had AREDS 3 AMD with drusen >125µm, typically with pigmentary changes.			
Results			
	Triple therapy, n=160[a]	**Triple therapy + zeaxanthin, n=80[a]**	**P Value**
% of fellow eyes that developed CNV	12.5	6.25	P=0.03

Comments: [a] Number of participants with CNV in the first eye and drusen in the fellow eye

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?	x		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			N/A
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?			N/A
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Beatty et al

Study details	Participant details
Beatty S, Nolan JM, Muldrew KA, et al. Secondary outcomes in a clinical trial of carotenoids with co-antioxidants versus placebo in early age-related macular degeneration. Ophthalmology 2013;120:600–6. *Country:* Ireland (UK and Republic) *Design:* RCT *Number of centres:* 2 *Funding:* commercial *Trial ID:* ISRCTN94557601	*Number of Participants*: total 433; supplement 216; placebo 217 *Number of eyes* total 614; supplement 304; placebo 310 *Sample attrition/dropout*: 1 placebo participant deemed ineligible as CNV was present (remained in the analysis) 88 participants withdrew before the 12-month follow-up and these were reported to be distributed equally between the two groups (Figure 1 not available to reviewers). Most withdrew for personal reasons, 5 withdrew because of gastrointestinal disturbances, 7 died, 6 had late AMD in the sole study eye. Also states 252 contributed 1 study eye (group 1) and 181 contributed 2 study eyes (group 2) to the analysis. *Sample crossovers:* none *Inclusion criteria:* ≥50 years. 2 groups: 1) any severity of early AMD in one eye (study eye) and late AMD (neovascular AMD or central GA) in the fellow eye. Visual acuity of at least 0.3 logMAR (≥70 ETDRS letters (equivalent to Snellen 20/40)) in the study eye; 2) features of early AMD in at least 1 eye when both eyes were free of

	late-stage AMD, minimum severity of 20 soft distinct or indistinct drusen in the central macular field, if fewer than 20 drusen, focal hyperpigmentation was required, same visual acuity as group 1. Both eyes included unless visual acuity didn't meet the criteria. *Exclusion criteria:* not stated

Intervention details	**Outcomes**
Intervention *1.* lutein, zeaxanthin, vitamin E, vitamin C, zinc, copper (Ocuvite) *2.* Placebo *Dose details:* lutein 12mg, zeaxanthin 0.6mg, vitamin E 15mg, vitamin C 150mg, zinc oxide 20 mg, copper 0.4mg (daily dose) one tablet twice daily *Dose modifications:* not stated *Concurrent treatment:* not stated *Duration of treatment:* 3 years	*Outcomes* BCVA (primary outcome) Contrast sensitivity Progression of AMD Macular pigment (raman counts, not extracted) Serum levels of antioxidants (not extracted) States publication reports secondary outcomes but BCVA was reported. *Length of follow-up:* average 18.3 months, maximum 3 years (but 12 months was the minimum follow-up (and primary outcome) and when numbers were not affected by large numbers of withdrawals).

Participant characteristics, %			
	Supplements, n=216	**Placebo, n=217**	**P value**
Age, years mean (SD)	NR	NR	
Sex, % male	42.6	42.9	
Smoking history, % *Never* *Ever* *Current*	 37.5 50.0 11.6	 42.9 40.6 16.1	
visual acuity	79.7 (6.6) in 304 eyes	79.9 (6.5) in 310 eyes	
Comments: states no imbalance in any measured variables at treatment assignment			
Results			
	Supplements, n=216	**Placebo, n=217**	**P Value**
BCVA, mean (SD), 12 months	79.7 (8.9) 243 eyes	80.4 (9.8) 250 eyes	NR[a]
Comments: data extracted for 12 months as this is the primary outcome and minimum follow-up of the trial and therefore the longest follow up with large numbers remaining in the study. Data at 36 months was analysed on 30 eyes and 28 eyes for the two groups respectively. [a]data presented in a figure suggests that the BCVA outcomes were not significantly different at any time point until 36 months when there was large drop out and data are unreliable. The text states that there were no differences at 1 year but that data are reported elsewhere, but no reference is available.			
AMD progression at 12 months, % (n/N eyes)	41.7 (96/230)	47.4 (108/228)	NS
Comments: defined as a change in at least 1 stage from a lower to a higher level of severity from baseline			
Severity stage			
Comments: text states that there were no statistically significant differences in the distribution of severity state in the study eyes at any point of follow-up.			
Progression to late AMD (central GA or CNV), n (% of total N eyes[b])	33 (14.3)	39 (17.1)	NS
[b]calculated by reviewer			
Contrast sensitivity: states no statistically differences observed, data not presented but available in online supplement			
Adverse events	NR	NR	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Computerised randomisation
Allocation concealment (selection bias)	Unclear	Not clear from details of randomisation whether allocation was concealed.
Blinding participants and personnel (performance bias), Objective outcomes	Low	Participants and study staff masked. Placebo was indistinguishable from the lutein supplement, in size, colour, smell and taste
Blinding participants and personnel (performance bias), Subjective outcomes	NA	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported
Blinding outcome assessors (detection bias), Subjective outcomes	NA	
Incomplete outcome data (attrition bias), Objective outcomes	High	High drop out rates and not reported clearly by study arm, some reasons given only. States intention to treat
Incomplete outcome data (attrition bias), Subjective outcomes	NA	
Selective reporting (reporting bias)	Low	
Other biases	Low	No other apparent bias

Bartlett et al

Study details	**Participant details**
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;61:1121-7. Protocol published: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC240108/ *Country:* UK *Design:* RCT *Number of centres:* 2 *Funding:* non-commercial and commercial funds *Trial ID:* ISRCTN 78467674	*Number of Participants*: total 30; lutein + vitamins 17; placebo 13 *Number of eyes* not reported *Sample attrition/dropout*: total 5; lutein + vitamins 2; placebo 3 (reasons not stated) *Sample crossovers:* assume none *Inclusion criteria:* no ocular pathology in at least one eye, or no ocular pathology other than age-related maculopathy (soft or hard drusen and areas of increased or decreased pigment associated with these drusen) *Exclusion criteria:* type I and II diabetes, prescribed anti platelet or anti-coagulant medication, concurrent use of nutritional supplements, AMD in one or both eyes.
Intervention details	**Outcomes**
Intervention *1.* lutein combined with vitamins and minerals. *2.* placebo *Dose details:* 6mg lutein, 750µg retinol, 250mg vitamin C, 34mg vitamin E, 10mg zinc, 0.5mg copper. Placebo tablets contained cellulose.	*Outcomes (state if primary)* Contrast sensitivity (primary outcome) Adverse events Compliance (pill count) Change in dietary intake of vitamins and minerals (not extracted) *Length of follow-up:* 9 months

One tablet daily. *Dose modifications:* not reported *Concurrent treatment:* encouraged not to alter their diets, or change their current supplementation regime *Duration of treatment:* 9 months	

Participant characteristics, %			
	Lutein + vitamins, n=15	**Placebo, n=10**	**P value**
Age, years mean (SD)	69.2 (7.8)		ns
Sex, % male	47		ns
Ethnic origin *% White*	100		
visual acuity	0.20 (0.28)	0.08 (0.15)	0.229
Contrast sensitivity, log units	1.36 (0.20)	1.43 (0.20)	
lesion size			
previous treatments *Vitamin C supplements, mg*	88.0 (53.7)	161.1 (71.0)	0.005
Comments: states narratively that there was no significant difference between groups for smoking history or dietary intake of lutein, vitamin E supplements, retinol, or zinc intakes.			
Results			
	Lutein + vitamins, n=15	**Placebo, n=10**	**P Value**
Contrast sensitivity mean change (SD), log units	-0.02 (0.18)	0.07 (0.07)	0.366
Compliance			
Comments: says averaged 94.4% and there was no significant difference between groups.			
Adverse events	0	0	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Used a random number generator.
Allocation concealment (selection bias)	Unclear	Not described
Blinding participants and personnel (performance bias), Objective outcomes	Low	Intervention and placebo tablets were identical in external and internal appearance and taste, and an assessment of the success of masking was undertaken. The manufacturer allocated distinguishing symbols to the packaging which was otherwise identical, Investigators and participants did not know which symbol represents which group.
Blinding participants and personnel (performance bias), Subjective outcomes	N/a	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	Used per protocol population No reasons provided for discontinuations
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	

Selective reporting (reporting bias)	High	Trial record and protocol list outcomes that were not reported.
Other biases	Low	No other apparent biases

Richer et al 2004{#722}

Study details	**Participant details**
Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry 2004;75:216-30. Linked publication, Richer S, Devenport J, Lang JC LAST II: Differential temporal responses of macular pigment optical density in patients with atrophic age related macular degeneration to dietary supplementation with xanthophylls. 2007 Optometry; 78, 213-219 reports secondary analyses on characteristics that increase MPOD *Country:* USA *Design:* RCT *Number of centres:* one *Funding:* commercial and non-commercial funding *Trial ID:* not reported	*Number of Participants*: total 90; Lutein 29; Lutein + others 30; placebo 31 *Number of eyes:* unclear, some results reported by eye (left or right) but unclear numbers. *Sample attrition/dropout*: at 12 months total 14; Lutein 4 (1 lost to follow-up, 1 died, 2 withdrew); Lutein + others 6 (2 lost to follow-up, 4 withdrew); placebo 4 (1 lost to follow-up, 2 died, 1 withdrew) *Sample crossovers:* none *Inclusion criteria:* atrophic AMD, at least one vision-degrading visual-psychophysical abnormality (contrast sensitivity, photo-stress glare recovery deficits, Amsler grid deficits) in one or both eyes, clear non-lenticular ocular media, free of advanced glaucoma and diabetes or any other ocular or systemic disease that could affect central or parafoveal macular visual function. *Exclusion criteria:* undergone recent (6 months) cataract or retinal surgery, taking photosensitizing drugs, taken lutein supplements (previous 6 months)

Intervention details	**Outcomes**
Intervention *1.* Lutein *2.* Lutein and carotenoids, antioxidants, vitamins, minerals (Lutein + others) *3.* Placebo *Dose details:* all 3 groups took 3 capsules twice per day with food. Contained: *1.* lutein 10mg. *2.* lutein + others (lutein 10mg, 2500 IU vitamin A, 15,000 IU natural beta carotene, 1,500-mg vitamin C, 400 IU vitamin D3, 500 IU natural vitamin E, 50mg vitamin B1, 10mg vitamin B2, 70mg vitamin B3, 50mg vitamins B5 and B6, 500mcg vitamin B12, 800mcg folic acid, 300mcg biotin, 500mg Calcium, 300mg magnesium, 75mcg iodine, 25mg zinc, 1mg copper, 2mg manganese, 200mcg selenium, 200mcg chromium, 75mcg molybdenum, 600mcg lycopene, 60mg bilberry extract, 150mg alpha lipoic acid, 200mg N-acetyl cysteine, 100mg quercetin; 100mg rutin, 250mg citrus bioflavonoids, 50mg plant enzymes, 5mg black pepper extract, 325mg malic acid, 900mg taurine, 100mg L-glycine,10mg L-glutathione, 2mg boron. *3.* Placebo maltodextrin	*Outcomes (state if primary)* Monocular visual acuity at distance (logMAR) Visual acuity at near, letters MPOD Contrast sensitivity function Lens opacity cataract scale (not extracted) Photostress recovery (not extracted) Compliance Food frequency questionnaires (not extracted) National Eye Institute VFQ-14 (measures activities of daily living, night driving, glare recovery symptoms) Subjective vision change (not extracted) Retinopathy (AREDS stage change, not extracted) Adverse events Subgroups on AREDS retinal stage (not extracted) Subgroups on temporal responses of MPOD in secondary publication (not extracted) *Length of follow-up:* 12 months

Dose modifications: participants were encouraged not to alter their diets *Concurrent treatment:* not reported *Duration of treatment:* 12 months	

Participant characteristics, %				
	Lutein, n=29	**Lutein + other, n=30**	**Placebo, n=30**	**P value**
Age, years mean (SD)	74.4 (6.4)	73.5 (8.5)	76.1 (6.4)	0.34
Sex, % male	93.1	96.7	96.8	
Smoking history, pack-years	5.2 (14.1)	7.1 (1 7.3)	9.2 (22.6)	0.71
visual acuity, Right (logMAR)	0.359	0.324	0.445	0.19
visual acuity, Left (logMAR)	0.279	0.303	0.286	0.15
Contrast sensitivity, right (log) *3 cc/degree* *6 cc/degree* *12 cc/degree* *18 cc/degree*	 1.55 (0.28) 1.56 (0.35) 1 .I10 (0.34) 0.60 (0.38)	 1.53 (0.23) 1.46 (0.33) 1.06 (0.43) 0.55 (0.34)	 1.62 (0.30) 1.65 (0.28) 1.20 (0.42) 0.64 (0.44)	 0.52 0.14 0.47 0.70
Contrast sensitivity, left (log) *3 cc/degree* *6 cc/degree* *12 cc/degree* *18 cc/degree*	 1.63 (0.24) 1.55 (0.21) 1.07 (0.36) 0.54 (0.42)	 1.51 (0.20) 1 .51 (0.32) 1.08 (0.36) 0.50 (0.29)	 1.62 (0.21) 1.56 (0.25) 1.10 (0.36) 0.51 (0.32)	 0.10 0.80 0.97 0.95
Results				
	Lutein, n=29	**Lutein + other, n=30**	**Placebo, n=30**	**P Value**
Near visual acuity change, letters (95% CI)	5.4 (2.5, 8.2)	3.5 (1.2, 5.8)	-0.2 (-3.0, 2.7)	0.013
Comments: also reports near visual acuity for left and right eyes individually, not extracted.				
Distance visual acuity change, logMAR, Right eye / Left eye (95% CI)	-0.10 (-0.19, -0.01) / -0.03 (-0.09, 0.03)	-0.03 (-0.12, 0.07) / -0.06 (-0.14, 0.03)	-0.14 (-0.30, 0.03) / 0.05 (-0.14, 0.23)	0.01 / NS
Comments: no data for average change across both eyes reported. negative numbers denote improvement				
Contrast sensitivity function				
Comments: Data for various spatial frequencies provided in a figure only (not extracted) and no comparison between groups provided. States significant within-group differences over time for the right eyes, measured at 3, 6, and 12 cycles(cc)/degree, and for the left eye, measured at 6 and 12 cc/degree. For each of these effects, within-group t-tests comparing baseline to final study visit showed the quality of vision improved significantly in both Lutein groups, and especially with a greater effect in Lutein + other group..				
MPOD, mean change, log units / % change at 12 months	0.09 / 36	0.08 / 43	-0.03 / NR	
Comments: reports also the MPOD for individual eyes, not extracted.				
VFQ-14 night driving				
Comments: no data reported, states not significant for any group				
VFQ-14 glare recovery				
Comments: no data reported except baseline, 4-month and 8-month results for the lutein + other group which showed 'trend towards' significant within group change (not extracted).				
Compliance: states 96% of participants took approximately 92% of assigned capsules, there was no difference in compliance among the three groups.				
Adverse events				
Major cardiovascular event or death (any cause)	4	0	3	
Comments: states no significant between-group differences in minor side effects among groups (data not shown)				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States randomisation was applied by consecutive random card, 3-choice, allocation sequence
Allocation concealment (selection bias)	Unclear	No further details
Blinding participants and personnel (performance bias), Objective outcomes	Low	Double masked, capsules for each group prepared by a separate institute who maintained and concealed the blinding and 4-digit allocation codes were sent to the assigned research pharmacist. All personnel were unaware of allocation codes. Participants were provided with opaque capsules of identical appearance in numbered containers.
Blinding participants and personnel (performance bias), Subjective outcomes	Low	As above
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No details
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	No details
Incomplete outcome data (attrition bias), Objective outcomes	Low	Numbers and reasons provided, similar rates of attrition between groups. States that no subjects were excluded from the data analysis, and no missing data were imputed as the estimation method permitted analysis even from those with missing values (unclear if refers to analyses in both papers).
Incomplete outcome data (attrition bias), Subjective outcomes	Low	As above
Selective reporting (reporting bias)	High	Data not presented for all outcomes for each group, see above.
Other biases	Low	No other apparent biases

Dawczynski et al

Study details	**Participant details**
Dawczynski J, Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J. Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: The LUTEGA study. Graefe's Archive for Clinical and Experimental Ophthalmology 2013;251:2711-23. *Country:* Germany *Design:* RCT *Number of centres:* one *Funding:* commercial funding *Trial ID:* NCT00763659	*Number of Participants*: total 172; dose 1 n=60; dose 2 n=66, placebo n=46 *Number of eyes* total 172; dose 1 n=60; dose 2 n=66, placebo n=46 *Sample attrition/dropout*: total 27; dose 1 n=10; dose 2 n=11, placebo n=6 *Sample crossovers:* none *Inclusion criteria:* non-exudative AMD in at least in one eye, classified according to AREDS classification; aged 50-95 years, no lutein, zeaxanthin or omega-3 fatty acid supplementation in last 6 months. One eye only was included. *Exclusion criteria:* central geographic atrophy, exudative forms of AMD (marked RPE proliferations or neovascularisation in the study eye); pronounced opacity in the intended study eye, subretinal haemorrhages, missing fixatino, optic nerve disease, unstable glaucoma, history of retina-vitreous surgery, advanced cataract.
Intervention details	**Outcomes**

Intervention	*Outcomes (state if primary)*
1. Dose 1 (10mg lutein, 1mg zeaxanthin, 225mg fish oil [of which 100mg docosahexaenoic acid, DHA, and 30mg eicosapentaenoic acid, EPA], antioxidants [60mg vitamin C, 20mg vitamin E, 10mg zinc, 0.25mg copper]) *2.* Dose 2 (20mg lutein, 2mg zeaxanthin, 500mg fish oil [of which 200mg DHA, and 60mg EPA], antioxidants [120mg vitamin C, 40mg vitamin E, 20mg zinc, 0.5mg copper]) *3.* Placebo capsule (no details). *Dose details:* As above *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 12 months	BCVA (ETDRS, distance 4 metres, logMAR) AREDS classification of reading letters MPOD Food questionnaire (not extracted) *Length of follow-up:* 12 months

Participant characteristics, %				
	Dose 1, n=60	**Dose 2, n=66**	**Placebo, n=46**	**P value**
Age, years mean (SD)	70 (10)			
Sex, % male	45.3			
Classification, % *AREDS stage 1* *AREDS stage II* *AREDS stage III* *AREDS stage IV*	 NR NR 40.1 15.1			
Smoking,%	31.4			
BCVA, logMAR (SD)	0.134 (0.17)	0.104 (0.14)	0.129 (0.16)	See below
Comments: placebo vs dosage 1 p=0.895; placebo vs dosage 2 p=0.43; dosage 1 vs dosage 2 p=0.338				
BCVA absolute reading letters	48.7 (8.7)			
MPOD parameters, mean (SD) *Mean Optical density* *Max Optical density* *Volume* *Area*	 0.236 0.581 1.412 6.027	 0.227 0.555 1.41 6.12	 0.227 0.577 1.456 6.322	
Key comorbidities, % *Hypertension* *Diabetes Type 2* *Hypercholesterolemia* *Lipid reducing medication*	 74.4 12.8 51.2 43.2			
Results				
	Dose 1, n=50	**Dose 2, n=55**	**Placebo, n=40**	**P Value**
BCVA, logMAR at 12 months	0.104 (0.18)	0.064 (0.16)	0.127 (0.16)	See comments
Comments: placebo vs dosage 1 p=0.526; placebo vs dosage 2 p=0.063; dosage 1 vs dosage 2 p=0.232				
BCVA change in reading letters at 12 months, mean (SD)	1.46 (2.8)	2.02 (3.1)	0.08 (2.8)	See comments
Comments: placebo vs dosage 1 p=0.038; placebo vs dosage 2 p=0.006; dosage 1 vs dosage 2 p=0.354				
MPOD parameters, mean (SD) *% change* *Mean Optical density* *Max Optical density* *Volume* *Area*	 7 8 20 12	 10 10 28.4 13	 -2 -1 -2 -1	

MPOD parameters, mean (SD) at 12 months				
Mean Optical density	0.252	0.252	0.223	
Max Optical density	0.625	0.606	0.574	
Volume	1.677	1.725	1.425	
Area	6.689	6.82	6.272	
Comments				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States 'randomly assigned' no further details
Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as double blind, no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	Differential drop out between groups, numbers but no reasons given, not included in the analysis set.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Outcomes reported in trial record were reported
Other biases	Low	No other apparent biases

Garcia-Layana et al.

Study details	**Participant details**
García-Layana A, Recalde S, Alamán AS, Robredo PF. Effects of lutein and docosahexaenoic acid supplementation on macular pigment optical density in a randomized controlled trial. Nutrients 2013;5:543-51 *Country:* Spain *Design:* RCT *Number of centres:* assume one *Funding:* commercial and non-commercial funding *Trial ID:* not reported	*Number of Participants*: total 44; lutein + DHA 23; placebo 21 *Number of eyes:* not reported *Sample attrition/dropout*: assume none *Sample crossovers:* assume none *Inclusion criteria:* early AMD (stage II-III AREDS classification: small/intermediate drusen and large drusen with/without pigment changes) *Exclusion criteria:* history of lactose intolerance, liver, kidney, or pancreatic disease, anaemia, insulin-dependent diabetes, hyperlipoproteinemia or alcoholism; current use of antihistamine drugs, steroids or nonsteroidal anti-inflammatory drugs; use of any nutrient supplement (< 2 months) or carotenoid supplements (< 6 months).
Intervention details	**Outcomes**
Intervention *1.* lutein, zeaxanthin, docosahexaenoic acid (DHA)	*Outcomes (state if primary)* Macular pigment ocular density (MPOD) (primary

2. placebo *Dose details:* intervention two tablets daily of 12 mg of lutein, 0.6 mg of zeaxanthin, 280 mg of DHA Placebo, containing sugar: two tablets daily. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 12 months	outcome) BCVA Contrast sensitivity Macular thickness (not extracted) *Length of follow-up:* 12 months

Participant characteristics, %			
	Lutein/zeaxanthin/DHA, n=23	**Placebo, n=21**	**P value**
Age, years mean (SEM)	69.2 (7.8)	67.8 (9.2)	
Sex, % male	43.5	38.1	
visual acuity, ETDRS letters, mean (SEM)	76.4 (8.7)	78.3 (6.2)	
lesion size			
MPOD, mean (SEM)	0.291 (0.016)	0.286 (0.017)	P>0.05
Contrast sensitivity letters, mean (SEM)	25 (5)	26 (5)	
Results			
	Lutein/zeaxanthin/DHA, n=23	**Placebo, n=21**	**P Value**
MPOD at 1 year, mean (SEM) units	0.453 (0.028)	0.345 (0.026)	P<0.01
MPOD change at 1 year, mean units	0.162	0.059	p<0.05
ETDRS letters, mean (SEM) at 1 year	74.3 (9.2)	75.9 (5.8)	ns
Contrast sensitivity letters, mean (SEM) at 1 year	26 (5)	26 (6)	ns
Adverse events	Not reported	Not reported	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Randomization was done by coin toss by the ophthalmologist who enrolled people into the study.
Allocation concealment (selection bias)	High	As above, not concealed.
Blinding participants and personnel (performance bias), Objective outcomes	Low	Placebo and intervention tablets had same look, smell, taste and packaging. Patients and ophthalmologists were blinded to study group until the end of the study
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	

Incomplete outcome data (attrition bias), Objective outcomes	Low	No attrition
Incomplete outcome data (attrition bias), Subjective outcomes	N/a	
Selective reporting (reporting bias)	Low	All outcomes reported as stated
Other biases	Low	No other apparent biases

Wolf-Schnurrbusch et al

Study details	**Participant details**
Wolf-Schnurrbusch UE, Zinkernagel MS, Munk MR, Ebneter A, Wolf S. Oral Lutein Supplementation Enhances Macular Pigment Density and Contrast Sensitivity but Not in Combination With Polyunsaturated Fatty Acids. Investigative Ophthalmology & Visual Science 2015;56:8069-74. *Country:* Switzerland *Design:* RCT *Number of centres:* one *Funding:* Novartis and non-commercial funding *Trial ID:* NCT00563979	*Number of Participants*: Total 79 1. Lutein n=40 2. Lutein + omega n=39 *Number of eyes* 79 *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* age over 50 years with early or intermediate AMD (ref provided). Only one eye of each patient included, the eye with more advanced AMD changes. *Exclusion criteria:* other eye disease in the study eye, opacities of optical media precluding fundus photography.

Intervention details	**Outcomes**
Intervention *1.* Lutein 10 mg *2.* Lutein 10 mg + Omega-3 fatty acid (DHA/EPA) 160 mg (130 mg) *Dose details:* The ingredients of the supplement in both arms also included: vitamin C 10mg, vitamin E 20 mg, niacin / vitamin B3 10mg, copper 0.25 mg, zinc 10 mg, zeaxanthine 1 mg. *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 6 months	*Outcomes (state if primary)* Contrast sensitivity and MPOD at 6 months (primary outcomes) Change in contrast sensitivity, MPOD, BCVA (EDTRS charts); compliance at 12 months *Length of follow-up:* 12 months

BCVA: best corrected visual acuity; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ETDRS: Early Treatment Diabetic Retinopathy study; MPOD: macular pigment ocular density

Participant characteristics, %			
	Lutein, n=40	**Lutein + Omega, n=39**	**P value**
Age, years mean (range)	75.2 (54–88)	72.5 (54–88)	>0.05
Sex, % male	45	39	>0.05
Classification, % *Early AMD* *Intermediate AMD*	 55 45	 46 54	
Smoking history	NR per group	NR per group	
visual acuity, ETDSR letters, mean (SD)	79.7 (7.4)	78.6 (10.5)	>0.05
Contrast sensitivity score, mean (SD)	1.286 (0.245)	1.227 (0.273)	>0.05

MPOD, density units, mean (SD)	0.543 (0.192)	0.564 (0.205)	>0.05
Results			
	Lutein, n=40	**Lutein + Omega, n=39**	**P Value**
MPOD, density units, mean (SD) at 6 months (primary endpoint)	0.66 (0.18)	0.60 (0.22)	P<0.01
MPOD, density units, mean (SD) at 12 months	0.61[a]	0.59[a]	
The MPOD levels over the entire study period of 1 year showed a relatively slow decrease. The differences between the groups were significant (ANOVA, P < 0.01). [a] Estimated from figure			
Contrast sensitivity score, mean (SD) at 6 months (primary endpoint)	1.69 (0.22)	1.30 (0.25)	P < 0.01
Contrast sensitivity score, mean (SD) at 12 months	1.32[a]	1.3[a]	
[a] Estimated from figure The CS score decreased after cessation of the supplementation after 6 months in the lutein group, whereas no changes were observed in CS in the lutein+omega group. The differences between the groups were significant (ANOVA, P < 0.01).			
BCVA letter score, ETDRS letters, mean (SD) at 6 months	79 (7)	80 (11)	
BCVA letter score, ETDRS letters, mean (SD) at 12 months	81 (5)	80 (10)	
Adverse events			
No subject developed any systemic or ocular disorders during the study period.			
Compliance: States all participants took supplements daily for 6 months			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Not reported, states randomised only
Allocation concealment (selection bias)	Unclear	Not reported, states randomised only
Blinding participants and personnel (performance bias), Objective outcomes	High	Open label
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	High	Open label
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Not reported
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	Low	Outcomes as reported on clinical trials register
Other biases	Low	No other biases

Piermarocchi et al

Study details	**Participant details**
Piermarocchi S, Saviano S, Parisi V,	*Number of Participants*: 145: Treatment group 103; controls 42 (text

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 2012;22:216-25. *Country:* Italy *Design:* RCT *Number of centres:* not reported (multicentre) *Funding:* states none *Trial ID:* not stated	also states 102 and 43) *Number of eyes* 145: Treatment group 103; controls 42 (or 102 and 43). States the eye with the best visual acuity was selected. When both eyes had the same visual acuity, the right eye was chosen for final analysis *Sample attrition/dropout*: withdrawals total 17: treatment group 14, control 3. Excluded from final analysis 35 (treatment group 19, control 16). Discontinued intervention (treatment group 20, control 17). *Sample crossovers:* assume none *Inclusion criteria:* aged between 55 – 80 years; dry AMD in at least one eye having extensive (drusen area) intermediate (≥63 mm, <125 mm) drusen; and at least one large (≥125 mm) drusen or geographic atrophy not involving the macula centre; BCVA in trial eye ≥20/32 (74 letters of ETDRS), no conditions that limit the view to the fundus (e.g., vitreous haemorrhage, cataracts, epiretinal membrane) agree to take only the nutritional supplement provided. *Exclusion criteria:* advanced AMD in one or both eyes; ocular disease that causes irreversible reduction of visual acuity; significant opacity of the dioptrical media; evolved cataract; lens opacity and score 4+ (Lens Opacity Classification System II), surgery within last 2 months; insufficient pupil dilation; already received laser treatment of the posterior pole for any other reason; macular changes not attributable to AMD.

Intervention details	**Outcomes**
Intervention *1.* nutritional supplementation with carotenoids (lutein, zeaxanthin, astaxanthin), oligoelements and antioxidant vitamins *2.* no nutritional supplements (control) *Dose details:* vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), astaxanthin (4 mg). 1 tablet a day, concurrent with food intake at the same time every day. *Dose modifications:* encouraged not to alter diets or change supplementation regimen *Concurrent treatment:* not reported *Duration of treatment:* 2 years	*Outcomes (state if primary)* mean changes in BCVA (primary outcome) contrast sensitivity National Eye Institute visual function questionnaire (NEI VFQ-25) score Compliance Adverse events *Length of follow-up:* 24 months

Participant characteristics, %			
	Supplementation, n=103	**Control, n=42**	**P value**
Age, years mean (SD)	72.5 (6.8)	72.6 (7.5)	0.30
Sex, % male	39.8	40.7	
Smoking history, % *Current* *Former* *Never*	 16.5 42.7 40.7	 16.6 28.5 54.7	 0.71 0.34 0.4
Mean (SD) BCVA (ETDRS score)	82 (5.7)	81.5 (5.9)	0.67
Mean (SD) contrast sensitivity (letter score)	32.1 (4.4)	31.8 (4.8)	0.34

Key comorbidities, %			
Diabetes	3.8	0	0.23
Hypertension	15.5	0	0.1
Heart disease	12.6	2.3	0.15
Other	30	0	0.06
Cataract surgery	30	0	0.07
Glaucoma	7.7	0	0.2
Diabetic retinopathy	0	0	-
Family history			
Mean (SD) NEI VFQ-25	81.6 (13.6)	82.9 (13.3)	0.56
Comments: also reports baseline Cataract (LOCS-III rating) and Nuclear opalescence (Right and Left eye). Not extracted.			
Results			
	Supplementation, n=84	**Control, n=26**	**P Value**
Mean (SD) BCVA at 24 months, ETDRS letter score[a]	81.4 (7.2)	76.8 (8.9)	P=0.003
Mean change in BCVA at 24 months, ETDRS letter score	–0.02 (95% CI –1.42 to 1.36)	-4.18 (95% CI –7.34 to –1.01)	p=0.008
% improved BCVA at 24 months	59.1	NR	
% maintained BCVA at 24 months	21.1	NR	
% worsened BCVA at 24 months	19.7	NR	
[a]Values in figure appear to differ from those in text Comments: reports that the ratio of % with a positive outcome (loss of ≤ 5 letters) was RR of 0.46 (0.23, 0.90)			
Mean (95% CI) change in contrast sensitivity at 24 months	2 (0.80, 3.19)	-1.15 (–2.86, 0.54)	P=0.01
% improved CS at 24 months	39.4	NR	
% maintained CS at 24 months	49.3	NR	
% worsened CS at 24 months	11.2	40.9	
Comments: states the RR of 3 or more letter visual loss was 0.26 (95% CI 0.11 to 0.59) in the treatment group.			
Development of CNV, %	(n=103) 12.7	(n=43) 9.3	P=0.760
Comments			
NEI VFQ-25 composite score, mean (SD) 24 months	82.1[a] (15.9)	74.2[b]	NR
NEI VFQ-25 composite score, mean (95% CI) change, 24 months	3.6 (0.50, 6.81)	-8.7 (-16.54, -0.97)	NR
[a]reported in text, 85.2 calculated by reviewer, likely difference in numbers participants at baseline and follow-up [b]calculated by reviewer Comments: says most subscale scores decreased by at least of 10 points at the end of 2 years follow-up (the RR was 0.16 [95% CI 0.38 to 0.89]), compared with scores in the control group			
Compliance: 95% took approximately 92% of their assigned tablets. The rate of compliance with the study protocol for treatment and examinations was high and similar for both groups. There was no difference in compliance between the 2 groups (p=0.57).			
Adverse events (significant systemic or ocular adverse events related to the nutritional supplementation)	0		
Adverse reaction leading to study withdrawal or discontinuation	0	0	
Comments			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation	Low	States the study coordinator allocated study

(selection bias)		numbers sequentially, as participants were enrolled. Participants were then randomly allocated to the treatment group. A permuted blocks allocation scheme was used to perform this random allocation.
Allocation concealment (selection bias)	Low	The allocation list was stored at a remote site.
Blinding participants and personnel (performance bias), Objective outcomes	High	Open label study, the drug was administered by a physician who had no other role in the study, but the physician was unmasked.
Blinding participants and personnel (performance bias), Subjective outcomes	Low	HRQoL measure was administered by trained study-site personnel who were masked to treatment assignment.
Blinding outcome assessors (detection bias), Objective outcomes	Low	An independent physician was assigned the role of masked evaluator.
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	No details of outcome assessment
Incomplete outcome data (attrition bias), Objective outcomes	High	Not all participants were included in the final analyses (treatment group 19, control 16) and differential drop-out rates between groups (treatment group 14, control 3).
Incomplete outcome data (attrition bias), Subjective outcomes	High	As above
Selective reporting (reporting bias)	Low	All outcomes reported
Other biases	Low	No other apparent bias

Fatty acids and antioxidants

Reynolds et al

Study details	**Participant details**
Reynolds R, Rosner B, Seddon JM. Dietary omega-3 fatty acids, other fat intake, genetic susceptibility, and progression to incident geographic atrophy. Ophthalmology 2013;120:1020-8 *Country:* USA *Design:* cohort study *Number of centres:* *Funding:* non-commercial funding *Trial ID:* none reported	*Number of Participants*: total 2531 (progressors 403; non-progressors 2128) *Number of eyes* total 4165 (progressors 525; non-progressors 4165) *Sample attrition/dropout*: not applicable *Sample crossovers:* not applicable *Inclusion criteria:* previously participated in the AREDs study; assigned a grade of no AMD, early AMD, intermediate AMD, or 2 forms of advanced or late stage AMD (GA and neovascular) – definitions for these five types were reported. *Exclusion criteria:* Exclusion criteria for the original AREDs study would have applied. Also those with intake < 600 calories and ≥4200 (men) or ≥3200 (women) were excluded from the analysis. Eyes with the end point (grade 4 or 5) at baseline were excluded from the analysis.
Intervention details	**Outcomes**
Intervention *1.* dietary omega-3 fatty acids and other fat intake	*Outcomes (state if primary)* Progression to GA

Dose details: Diet details from food frequency questionnaires, measurements of total fat, saturated fat, total polyunsaturated fatty acids, monounsaturated fat, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), combined long chain polyunsaturated fatty acids DHA and EPA, linolenic, and linoleic acid (an omega-6 fatty acid). *Dose modifications:* not applicable *Concurrent treatment:* antioxidant and/or zinc as per group allocation in the AREDs study *Duration of treatment:* not stated	*Length of follow-up:* up to 12 years

Participant characteristics, %			
	Progressors, n=403	**Non-progressors, n=2128**	**P value**
Age, <70 years, n (%) *Age, ≥ 70 years, n (%)*	185 (46) 218 (54)	1290 (61) 838 (39)	 <0.0001
Sex, % male	48	44	0.48
Classification, grade in eye 1,1/1,2/2,2 1,3/2,3/3,3 1,4/2,4/3,4 1,5/2,5/3,5	 5 72 10 13	 57 30 1 12	<0.0001
Smoking history[a] *Never* *Past* *Current*	 43 50 6	 47 47 5.5	
Baseline characteristics for the entire cohort not reported, only those within the progressed and non-progressed groups (the results groups). [a]Calculated by reviewer, p values presented in paper for <70 and ≥70 years subgroups. Genetic subgroups reported not extracted Comments: states those with intermediate AMD in the worse eye, or GA in one eye and a non-advanced fellow eye, were at increased risk of progression to GA. Progressors tended to be older, were more likely to have smoked (among those less than 70 years of age), and had higher BMI than non-progressors. CFH variants, ARMS/HTRA1, C3 and CFI were all significantly associated with increased risk of progression. CFB, C2, and LIPC were all significantly associated with decreased risk of progression.			
Results			
	All participants, n=2531 (4165 eyes)		**P Value**
Progression to GA, n	403 (525 eyes)		
Non-progression to GA	2128		
Participants progressing to GA over 5 years, %	8.1		
Participants progressing to GA over 10 years, %	16.9		

Controlling for age and initial eye grade, progressors had significantly higher intake of monounsaturated fat (P- trend= 0.02) that non-progressors. Progressors had a lower intake of docosahexaenoic acid (DHA) (P-trend = 0.03)

In multivariate analysis, controlling for baseline AMD grade, sex, age, AREDS treatment, education, smoking, BMI, and caloric intake there was a significant trend for reduction in risk of progression to GA with increasing intake of DHA (P-trend= 0.03). There was also a trend for increased risk of progression with increasing intake of monounsaturated fat (P-trend= 0.05).

In multivariate analysis, controlling for above covariates and genetic variants there was a significant trend for reduction in risk of progression to GA with increasing intake of DHA (P-trend= 0.008, HR 0.68 for quintile 1 vs quintile 5 (95% CI 0.48 – 0.94)). There was also a significant trend between a combination of DHA + EPA intake and reduced risk of progression with this model (P=0.02).

Other, non-significant trends were reported but have not been extracted.

In multivariate analysis, controlling for baseline AMD grade, demographic, environmental factors, DHA and all 8 genetic variants there was a significant protective effect of DHA among people with the ARMS2/HTRA1homozygous risk genotype (HR = 0.4, P = 0.002) while no association was seen among individuals with the homozygous non-risk genotype (HR = 1.0, P = 0.9, P– interaction = 0.05). In contrast, there was a significant protective effect of DHA among individuals with the CFH:Y402H homozygous non-risk genotype (HR = 0.5, P = 0.02), but no significant effect of DHA among those with the CFH:Y402H homozygous risk genotype.

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			CD
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Fair/poor

*CD, cannot determine; NA, not applicable; NR, not reported

Feher et al.

Study details	Participant details
Feher J, Kovacs B, Kovacs I, Schveoller M, Papale A, Balacco Gabrieli C. Improvement	*Number of Participants*: total 106; 51 phototrop; 55 placebo

of visual functions and fundus alterations in early age-related macular degeneration treated with a combination of acetyl-L-carnitine, n-3 fatty acids, and coenzyme Q10. Ophthalmologica 2005;219:154-66. *Country:* Hungary *Design:* RCT *Number of centres:* one *Funding:* not reported *Trial ID:* not reported	*Number of eyes* used the most affected eye at baseline for the study eye (phototrop 48; placebo 53) but secondary analysis also undertaken on the fellow (less affected) eye (phototrop 43; placebo 45). *Sample attrition/dropout*: interrupted study medication total 5. Phototrop 3 (1 no post-baseline efficacy data, 2 adverse events unrelated to treatment); placebo 2 (1 no post-baseline efficacy data and 1 adverse events unrelated to treatment) *Sample crossovers:* assume none *Inclusion criteria:* early bilateral AMD, BCVA between 0.8 – 0.4 (Snellen chart) in the most affected eye; 55-70 years, Caucasian origin; agree to discontinue current vitamin regimen. *Exclusion criteria:* late AMD (GA or macular scarring); exudative retinal diseases; significant corneal opacity or cataracts; inherited retinal dystrophies; unstable glaucoma; retinal detachment; optic nerve disease; ocular inflammatory disease; refractive errors (defined); significant cardiovascular or cerebrovascular diseases; severe hepatic, renal, pulmonary, thyroid, HIV, hepatitis B or C or other immunosuppressive disorders; practising vegetarian or abnormal diet; poor general health; known hypersensitivities to study compounds; use of corticosteroids, phenothiazine or antimalarial drugs within 1 month prior to baseline or during the 12 month study period.

Intervention details	**Outcomes**
Intervention *1.* Phototrop (acetyl-L-carnitine, n-3 fatty acids, co-enzyme Q10) *2.* Placebo (soy oil) *Dose details:* two oral capsules per day. Phototrop: 100mg acetyl-L-carnitine, 530mg n-3 fatty acids, 10mg co-enzyme Q10). Placebo: equal quantities of soy oil. *Dose modifications: assume none* *Concurrent treatment:* any concomitant treatments were recorded. Not to take any AMD medications, corticosteroids, phenothiazine or antimalarial drugs (as above) *Duration of treatment:* 12 months	*Outcomes (state if primary)* Visual field mean defect (reciprocal of visual field mean sensitivity) (primary outcome) Visual acuity (Snellen, ETDRS, logMAR) Foveal sensitivity Fundus alterations (drusen-covered area)(not stated as a secondary outcome but results reported) Compliance (pill count) *Length of follow-up:* 12 months

Participant characteristics, %			
	Phototrop, n=51	**Placebo, n=55**	**P value**
Age, years mean (SD)	63.5 (2.45)	63.0 (2.95)	
Sex, % male	33		
Ethnic origin *% White*	100		
Smoked tobacco, %	15.1		
visual acuity of study eye, Snellen[a]	0.55	0.55	
Mean foveal sensitivity[a] *of study eye*	31.8	31.2	
[a]estimated from figure			
Results			
	Phototrop, n=48	**Placebo, n=53**	**P Value**

Mean (SD) change from baseline in visual field mean defect study eye (study eye) at 12 months, dB	0.77 (2.57)	-0.31 (3.70)	States not significant
Change in visual field mean defect, study eye (study eye) at 12 months, % *Improved or unchanged* *Deteriorated*	 98 2	 83 17	 0.006[a]
Comments: a ± 2.0 dB range for long-term fluctuation (no change) was applied. [a]The odds ratio between groups was 10.93			
Mean foveal sensitivity at 12 months (study eye)[b]	32.8	31.0	
Comments: states no significant difference in the mean change in foveal sensitivity between groups at 12 months (p>0.05). [b]estimated from figure, as baseline figure was also an estimate, not calculated the mean change.			
Change in foveal sensitivity at 12 months (study eye) *Improved or unchanged, %* *Deteriorated*	 69 31	 49 51	 0.035[c]
Comments: [c]the OR between groups was 2.29			
Mean visual acuity at 12 months (study eye), Snellen[d]	0.6	0.52	
Change in visual acuity, Snellen, at 12 months (study eye) *Improved or unchanged, %* *Deteriorated*	 77 23	 55 45	 0.015[e]
Mean (SD) change in visual acuity at 12 months, logMAR (study eye)	0.009 (0.23)	-0.14 (0.23)	Says not significant
Change in visual acuity, logMAR, at 12 months (study eye) *Improved or unchanged, %* *Deteriorated*	 75 25	 55 45	 0.027[f]
[d]estimated from figure, as baseline figure was also an estimate, not calculated the mean change. [e]the OR was 2.78 [f]the OR was 2.48 Comment: states that the mean change in visual acuity using the Snellen chart was significant between the two groups at 3 months (results not extracted) but no data are provided for longer follow-up even though the narrative states that the improvement in the phototrop group was maintained and there was a deterioration in the placebo group by the end of the study period. Also says visual acuity using ETDRS shows a similar trend, however, with no significant differences at any time point.			
	Phototrop, n=43	**Placebo, n=45**	**P Value**
Mean (SD) change from baseline in visual field mean defect (fellow eye) at 12 months, dB	0.53 (2.36)	-0.39 (1.52)	0.004
Change in visual field mean defect, (fellow eye) at 12 months, % *Improved or unchanged* *Deteriorated*	 100 0	 89 11	 0.031
Comments: a ± 2.0 dB range for long-term fluctuation (no change) was applied. Also state that data were modified by adding 0.5 to each value to allow computation of the OR which was 11.81 (says 6.61 in the text). States that changes on the secondary outcomes (visual acuity measures) were not significant, no data presented.			
Additional outcome of fundus alteration, (study eye)	**Phototrop, n=46**	**Placebo, n=52**	**P Value**

Drusen-covered area (ratio of drusen area at 12 months to screening (SD))	0.85 (0.39)	1.11 (0.65)	0.045
The drusen area decreased by 15% in the phototrop group while it increased by 11% in the placebo group.			
Drusen-covered area *Improved or unchanged* *Deteriorated*	 83 17	 75 25	 0.25[g]
[g]the OR was 1.58			
Additional outcome of fundus alteration, (fellow eye)	**Phototrop, n=46**	**Placebo, n=44**	**P Value**
Drusen-covered area (ratio of drusen area at 12 months to screening (SD))	0.77 (0.43)	1.13 (0.77)	0.017
The drusen area decreased by 23% in the phototrop group while it increased by 13% in the placebo group.			
Drusen-covered area *Improved or unchanged* *Deteriorated*	 91 9	 70 30	 0.01[h]
[h]the OR was 4.40			
Adverse events	2	1	
Comments: state unrelated to treatment, no further details Says compliance was 80% or more			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Computer produced randomisation schedules generated by statisticians at a contract research organisation
Allocation concealment (selection bias)	Unclear	States was masked but no details of masking
Blinding participants and personnel (performance bias), Objective outcomes	Low	Both products were indistinguishable in appearance.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported, described as double blind but no further details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Low	Data analysed for all who received at least one dose and one return visit, described as ITT population but is modified ITT. Small numbers or drop outs and reasons given.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes stated were reported
Other biases	Low	No other biases

Souied et al., 2013{#90}

Study details	**Participant details**
Souied EH, Delcourt C, Querques G,	*Number of Participants*: total 300: DHA 150; placebo 150

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;120:1619-31. *Country:* France *Design:* RCT *Number of centres:* one *Funding:* commercial funding *Trial ID:* ISRCTN98246501.	*Number of eyes* total 300: DHA 150; placebo 150 *Sample attrition/dropout*: Total 63: DHA 29 (12 AE, 10 consent withdrawn, 4 disease worsening, 3 other), 3 of 29 were deaths unclear where these are counted); Placebo 34 (7 AE, 19 consent withdrawn, 1 disease worsening, 7 other), 6 of 34 were deaths unclear where these are counted); *Sample crossovers:* none *Inclusion criteria:* early age-related maculopathy (any drusen or reticular pseudodrusen with or without pigmentary changes) in the study eye, neovascular AMD in the fellow eye; age ≥55 years to <85 years, visual acuity ≥ +0.4 logMAR units in the study eye *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 (e.g cancer, stroke), known allergy to fish oil, fluorescein, indocyanine green, anticoagulant therapy or bleeding tendency, treatment (within 6 months) with nutritional supplements (containing longchain omega-3 fatty acids or α-tocopherol acetate), any concomitant nutritional supplement, participation in a clinical trial in 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, not covered by the French National Health system.

Intervention details	**Outcomes**
Intervention *1.* docosahexaenoic acid (DHA) *2.* Placebo *Dose details:* 1. 3 oral capsules daily (280mg DHA, 90mg eicosapentaenoic acid, EPA, 2mg vitamin E). 2. Placebo (602mg olive oil). *Dose modifications:* not reported *Concurrent treatment:* Prohibited medication or use of any other drugs was checked at each visit and recorded in the case report form. *Duration of treatment:* 3 years	*Outcomes (state if primary)* Time to occurrence of CNV (primary outcome) Incidence of CNV BCVA (logMAR) Proportion with a visual acuity decrease of 15 letters on ETDRS charts. Occurrence and progression of drusen, changes in EPA plus DHA levels (not extracted) Safety. Food frequency questionnaire Compliance (unused capsules) *Length of follow-up:* 3 years

Participant characteristics, %			
Full analysis set only:	**DHA, n=134**	**Placebo, n=129**	**P value**
Age, years mean (SD)	73.9 (6.6)	73.2 (6.8)	
Sex, % male	31.3	39.5	
Classification, % *Cataract* *Stage of maculopathy* *- 1 (≥1 soft drusen or pigmentary changes)* *2 (≥1 soft drusen with pigmentary changes)* *Noncentral atrophy*	 61.2 77.6 22.4 18.7	 62.0 78.3 21.7 12.4	

Smoking history *Current* *Former* *Nonsmoker*	 6.7 14.2 79.1	 8.5 17.1 74.4	
visual acuity, mean (SD) logMAR	0.41 (0.14)	0.12 (0.15)	
Key comorbidities, % *Cardiovascular* *Metabolic and nutrition* *Musculoskeletal and connective tissue* *Gastrointestinal*	 92.5 53.0 44.8 29.9	 79.8 58.9 48.8 32.6	
Family history	21.6	27.1	
Results			
	DHA, n=134	**Placebo, n=129**	**P Value**
Mean time to occurrence of CNV, months	19.5 (10.9)	18.7 (10.6)	0.613[a]
Proportion in whom CNV developed over 3 years	28.4	25.6	
Comments: [a]hazard ratio, 0.89; standard error, 0.272; 95% CI, 0.55–1.42, analysis adjusted for age at randomization, smoking status, and stage of maculopathy			
Mean (SD) BCVA change, logMAR at 3 years	-0.155 (0.297)	-0.116 (0.258)	0.311
Proportion with a decrease of >15 letters on ETDRS at 3 years	17.8	14.3	0.469
Comments:			
Small drusen, mean (SD) area, n of drusen *Baseline* *At 3 years*	 30.5 (43.2), n=96 32.3 (34.7), n=86	 38.1 (47.1), n=96 40.9 (37.8), n=83	 0.270
Intermediate drusen, mean (SD) area, n of drusen *Baseline* *At 3 years*	 47.3 (51.5), n=96 40.7 (40.1), n=86	 54.2 (57.5), n=96 51.9 (46.7), n=83	 0.763
large drusen, mean (SD) area, n of drusen *Baseline* *At 3 years*	 49.8 (46.3), n=96 50.8 (47.0), n=86	 57.4 (53.4), n=96 60.6 (53.0), n=83	 0.423
Total area of all drusen, µm *At baseline* *At 3 years*	 1614594 (1855703), n=96 1889351 (2112253), n=86	 1820091 (1830451), n=96 2006937 (2040908), n=83	 0.851
Comments: Small drusen, <63 µm; intermediate drusen, between 63 and 125 µm; large drusen, >125 µm.			
Compliance: states the proportion of compliant patients was similar in both groups; a minimum compliance of 78% was observed at years 1, 2, and 3.			
Adverse events, %			
At least 1 treatment emergent AE[a]	4.7	1.6	ns
Ocular AE	58.7	50	ns
Worsening of cataract	50	62.5	0.032
Serious non ocular event[b]	23.1	23.6	ns
Deaths[c]	2.2	4.7	
Comment: [a] considered to be probably related to the study treatment: gastrointestinal disorders, allergic dermatitis, or breath odour [b] considered to be unlikely to be related to the study treatment, except for 2 undetermined serious AEs (pulmonary embolism in the DHA group and cerebral hemorrhage in the placebo group). [c] All deaths were considered unlikely to be related to the study protocol or treatment			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Used proprietary randomisation software to generate the randomisation list.
Allocation concealment (selection bias)	Unclear	Says patients and study personnel were blind to the treatment assignment, but no details of how allocation was concealed
Blinding participants and personnel (performance bias), Objective outcomes	Low	Double blind study (states patients and study personnel were blind to the treatment assignment), capsules had the same appearance, size, and weight (602 mg) in both groups. No masking flavour was added to the capsules, which were otherwise odourless.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Numbers and reasons for withdrawal provided, slight imbalance only. Analysis set was all people with at least 1 unit of medication and 1 post baseline visit.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes reported as stated
Other biases	Low	No other apparent bias

Tao et al

Study details	**Participant details**
Tao Y, Jiang P, Wei Y, Wang P, Sun X, Wang H. alpha-Lipoic Acid Treatment Improves Vision-Related Quality of Life in Patients with Dry Age-Related Macular Degeneration. Tohoku J Exp Med 2016;240:209-14. *Country:* China *Design:* RCT *Number of centres:* one *Funding:* non-commercial *Trial ID:* Not reported	*Number of Participants*: Total 100 (α -lipoic acid 50, placebo 50) *Number of eyes* not reported *Sample attrition/dropout*: not reported *Sample crossovers:* assume none *Inclusion criteria:* Dry AMD, no diabetes or hypertension that may affect to retinal function; transparent lens opacity and ocular media; no family history of glaucoma, intra-ocular pressure normal and cyc / degree ≤ 0.4; no high myopia, uveitis and retinal detachment which may affect the macular function *Exclusion criteria:* no additional criteria reported

Intervention details	**Outcomes**
Intervention *1.* α -lipoic acid *2.* Vitamin C, stated as a placebo *Dose details:* α -lipoic acid 0.2 g orally daily. Vitamin C 1.0 g daily	*Outcomes (state if primary)* Serum superoxide dismutase activity (not extracted) BCVA Contrast sensitivity Chinese-Version Low Vision Quality of Life (CLVQOL) *Length of follow-up:* 3 months

Dose modifications: Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 3 months	

Participant characteristics, %			
	α -lipoic acid, n=50	**Placebo, n=50**	**P value**
Age, years mean (SD)	70.86 (7.74)	72.06 (7.38)	0.43
Sex, % male	52	56	0.69
Smoking history *Tobacco use, %*	 24	 32	0.37
BCVA (LogMAR)	0.64 (0.34)	0.61 (0.39)	NS
Lesioned disk area, mean (SD)	0.84 (0.23)	0.79 (0.31)	0.32
CLVQOL, mean (SD)	73.53 (17.89)	74.33 (16.82)	NS
Contrast sensitivity, mean (SD) 3 cyc/degree, log 6 cyc/degree, log 12 cyc/degree, log 18 cyc/degree, log	 0.90 (0.29) 1.11 (0.33) 0.85 (0.31) 0.46 (0.36)	 0.89 (0.32) 1.19 (0.39) 0.84 (0.33) 0.49 (0.33)	 NS NS NS NS
Comments States no significant differences between groups			
Results			
	α -lipoic acid, n=50	**Placebo, n=50**	**P Value**
BCVA (LogMAR), mean (SD) at 3 months	0.66 (0.41)	0.63 (0.42)	ns
Comments No significant difference pre-and post treatment in either group.			
Contrast sensitivity, mean (SD) 3 cyc/degree, log 6 cyc/degree, log 12 cyc/degree, log 18 cyc/degree, log	 1.02 (0.28) 1.26 (0.39) 0.92 (0.30) 0.51 (0.34)	 0.87 (0.29) 1.15 (0.36) 0.88 (0.35) 0.44 (0.31)	 <0.05 ns ns ns
Comments Treatment group significantly different from baseline for 3 cycles/degree and 6 cycles per degree.			
CLVQOL, mean (SD)	82.6 (19.36)	72.81 (18.05)	<0.05
Comments CLVQOL significantly different from baseline in treatment group only,			
Adverse events	Not reported		

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States randomly assigned, no further details
Allocation concealment (selection bias)	Unclear	No details reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Blinding not reported, the control group were given Vitamin C as a placebo, unclear if this was similar in appearance
Blinding participants and personnel (performance bias), Subjective outcomes	Unclear	Blinding not reported, the control group were given Vitamin C as a placebo, unclear if this was similar in appearance
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	States examiner was blind for contrast sensitivity, not reported for other outcomes
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	Not reported
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Not reported
Incomplete outcome data (attrition	Unclear	Not reported

bias), Subjective outcomes		
Selective reporting (reporting bias)	low	Outcomes reported as stated in methods, but no trial record
Other biases	low	No other bias

Cougnard-Grégoire et al

Study details	**Participant details**
Cougnard-Gregoire A, Merle BM, Korobelnik JF, Rougier MB, Delyfer MN, Le Goff M, et al. Olive Oil Consumption and Age-Related Macular Degeneration: The Alienor Study. PLoS One 2016;11:e0160240 Linked to Delcourt 2010, not in file *Country:* France *Design:* Cohort study *Number of centres:* 3 *Funding:* commercial and non-commercial funding *Trial ID:* Not reported	*Number of Participants*: Total 963; 654 analysed *Number of eyes* 1269 *Sample attrition/dropout*: 309 with incomplete data for AMD status or potential confounders *Sample crossovers:* not applicable *Inclusion criteria:* community-dwelling persons aged 65 years and older from three French cities (recruited from ongoing population-based study on risk factors for dementia) *Exclusion criteria:* Not stated

Intervention details	**Outcomes**
Intervention *1. Olive oil consumption, 'regular users'* *2. 'Non users' of olive oil (also described as 'occasional users'* *Dose details:* not applicable (typical foods consumed reported) *Dose modifications:* not applicable *Concurrent treatment:* not applicable *Duration of treatment:* not applicable	*Outcomes (state if primary)* Early and late AMD prevalence. Early AMD soft distinct drusen and/or soft indistinct drusen (>125 μm in diameter) and/or reticular drusen and/or pigmentary abnormalities, in the absence of late AMD. Late AMD neovascular AMD or geographic atrophy. Definitions reported. *Length of follow-up:* approx. 7 years

Participant characteristics, %			
	Olive oil, n=479	No olive oil, n=175	P-value
Age, years mean (SD)	72.8 (4.4)	73.5 (4.2)	0.51
Sex, % male	38.2	40	0.68
Classification, n (%) *Early AMD* *Late AMD*	(All participants n=654) 189 (28.9) 36 (5.5)		
Smoking history *none*	64.7	64.6	0.25
visual acuity			
lesion size			
Key comorbidities, % *Hypertension* *Diabetes* *Cardiovascular disease*	 73.3 6.3 8.1	 77.1 10.3 8.0	 0.32 0.08 0.95
Comments: regular users of olive oil were more educated, were more frequently married, and with borderline significance had a higher monthly income than non-users. No significant associations were found between olive oil use and age, gender, smoking, physical activity or alcohol use (data presented, not extracted)			

Results			
	Olive oil, n=936 eyes	**No olive oil, n=333 eyes**	**P Value**
No AMD (n=945 eyes), n eyes (%)	712 (75.3)	233 (24.7)	
Early AMD (n=268 eyes), n eyes (%)	191 (71.3)	77 (28.7)	
Late AMD (n=56 eyes), n eyes (%)	33 (58.9)	23 (41.1)	
Comments After multivariate adjustment, regular consumption of olive oil was significantly associated with late AMD (OR = 0.44, 95% CI: 0.21;0.91, p = 0.03), but not with early AMD (OR = 0.84, 95%CI: 0.59;1.24 (1.21 in the table), p = 0.36) (adjusted for age, gender, educational level, marital status, smoking, BMI, regular consumption of raw fruits, regular consumption of cooked fruits and vegetables, plasma HDL-cholesterol, plasma total n-3 PUFAs, plasma total n-6 PUFAs and total energy intake. Eyes without AMD were the reference). After also adjusting for genetic factors (n=1067 eyes with genetic data) (CFH rs1061170 and ARMS2 rs10490924, LPL rs12678919 and LIPC rs493258), associations were (OR = 0.27, 95CI: 0.11; 0.65, p = 0.003 for late AMD and OR = 0.92, 95% CI: 0.61;1.38, p = 0.69 for early AMD). No associations were found between regular consumption of n-3 rich oils, n-6 rich oils, mixed oils, butter and margarine and AMD, whatever the stage (not data extracted). No significant interaction between genetic factors (CFH rs1061170, ARMS2 rs10490924, LPL rs12678919 and LIPC rs493258 polymorphisms) and consumption of olive oil (all p>0.05) for early AMD models and no interactions for late AMD models			

Cohort and Cross-Sectional Studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?		x	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating:Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Homocysteine levels, folic acid and B vitamins

Christen et al

Study details	Participant details
Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Archives of Internal Medicine 2009;169:335-41. *Country:* USA *Design:* RCT (secondary aim from a cardiovascular risk factor trial) *Number of centres:* not reported *Funding:* non-commercial funding. Investigational agents provided by commercial entity. *Trial ID:* not reported	*Number of Participants*: total 5205; folic acid + vitamins 2607; placebo 2598 *Number of eyes*: total 5205; folic acid + vitamins 2607; placebo 2598 (individuals were the unit of analysis, classified according to status of the worst eye) *Sample attrition/dropout*: not reported *Sample crossovers:* none *Inclusion criteria:* women included in the Women's Antioxidant and Folic Acid Cardiovascular Study (included those at high risk of cardiovascular disease) without a diagnosis of AMD. *Exclusion criteria:* those with a diagnosis of AMD at baseline

Intervention details	Outcomes
Intervention *1.* Folic acid, vitamin B6, Vitamin B12 *2.* Placebo *Dose details:* folic acid (2.5 mg/day), vitamin B6 (50 mg/day), and vitamin B12 (1 mg/day) *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 7.3 years	*Outcomes (state if primary)* Total AMD (includes neovascular) Visually-significant AMD (BCVA loss to 20/30 or worse) Compliance *Length of follow-up:* 7.3 years

Participant characteristics, %			
	Folic acid/B6/B12 (n=2,607)	**Placebo (n=2,598)**	**P value**
Age, years mean	62.6	62.6	
Sex, % male	0	0	
Smoking history, % *Current* *Past* *Never*	 11.4 43.6 45.0	 12.2 45.0 42.7	
Key comorbidities, % *Hypertension* *Elevated cholesterol* *Diabetes* *Cardiovascular disease*	 86.6 77.6 21.3 64.4	 85.7 78.8 21.6 62.6	
Results			
	Folic acid/B6/B12 (n=2,607)	**Placebo (n=2,598)**	**P Value**
Total AMD, n cases	55	82	0.02
Relative risk: 0.66; 95% CI, 0.47–0.93			
Visually significant AMD, n cases	26	44	0.03

RR, 0.59; CI, 0.36–0.95 Reports cumulative incidence rates according to year of follow-up, not data extracted. Reports specific signs of visually significant AMD (drusen, RPE, GA, exudative changes) but for all cases, not by treatment group so not extracted. Reports results for visually significant AMD by treatment group and risk factors of age categories, smoking status, alcohol status, BMI, Hypertension, Hyperlipidemia, Diabetes, Prior cardiovascular disease, hormone replacement therapy use, multivitamin use, aspirin use (not extracted, test for interaction not statistically significant for all subgroups)			
Adverse events			
Compliance: approximately 84% took at least 2/3 of study pills with no significant difference between active and placebo group			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Not described for this substudy or the original RCT
Allocation concealment (selection bias)	Unclear	Not described for this substudy or the original RCT
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	States double blind but no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	No discussion of discontinuations or losses to follow-up
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Outcomes reported as stated
Other biases	Low	No other apparent biases.

Merle et al., 2016 {#6}

Study details	**Participant details**
Merle BM, Silver RE, Rosner B, Seddon JM. Dietary folate, B vitamins, genetic susceptibility and progression to advanced nonexudative age-related macular degeneration with geographic atrophy: a prospective cohort study. Am J Clin Nutr 2016;103:1135-44. *Country:* USA *Design:* Prospective cohort study *Number of centres:* 11 *Funding:* various non-commercial grants *Trial ID:* For feeder RCT: NCT00594672	*Number of Participants*: 4757 enrolled, 2525 in analysis (405 progressed; 2120 unprogressed) *Number of eyes* 4663 of the 2525 participants included in the analysis *Sample attrition/dropout*: 2232 (618 eye research consent only; 995 no genetic specimen; 111 lost to follow up; 39 advanced bilateral AMD; 343 incomplete genetic profile; 126 invalid total energy intake) *Sample crossovers:* not applicable *Inclusion criteria:* Participants of AREDs RCT, aged 55-80 years, at least one eye with a visual acuity no worse than 20/32, at least one eye free from disease that could complicate the assessment of AMD, no previous ocular surgery in that eye (except cataract or photocoagulation for AMD). *Exclusion criteria:* conditions that would have made long-term follow-

	up or compliance with study protocol unlikely or difficult. Eyes with advanced AMD excluded from analysis

Intervention details	**Outcomes**
Intervention *1.* Folate and vitamin B (all) *Dose details:* Median quintiles consumed per day were reported as log-transformed, calorie-adjusted rates, for men and women in supplementary tables. These ranged as follows: Thiamin (Men 1.10-1.90; Women 0.85-1.43) Riboflavin (Men 1.24-2.41; Women 0.94-1.93) Niacin (Men 14.01-24.44; Women 10.30-18.46) Vitamin B6 (Men 1.22-2.46; Women 0.90-1.89) Folate (Men 260.37-571.66; Women 202.99 – 423.7) Vitamin B12 (Men 2.63-8.3; Women 1.95 - 6.14) *Dose modifications:* not reported *Concurrent treatment:* participants either on Age-Related Eye Disease Study (AREDs) intervention (antioxidant and mineral supplements) or placebo. *Duration of treatment:* not reported	*Outcomes (state if primary)* Progression to GA (either eye advancing from no, early, or intermediate AMD to GA at any point in follow-up). Interactions between AMD genes and folate and B vitamin intake. *Length of follow-up:* mean 8.7 years (range 0.5-13 years). 13 years in the survival analysis. Follow-up ended when an eye progressed to GA, or were censored when reached grade 5 clinical age-related maculopathy staging (CARMS)

Participant characteristics, %	Presented for progressors and non progessors, not total group		
	Progressors, n=405	**Non-progressors, n=2120**	**Difference, p-value, HR (95% CI)**
Age, years, % ≤ 64 65-74 >74	 14.6 58.8 26.6	 18.4 66.9 14.7	 p=0.0002 1.23 (0.96, 1.57) 1.67 (CI 1.26, 2.21)
Sex, % male	48.6	43.7	1.11 (CI 0.93, 1.31), p=0.25
Ethnic origin *% White*	Not reported	Not reported	
Classification	Not reported	Not reported	
Smoking history, pack-years *Never* *<20* *≥20*	 42.5 21.5 36.0	 47.7 23.7 28.6	 P=0.14 0.98 (0.74, 1.28) 1.21 (CI 0.95, 1.54)
visual acuity	Not reported	Not reported	
lesion size	Not reported	Not reported	
CARMS grades in each eye *1,1/1,2/2,2* *1,3/2,3/3,3* *1,4/2,4/3,4* *1,5/2,5/3,5*	 5.2 71.1 10.4 13.3	 56.5 29.9 0.8 12.8	 P<0.0001 25.22 (16.69, 38.10) 114.96 (69.45, 190.28) 17.3 (10.66, 28.07)
previous treatments *Multivitamins never* *Multivitamins ever*	 29.4 7.6	 32.2 67.8	 P=0.86 1.02 (0.81, 1.28)
Key comorbidities	Not reported	Not reported	
Family history	Not reported	Not reported	
Comments: 20% of progressors and 32.6% of non progressors had received placebo in the AREDs RCT; 80% and 67.4% received AREDs supplements respectively.			
Results			
	All, n=2525		**P Value**
Progression to GA using CARMS	16%		

Comments: CARMS grades: no AMD (grade 1); intermediate drusen (grade 2); large drusen (grade 3, intermediate AMD); GA (central and non-central, grade 4); definitive signs of neovascular AMD (grade 5). Converted from AREDS staging based on all available phenotype data, combined intermediate AMD with nonecentral GA into one category (category 3) and central atrophy and neovascular disease with visual loss into category 4. For genetic analysis classified central or noncentral into one category and neovascular into another.
Compared with Cox Proportional Hazards, adjusted for age, sex, and AMD grade with individual eye as the unit of analysis. Multivaraite models also undertaken (adjustment factors stated).

Those progressing tended to be older (p-trend = 0.0002) and to have a higher BMI (P-trend = 0.02). Sex, education, smoking, AREDs treatment and multivitamin use did not significantly differ between progressors and non-progressors (p-values reported). Those with intermediate or advanced AMD in the worst eye were at higher risk of progression to GA (P-trend <0.0001).

After adjustment, progressors had a lower intake of thiamine (p=0.01), riboflavin (p=0.03) and folate (p=0.001) than non-progressors. No statistically significant variation was seen for niacin, vitamin B-6 or vitamin B-12. Multivariate analysis showed a significant trend for a lower risk of progression with increasing folate (p=0.007), a borderline association for thiamine (p=0.053), and no association with riboflavin (p=0.20). Subgroups of quintiles for these three factors were also reported but have not been data extracted.

Subgroups			
10 Single-nucleotide polymorphisms, %	**Progressors, n=405**	**Non-progressors, n=2120**	**Difference, p-value, HR (95% CI)**
CFH Y402H rs1061170			
TT	15.8	32.6	Reference, p<0.0001
CT	39.8	46.4	1.49 (1.09, 2.02)
CC	44.4	21.0	2.03 (1.51, 2.74)
CFH rs1410996			
TT	4.0	14.2	Reference, p<0.0001
CT	28.1	42.7	2.19 (1.27, 3.80)
CC	67.9	43.1	3.35 (1.98, 5.67)
CFH R121OC rs121913059			
CT	98.8	99.7	Reference, p=0.10
CC	1.2	0.3	2.05 (0.87, 4.84)
ARMS2/HTRAI rs10490924			
GG			
GT	30.9	54.1	Reference, p<0.0001
TT	49.9	37.1	1.75 (1.38, 2.21)
	19.2	8.8	2.01 (1.48, 2.73)
C2 E318D rs9332739			
GG	97.8	92.1	Reference, p=0.006
CG/CC	2.2	7.9	0.38 (0.19, 0.76)
CFB R32Q rs641153			
CC	91.6	85.5	Reference, p=0.007
CT/TT	8.4	14.5	0.60 (0.41, 0.87)
C3 R102G rs2230199			
CC	49.2	58.9	Reference, p=0.04
CG/GG	50.8	41.1	1.25 (1.01, 1.53)
C3 K155Q rs147859257			
TT	95.6	98.4	Reference, p=0.006
GT	4.4	1.6	2.26 (1.42, 3.62)
COL8A1 rs13095226			
TT	76.3	80.9	Reference, p=0.05
CT/CC	23.7	19.1	1.28 (1.00, 1.63)
RAD51B rs8017304			
AA	40.7	41.6	Reference, p=0.62
AG	49.4	45.2	1.07 (0.86, 1.33)
GG	9.9	13.2	0.82 (0.57, 1.19)

Comments:
CFH: Complement factor H; CFB: complement factor B; ARMS2: age-related maculopathy susceptibility 2; C2: complement component 2; C3: complement component 3; COL8A1: collagen type VIII α1; RAD51B: RAD51 paralog B. CFH Y402H, CFH rs1410996, ARMS2, and RAD51B were coded with 3 levels (0|1|2) according to the number of risk alleles. Other variants were coded with 2 levels (0|1), no further details reported.

CFH Y402H, CFH rs1410996, ARMS2/HTRA1, C3 R102G rs2230199 and C3 K155Q rs147859257 were significantly associated with an increased risk of progression to GA. C2 E318D rs9332739 and CFB R32Q rs641153 were significantly associated with a decreased risk of progression. CFH R1210C, COL8A1, and RAD51B were not significantly associated with risk of progression to GA.

Also reports effect of folate on progression to GA according to these genotypes and a composite genetic risk score (Low: <median; High: ≥median). Folate was significantly associated with lower risk of incident GA among subjects homozygous for CFH C3 R102G rs2230199 nonrisk genotype (CC) (HR = 0.43; 95% CI: 0.27, 0.70; P = 0.0005) but not for risk genotype (G) (P = 0.76). Other interactions were reported and were not statistically significant (data not extracted).

CI: confidence Interval; HR: Hazard Ratio

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?	x		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?	x		
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?		x	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Good

*CD, cannot determine; NA, not applicable; NR, not reported

Gopinath et al.

Study details	Participant details
Gopinath B, Flood VM, Rochtchina E, Wang JJ, Mitchell P. Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration. Am J Clin Nutr 2013;98:129-35. *Country:* Australia	*Number of Participants*: 2334 in total sample at baseline, 1760 with follow-up. 1390 of whom had the exposure and an assessment of the outcome of interest. *Number of eyes* not reported *Sample attrition/dropout*: 574

Design: Prospective cohort study *Number of centres:* not applicable *Funding:* non-commercial grants *Trial ID:* none	*Sample crossovers:* not applicable *Inclusion criteria:* noninstitutionalized residents aged >49 years who were invited to attend a detailed baseline eye examination after a door-to-door census of the study area. *Exclusion criteria:* not reported

Intervention details	**Outcomes**
No intervention as such, is an exposure study *1*. assessment of serum tHcy, folate, and vitamin B-12 levels *2*. intake of folate and vitamin B-12 (by food frequency questionnaire) *Dose details:* serum levels of exposures reported; total intakes recorded; proportion consuming supplements recorded (details in results below) *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* Not applicable	*Outcomes (state if primary)* Incidence of any AMD - graded for early or late, defined as: Early AMD, absence of late AMD and presence of either 1) large (>125-µm diameter) indistinct soft or reticular drusen or 2) both large distinct soft drusen and retinal pigmentary abnormalities at 5 or 10 years in either eye of those free of early AMD in both eyes at baseline. Late AMD, appearance of neovascular AMD or geographic atrophy at 5 or 10 years in either eye of those without late-AMD lesions in both eyes at baseline. *Length of follow-up:* 5 or 10 years

Participant characteristics, %			
	With AMD, n=219	**Without AMD, n=1171**	**P value**
Age, years mean (SD)	71.6 (6.7)	66.7 (7.4)	<0.0001
Sex, % male	31.5	43.5	0.001
Smoking history *Current, %*	8.2	7.7	0.79
Results			
Mean (SD) unless stated	**With AMD, n=219**	**Without AMD, n=1171**	**P Value**
Serum tHcy (µmol/L)	13.0 (4.6)	12.0 (4.2)	P=0.002
Serum folate (nmol/L)	18.0 (9.6)	18.0 (8.5)	P=0.96
Serum vitamin B-12 (pmol/L)	263.4 (116.6)	284.3 (138.0)	P=0.02
Fish consumption (≥1 serving/week), n (%)	130 (66.7)	716 (67.3)	P=0.86
Consumed folate supplement, n (%)	23 (11.8)	138 (13.0)	P=0.65
Consumed vitamin B-12 supplement, n (%)	23 (11.8)	195 (18.3)	P=0.03
Total intake of folate equivalents (µg/d)[a]	440.8 (228.4)	462.5 (257.0)	P=0.23
Total intake of vitamin B-12 (µg/d)[a]	7.9 (9.9)	11.2 (20.0)	P=0.0004
[a]calculated by adding crude dietary and supplement intakes AMD includes any subtype, no data specifically for GA or dry AMD.			
Subgroups of any AMD, early AMD, Late AMD, Odds ratios (95% CI) for each exposure:	Incident any AMD (n = 219)	Incident early AMD (n = 162)	Incident late AMD (n = 57)
Serum homocysteine per 1-SD increase[b]	1.33 (1.11, 1.60)	1.33 (1.09, 1.63)	1.25 (0.93, 1.69)
Serum vitamin B-12 per 1-SD increase[c]	0.73 (0.60, 0.89)	0.77 (0.62, 0.96)	0.66 (0.45, 0.96)
Serum folate per 1-SD increase[d]	0.91 (0.77, 1.07)	0.93 (0.77, 1.13)	0.89 (0.66, 1.20)

Analyses adjusted for covariates: age, sex, smoking, white cell count, and fish consumption
[b]One SD = 5.09 mmol/L.; [c]One SD = 144.9 pmol/L.; [d]One SD = 9.1 nmol/L.
Also reports subgroups of homocysteine, vitamin B-12 and folate by diagnostic cut-offs, and tertiles of vitamin B-12 and folate, but not extracted.
Comments: no data specifically for GA or dry AMD

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?	x		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x		

Quality Rating: Good

*CD, cannot determine; NA, not applicable; NR, not reported

Antioxidant effect of vitamins

Christen et al.

Study details	Participant details
Christen WG, Manson JE, Glynn RJ, Gaziano JM, Chew EY, Buring JE, et al. Beta carotene supplementation and age-related maculopathy in a randomized trial of US physicians. Archives of Ophthalmology 2007;125:333-9. *Country:* USA *Design:* RCT *Number of centres:* Not reported *Funding:* Public bodies *Trial ID:* Not reported	*Number of Participants*: Total 21,142 (from 22,071 initially randomised): Beta carotene 10,585; Placebo 10,557 *Number of eyes* unclear; participants not eyes were unit of analysis *Sample attrition/dropout*: 99.2% were providing information on morbidity at end of 11 years follow-up *Sample crossovers:* 6% if placebo group reported taking supplemental beta carotene or vitamin A. *Inclusion criteria:* Healthy male physicians age 40-82 years in 1982. *Exclusion criteria:* Not explicitly reported. States worse eye could be excluded due to other ocular abnormalities. Physicians who died during the first seven years of follow-up, and therefore did not respond to the 84-month questionnaire, were excluded.

Intervention details	Outcomes
Intervention *1.* Beta carotene *2.* Placebo *Dose details:* Beta carotene, 50-mg supplement every other day *Dose modifications:* Not reported *Concurrent treatment:* in beta-carotene arm only: low-dose aspirin, 325 mg every other day (terminated early in 1988) *Duration of treatment:* 12 years (range, 11.6 to 14.2)	*Outcomes (state if primary)* Incident age-related maculopathy (ARM) responsible for a reduction in best-corrected visual acuity to 20/30 or worse (primary endpoint). ARM with or without vision loss, comprised of all incident cases. Advanced ARM, comprised of those cases of visually-significant ARM with pathological findings of geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar. Participants were classified according to the status of the worse eye as defined by disease severity *Length of follow-up:* ≥7 years (average 12 years)

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Details not reported
Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as double-blind but no further details reported
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Described as double-blind, details of outcome assessors for ARM not reported and element of subjectivity
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	High	Excluded participants who died during first 7 years
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	Low	Outcomes as stated in methods
Other biases	Low	No other biases

Christen et al 2010

Study details	Participant details
Christen WG, Glynn RJ, Chew EY, Buring JE. Vitamin E and age-related macular degeneration in a randomized trial of women. Ophthalmology 2010;117:1163-8. *Country:* USA *Design:* RCT (substudy of RCT of cardiovascular prevention) *Number of centres:* not reported	*Number of Participants*: total 39421: vitamin E 19,697; Placebo 19,724 *Number of eyes* total 39421: vitamin E 19,697; Placebo 19,724 (individuals were the unit of analysis, classified according to the worst eye) *Sample attrition/dropout*: 455 were excluded as had a diagnosis of AMD (vitamin E 240; placebo 215). No details of any exclusions after baseline. *Sample crossovers:* not reported

Funding: non-commercial grants and pills and packaging from commercial entities *Trial ID:* NCT00000161	*Inclusion criteria:* Women's Health Study participants, aged 45 years or older; postmenopausal or no intention of becoming pregnant; no history of cardiovascular disease, cancer, gout, peptic ulcer, chronic renal or liver disease, or other serious illness precluding participation; no history of serious side effects to the study treatments; not currently taking aspirin, aspirin containing medication, or nonsteroidal anti-inflammatory drugs >1 day per week; not taking supplements of vitamin E or beta carotene >1 day per week; not currently taking anticoagulants or corticosteroids, those who didn't report a diagnosis of AMD. *Exclusion criteria:* those with a diagnosis of AMD

Intervention details	**Outcomes**
Intervention *1.* vitamin E (natural-source) and low dose aspirin *2.* Placebo *Dose details:* vitamin E 600 IU on alternate days *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 10 years	*Outcomes (state if primary)* visually-significant AMD, BCVA reduced to 20/30 or worse (primary outcome) Advanced AMD (includes exudative and GA) AMD with or without vision loss (incident AMD) Compliance *Length of follow-up:* 10 years

Participant characteristics, %			
	Vitamin E, n=19,697	**Placebo, n=19,724**	**P value**
Age, years mean (SD)	54.5	54.5	
Smoking history *Current* *Past/Never*	 13.1 86.9	 13.3 86.7	
Key comorbidities, % *Hypertension* *Hyperlipidemia* *Diabetes mellitus*	 25.4 29.1 2.5	 26.0 29.5 2.5	
Results			
	Vitamin E, n=19,697	**Placebo, n=19,724**	**P Value**
Visually significant AMD, n cases	117	128	0.54
relative risk 0.93; 95% CI, 0.72 to 1.19 Reports cumulative incidence rates of visually significant AMD by year, not extracted (no benefit at any point during follow-up). Reports results for visually significant AMD by treatment group and risk factors of age, smoking, alcohol, BMI, hypertension, diabetes, menopausal status, parental history of MI, multivitamin use, eye examination, not extracted (no subgroups were statistically significant).			
Advanced AMD, n cases	29	26	0.65
RR, 1.13; CI, 0.67–1.92			
All AMD +/- vision loss, n cases	280	313	0.20
RR, 0.90, CI, 0.77 to 1.06			
Adverse events			
Compliance (taking at least two thirds of the study capsules) was 78.9% at 5 years, 71.6% at 10 years, and 75.8% throughout the trial.			
Subgroups			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States randomised but no further details
Allocation concealment (selection bias)	Unclear	States randomised but no further details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Double masked but no details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	People with AMD at baseline were excluded after randomisation, although numbers low and similar between groups. No details of any discontinuations/ withdrawals post baseline
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes stated are reported
Other biases	Low	No other apparent biases

Christen et al. 2014

Study details	**Participant details**
Christen WG, Glynn RJ, Manson JE, MacFadyen J, Bubes V, Schvartz M, et al. Effects of multivitamin supplement on cataract and age-related macular degeneration in a randomized trial of male physicians. Ophthalmology 2014;121:525-34. *Country:* USA *Design:* RCT (substudy of RCT of cancer and cardiovascular prevention) *Number of centres:* not stated *Funding:* non-commercial grants and pills and packaging from commercial entities *Trial ID:* NCT00270647	*Number of Participants*: total 14,233; multivitamin 7,111; placebo 7122 *Number of eyes* total 14,233; multivitamin 7,111; placebo 7122 (individuals were the unit of analysis, classified according to status of the worst eye) *Sample attrition/dropout*: those with cataract or AMD at baseline were excluded (n=3552). No details of any attrition after baseline. *Sample crossovers:* not reported *Inclusion criteria:* healthy male physicians, aged ≥50 years, no history of serious illness that would preclude study participation, no history of significant adverse events attributed to study agents, no other concurrent vitamin and/or multivitamin supplementation, no concurrent vitamin K-depleting anticoagulants (e.g., warfarin). *Exclusion criteria:* those with cataract or AMD at baseline.

Intervention details	**Outcomes**
Intervention *1.* multivitamin *2.* Placebo *Dose details:* daily multivitamin, no details	*Outcomes (state if primary)* Were prespecified secondary outcomes of the original trial Cataract (not extracted) Visually-significant AMD, BCVA reduced to 20/30 or worse (co-primary outcome)

Dose modifications: not reported *Concurrent treatment:* not reported *Duration of treatment:* average 11.2 years	Total AMD with or without vision loss. Advanced AMD (includes GA and exudative neovascular AMD) Compliance Adverse events *Length of follow-up:* mean 11.2 years

Participant characteristics, %			
	multivitamin, n=7111	**Placebo, n=7122**	**P value**
Age, years mean (SD)	63.9 (8.9)	64.0 (9.0)	
Sex, % male	100	100	
Smoking history, % *Never* *Former* *Current*	 57.1 39.4 3.5	 56.4 39.9 3.6	
Key comorbidities, % *Hypertension* *High cholesterol* *Diabetes mellitus* *Cardiovascular disease (self reported)*[a]	 41.0 36.1 6.3 5.0	 42.3 37.3 5.7 5.0	
Comments [a]included nonfatal myocardial infarction or nonfatal stroke.			
Results			
	multivitamin, n=7111	**Placebo, n=7122**	**P Value**
Visually significant AMD, n cases	152	129	0.15
Hazard ratio 1.19; 95% CI, 0.94 to 1.50 Reports HRs over time, not extracted. Reports results for all AMD by age, smoking, alcohol, BMI, hypertension, high cholesterol, diabetes, exercise status, and self-report of cardiovascular disease, and previous active intervention, not extracted (the effect of multivitamins on visually-significant AMD did not differ within categories).			
Total AMD +/- vision loss, n cases	294	244	0.02
HR, 1.22; 95% CI, 1.03 to 1.44			
Advanced AMD, n cases	79	65	0.23
HR, 1.22; 95% CI, 0.88 to 1.70			
Adverse events	Not reported		
Compliance at 6 years (at least 2/3 study agents taken) 73.6% multivitamin and 73.3% placebo (P=0.68).			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States randomised but no further details
Allocation concealment (selection bias)	Unclear	States randomised but no further details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Double masked but no details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described, says review of cases was undertaken by masked investigator but no details for main outcome assessor
Blinding outcome assessors (detection bias), Subjective	N/A	

outcomes		
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	People with AMD at baseline were excluded after randomisation, although numbers similar between groups. No details of any discontinuations/ withdrawals post baseline
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes stated are reported
Other biases	Low	No other apparent biases

Cangemi et al

Study details	**Participant details**
Cangemi FE. TOZAL Study: an open case control study of an oral antioxidant and omega-3 supplement for dry AMD. BMC Ophthalmology 2007;7:3. *Country:* USA *Design: 1. RCT, 2. Cohort with historical controls (overlapping patients)* *Number of centres:* 5 *Funding:* Commercial funding *Trial ID:* Not reported	*Number of Participants*: RCT: Total 73 (microstimulation + supplement 36; sham + supplement 37). Cohort (sham + supplement): 37, historical control 15 *Number of eyes* analysis performed with patients and eyes as unit of analysis (not reported) *Sample attrition/dropout*: 3 from nutrition group withdrawn, reasons not provided. *Sample crossovers:* not applicable *Inclusion criteria:* age 50-90 years, at least 1 eye diagnosed with dry AMD having > 10 large soft drusen 63 μm in diameter, within 3,000 um of the fovea centre, documented on macular exam, retinal angiography and fundus photographs, BCVA in the trial eye(s) of 20/32 to 20/125 inclusive (ETDRS), no conditions that limit the view to the fundus *Exclusion criteria:* Eyes with concomitant macular or choroidal disorders other than AMD and with indefinite signs of AMD, exudative AMD with active subretinal neovascularization or CNV lesions requiring laser photocoagulation in the study eye, significant ocular lens opacities causing vision decrease, amblyopia, optic nerve disease, unstable glaucoma, history of retina-vitreous surgery, degenerative myopia, active posterior intraocular inflammatory disease, chronic use of topical ocular steroid medications, vasoproliferative retinopathies (other than AMD), rhegmatogenous retinal detachment, and inherited macular dystrophies, uncontrolled hypertension, stroke, epilepsy, previous experimental procedure in either eye or the use of any investigational drug or treatment within 30 days, intraocular surgery in trial eye within 3 months prior to enrolling in the trial, smokers or any tobacco use

Intervention details	**Outcomes**
Intervention **RCT** *1.* microcurrent stimulation and nutritional supplement (data not reported) *2.* sham microcurrent stimulation and nutritional Supplement **Cohort study** *1.* sham microcurrent stimulation and nutritional Supplement *2.* Placebo arm from MIRA-1 study (Pulido et al., 2002, in file)	*Outcomes (state if primary)* Change in BCVA (ETDRS) (primary outcome) Contrast sensitivity Macular function Adverse events Compliance Visual function questionnaire-25 *Length of follow-up:* 6 months

Dose details: microcurrent was self-administered by the patient, 2 treatments each day, using an automated microcurrent stimulator with a preset current of 800 micro-amps at frequency settings of 292 Hz (6 minutes), 30 Hz (3 minutes), 9.1 Hz (2 minutes), and 0.3 Hz (1 minute) for a total of 12 minutes. Supplement: Vitamin A (total) 28,640 IU; Vitamin C 452 mg; Vitamin E 200 IU; Zinc Oxide 69.6 mg; Copper 1.6 mg; Taurine 400 mg; EPA Omega-3 Fatty Acids 180 mg; DHA Omega-3 Fatty Acids 120 mg; Lutein (free, not esterified) 8 mg; Zeaxanthin 400 mcg. 2 capsules three times per day *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 6 months	

Participant characteristics, %			
	Sham + supplement (RCT and cohort study) n=37	**Placebo (cohort study, matched from Pulido), n=15**	**P value**
Age, years mean (SD)	76.3 (7.8)	74.7 (5.9)	
Sex, % male	45.9	33.0	
Ethnic origin % White	91.9	100	
Smoking history *Current* *Never* *Former*	 0 67.6 29.7		
BCVA (logMAR), mean (SD)	0.41 (0.17)	0.39 (0.17)	
Cataract surgery	83.8		
Glaucoma	10.8		
Key comorbidities *Diabetes* *Hypertension* *Heart disease* *Other*	 10.8 43.2 35.1 83.8		
Family history	24.3		
Results: RCT			
	Microcurrent stimulation and supplement, n=36	**Sham and supplement, n=37**	**P Value**
States: microstimulation treatment was found to have little significant effect on any of the efficacy endpoints and thus was abandoned. No further details reported.			
Results: cohort study with historical controls			
	Sham + supplement, n=34	**Placebo, n=15**	**P Value**
Change in visual acuity, ETDRS lines at 6 months	0.54 P=0.045 from baseline	-1.49	
Comments			
BCVA (logMAR) *Improved* *Maintained* *Worsened*	 56.7 20.0 23.3		
Average visual acuity at 6 months (SD)	0.355 (0.283)		
Average change in visual acuity at 6 months, mean (95% CI)	-0.054 (-0.107, -0.0013)		
Comments Text states improvement in visual acuity, but tables and figures show a decrease in values. Units of visual acuity unclear, assume logMAR.			

Comments: states Fluorescein angiogram, retinal photographs, contrast sensitivity, full-threshold visual fields, macular testing (central 10° threshold visual field), and the Visual Function Questionanaire-25 (VFQ-25) were found to have little significant change at 6 months.			
Adverse events: significant systemic or ocular adverse events related to the nutritional supplement	0	NR	
Comments: States The most frequent events were systemic gastrointestinal reactions, including gastric upset, reflux, nausea, and taste perversion, majority resolved after administering with food.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Details not reported
Allocation concealment (selection bias)	Unclear	Details not reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as double blind, no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Described as double blind, no further details
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Details not reported, states is a per protocol analysis
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	High	No data reported
Other biases	Unclear	Unknown as no details reported

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?		x	
5. Was a sample size justification, power description, or variance and effect estimates provided?	x		
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?	x		
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD

12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Fair
Weaknesses: recruitment period, outcome assessment, limited data on outcomes, limited comparison with controls

*CD, cannot determine; NA, not applicable; NR, not reported

Taylor et al

Study details	**Participant details**
Taylor HR, Tikellis G, Robman LD, McCarty CA, McNeil JJ. Vitamin E supplementation and macular degeneration: Randomised controlled trial. British Medical Journal 2002;325:11-4. *Country:* Australia *Design:* RCT *Number of centres:* one *Funding:* commercial and non-commercial funding *Trial ID:* not reported	*Number of Participants*: total 1204 randomised (groups not specified); total after exclusion of 11: 1193, vitamin E 595; placebo 598 *Number of eyes* not reported *Sample attrition/dropout*: 11 participants were excluded after randomisation (outside the required age range, group not specified). Withdrawals total 150; Vitamin E 78 (died 11; adverse event 4; cataract extraction 1; relocated 4; health related 24; personal 23; taken own vitamin E 4; contraindication to vitamin E 4; unknown 3); Placebo 72 (died 7; adverse event 7; cataract extraction 1; relocated 5; health related 21; personal 24; taken own vitamin E 1; contraindication to vitamin E 3; unknown 3). In addition, 144; Vitamin E 74 and placebo 70 discontinued treatment (reasons reported). Excluded from final analysis 14: Vitamin E 8 (diabetic retinopathy 6, myopic degeneration 1, missing data 1); Placebo 6 (adult vitelliform macular degeneration 4, missing data 2) *Sample crossovers:* none *Inclusion criteria:* healthy volunteers, aged 55-80 years; lens and retina of at least one eye could be photographed. *Exclusion criteria:* bilateral cataract surgery, advanced bilateral cataract, other serious disease, sensitivity to vitamin E, taking steroids or anticoagulant treatment.

Intervention details	**Outcomes**
Intervention *1.* Vitamin E *2.* Placebo *Dose details:* 1. vitamin E, 500 international units (335 mg d-α tocopherol) in a soybean oil suspension in gelatin capsule, daily. 2. Placebo: matched capsule with soybean oil only. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 4 years	*Outcomes (state if primary)* Development of early AMD (at least one eye, primary outcome, also other definitions of AMD assessed) AMD progression Late AMD development Incidence of drusen (intermediate, distinct, indistinct) Incidence of hypo and hyperpigmentation Visual acuity (letters, logMAR) Changes in visual function (VF-14 score) Compliance Adverse events *Length of follow-up:* varied up to 4 years

Participant characteristics, %			
	Vitamin E, n=595	**Placebo, n=598**	**P value**
Age, years mean (SD)	65.72	65.73	Ns
Sex, % male	46	42	ns

Classification, % *Early AMD* *Late AMD*	 17.5 0.5	 18 0.5	 ns
Smoking history *Current* *Ever*	 2.3 48	 1.7 49	 ns
BCVA (≥ 40 letters on logMAR), %	99	99	ns
Key comorbidities *Hypertension* *Hyperlipidaemia* *Ischemic heart disease* *Diabetes*	 38 25 11 4.9	 33 24 9 3.5	 ns
Family history, % *Cataract* *AMD* *Glaucoma* *Blindness*	 28 2 9 7	 29 2 10 6	 ns
Comments: ns: states no significant differences between groups on any of these characteristics			
Results			
	Vitamin E, n=587	**Placebo, n=592**	**RR (95% CI)**
4-year incidence of early AMD, % *Photographs*[a] *Clinical grading*[b]	 8.6 7	 8.1 7	 1.05 (0.69, 1.61) 1.12 (0.66, 1.9)
Comments: by primary outcome definition. [a]Soft distinct or soft indistinct or pigment changes (hyperpigmentation or hypopigmentation); [b] Large/soft drusen or non-geographical RPE atrophy Also reports incidence of early AMD by 3 other definitions, not extracted (all not significant). Also reports the prevalence of early AMD (not extracted, not statistically significant)			
Incidence of late AMD, % *Photographs* *Clinical grading*	 0.8 1	 0.6 1	 1.36 (0.67, 2.77) 1.00 (NA)
Comments: included neovascular AMD with serious or haemorrhagic detachment of the retinal pigment epithelium or sensory retina, characteristic haemorrhages, or subretinal fibrous scars Also reports the prevalence of late AMD (not extracted, not statistically significant)			
Incidence of drusen at 4 years, % *Soft intermediate* *Soft distinct* *Soft indistinct*	 19 6 2	 18 6 2	 1.05 (0.80, 1.39) 1.05 (0.60, 1.82) 1.03 (0.77, 1.38)
Incidence (%) hypopigmentation at 4 years	1	3	0.38 (1.16, 0.93)
Incidence (%) hyperpigmentation at 4 years	5	7	0.68 (0.41, 1.14)
Comments: States hypopigmentation was significantly less common in those on vitamin E, although the clinical significance of this is unclear; uncertain what this is referring to as 95% CI suggest not significant.			
Progression of AMD, %, 4 years, *Photographs* *Clinical grading*	 19 7.9	 18 6.0	 1.09 (0.84, 1.42) 1.31 (0.83, 2.07)
BCVA			
Comments: states no differences between groups, no data shown. Also states similar numbers of people lost > 9 letters (two lines) of visual acuity (59 in vitamin E group, 57 in placebo group).			
VF-14 score, mean *Baseline*	 92.58	 92.74	
Comments: does not report final VF-14 scores, states no differences between groups only.			
Compliance			
Comments: 78% had a compliance rate of at least 80%; there was no difference between groups, p=0.46			

Adverse events potentially related to study capsule, %	15	14	0.49
Ocular adverse events, %	18	15	0.23
Serious adverse events, %	0	0	
Adverse reaction leading to withdrawal	0.7	1.2	
Comments States there was no significant difference between overall number and type of adverse event between the two groups (P=0.97).			
Subgroups			
Comments: states subgroup analyses included current smokers, those with a family history of AMD, and those with a high ocular exposure to visible light or to ultraviolet-B radiation. In none of these analyses was there a difference between the two treatment groups (data not presented)			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	States participants were randomly allocated to treatment using a "permuted blocks" allocation scheme.
Allocation concealment (selection bias)	Unclear	Study numbers were allocated sequentially by the study coordinator as participants were enrolled in the study. The allocation list was stored at a remote site and was not broken until the dataset had been locked.
Blinding participants and personnel (performance bias), Objective outcomes	Low	Vitamin E and placebo capsules were of identical appearance and taste. Neither study staff nor examiners or participants were aware of the treatment allocation
Blinding participants and personnel (performance bias), Subjective outcomes	Low	As above
Blinding outcome assessors (detection bias), Objective outcomes	Low	States examiners were not aware of treatment allocation. States 10% of the retinal photographs were checked in a masked regrading
Blinding outcome assessors (detection bias), Subjective outcomes	Low	As above
Incomplete outcome data (attrition bias), Objective outcomes	High	States analyses undertaken based on intention to treat, however, 8 and 6 people respectively were excluded from the analysis in the vitamin E and placebo groups (reasons provided). Also, withdrawal rate high (although balanced)
Incomplete outcome data (attrition bias), Subjective outcomes	High	As above
Selective reporting (reporting bias)	High	Not all outcomes data were reported
Other biases	Low	No other apparent biases

Teikari et al

Study details	**Participant details**
Teikari JM, Laatikainen L, Virtamo J, Haukka J, Rautalahti M, Liesto K, et al. Six-year supplementation with alpha-tocopherol and beta-carotene and age-related maculopathy. Acta Ophthalmol Scand 1998;76:224-9. *Country:* Finland	*Number of Participants*: total sample 941: alpha-tocopherol 237; beta-carotene 234; alpha-tocopherol + beta-carotene 257; placebo 213 *Number of eyes:* assume total sample 1882: alpha-tocopherol 474; beta-carotene 468; alpha-tocopherol + beta-carotene 514; placebo 426 *Sample attrition/dropout*: none (as sample were those that agreed to participate in the substudy)

Design: RCT (subgroup analysis of an RCT for lung cancer prevention) *Number of centres:* two *Funding:* non-commercial funding *Trial ID:* not reported	*Sample crossovers:* none *Inclusion criteria:* male, ≥65 years, smoking ≥5 cigarettes per day. *Exclusion criteria:* history of cancer or serious disease, taking supplements of vitamin E, vitamin A, or beta-carotene in excess of predefined doses, being treated with anticoagulants.

Intervention details	**Outcomes**
Intervention *1.* alpha-tocopherol *2.* beta-carotene *3.* alpha-tocopherol and beta-carotene *4.* Placebo *Dose details:* daily supplements. Alpha-tocopherol (50mg); beta-carotene (20mg) *Dose modifications:* not reported (see below for compliance) *Concurrent treatment:* not reported *Duration of treatment:* 6.6-6.7 years	*Outcomes (state if primary)* Incidence of AMD Compliance (% capsule taken) *Length of follow-up:* 5-8 years (median 6.1)

Participant characteristics, %					
	alpha-tocopherol n=237	**beta-carotene n=234**	**alpha-tocopherol + beta-carotene n=257**	**placebo n=213**	**P value**
Age, years mean (SD)	68.8	68.7	68.6	68.1	
Sex, % male	100	100	100	100	
Smoking cigarettes n / day	15	15	15	15	
Smoking history, years	42	41	42	42	
visual acuity *right eye with glasses* *left eye with glasses* *right eye without glasses* *left eye without glasses*	 1.0 1.0 0.5 0.5	 1.0 1.0 0.5 0.5	 0.9 1.0 0.5 0.5	 0.9 1.0 0.5 0.6	
Key comorbidities *Hypertension* *Diabetes*	 30.8 6.8	 31.6 4.7	 23.3 4.3	 25.4 3.8	
Results					
	alpha-tocopherol n=237	**beta-carotene n=234**	**alpha-tocopherol + beta-carotene n=257**	**placebo n=213**	**P Value**
ARM overall incidence, %	31.6	29.1	28.4	24.9	0.468
ARM class, n *No ARM* *I* *II* *III* *IV*	 162 65 2 6 2	 166 64 2 2 -	 184 64 6 2 1	 160 46 6 0 1	

Comments: I = dry maculopathy, with hard drusen and/or pigmentary changes, II= soft macular drusen, III = disciform degeneration, IV = geographic atrophy. States that supplementation with alpha-tocopherol showed no association with the prevalence of ARM (Odds Ratio 1.10, 95% CI 0.83-1.45) in the univariate model. No association was seen with beta-carotene in a general estimation equation model (OR 1.01, CI 0.77-1.33) controlling for relevant factors (includes right / left eye; diabetes; hypertension; cigarettes; alcohol intake; cholesterol; BMI; education; myopia at adolescence; nuclear cataract). No statistically significant protective effect of either alpha-tocopherol or beta-carotene could be detected in the general estimation equation analysis, even after adjusting for potential risk factors for ARM					
Compliance, % of capsules taken	99.3	99.3	99.2	99	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Says randomly assigned, no further details
Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Says is double blind study but no details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Low	Retinal specialist assessed ARM from fundus photographs without knowledge of participants treatment group, medical history or physical findings
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Low	No attrition
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Outcomes as reported in aim/methods
Other biases	Low	No other apparent biases

HESA-A

Ahmadi et al

Study details	**Participant details**
Ahmadi A, Ghanbari H, Soheilian M, Naseri M. The EFFEct of HESA-A (natural drug) on visual acuity in age related macular degeneration: a randomized double blind controlled clinical trial. African journal of traditional, complementary, & alternative medicines 2009;6:549-53. *Country:* Iran *Design:* RCT *Number of centres:* not stated, > 1 *Funding:* not stated *Trial ID:* not reported	*Number of Participants*: total 280; HESA-A 140; control 140 *Number of eyes* total: 280; HESA-A 140; control 140 *Sample attrition/dropout*: not reported *Sample crossovers:* none *Inclusion criteria:* clinical diagnosis of wet or dry AMD *Exclusion criteria:* diagnosis of cataract, glaucoma, corneal lesions and other macular pathologies

Intervention details	**Outcomes**
Intervention *1.* HESA-A (a drug of herbal-marine origin) *2.* Placebo *Dose details:* oral tablet 25mg/kg twice daily *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 4 weeks	*Outcomes (state if primary)* BCVA (ETDRS charts converted to logMAR score). Adverse events Compliance *Length of follow-up:* 6 months (5 months after end of treatment period)

Participant characteristics, %			
	HESA-A, n=140	**Control, n=140**	**P value**
Age, years mean (SD)	69.41 (8.98)	68.72 (7.99)	0.50
Sex, % male	45.7	42.1	0.63
BCVA (logMAR), mean (SD)	1.69 (0.65)	1.71 (0.65)	0.81
Comments			
Results			
	HESA-A, n=140	**Control, n=140**	**P Value**
BCVA (logMAR), mean (SD) at 1 month	1.03 (0.40)	1.72 (0.66)	0.0001
Comments: states visual acuity improved in 100% of participants in the treatment group at 4 weeks and after 5 months follow-up but the same effect was not seen in the control group (no data).			
Adverse events	0	0	
Comments: states no drug noncompliance during 4 weeks of treatment or 5 months follow-up			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States randomly assigned but no further details
Allocation concealment (selection bias)	Unclear	Not described
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Says double blind, and that patient and physician were blind to the drug or placebo group although no details provided.

Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	No details of any losses or withdrawals
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Outcomes reported as stated
Other biases	Low	No other apparent biases

Saffron

Riazi et al

Study details	**Participant details**
Riazi A, Panahi Y, Alishiri AA, Hosseini Ma, Karimi Zarchi AA, Sahebkar A The Impact of Saffron (Crocus Sativus) Supplementation on Visual Function in Patients with Dry Age-Related Macular Degeneration. 2017. Italian Journal Medicine, 11; 2: 1-6 *Country:* Iran *Design:* RCT *Number of centres:* one *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 69 randomised; completing study 54; saffron 29, placebo 25 *Number of eyes* not stated if one or both eyes were assessed *Sample attrition/dropout*: 15 did not continue 'for various reasons' mainly lack of satisfaction with the impact of the capsules during month 1 and medical problems. *Sample crossovers:* none *Inclusion criteria:* >50 years, with dry AMD mild (small drusen or a few medium-sized drusen) to moderate (many medium or at least one big drusen or GA without any sub-foveal involvement), confirmed by a retinal specialist. *Exclusion criteria:* wet and severe dry type AMD, systemic diseases such as hypertension, diabetes, or glaucoma, AMD secondary to retinal diseases, taking any other dietary supplements.

Intervention details	**Outcomes**
Intervention *1.* Saffron supplement *2.* Placebo (300mg starch, also states 200mg) *Dose details:* 50 mg saffron extract and 250 mg of starch in gelatin (also states 150mg starch), one per day *Dose modifications:* none reported *Concurrent treatment:* telephoned twice in month 1 and 2 to ensure compliance and for any adverse events. *Duration of treatment:* 3 months	*Outcomes* Quality of life and related activities (Melbourne low vision index), score up to 36 (no problems with daily activities) Adverse events BCVA Contrast Sensitivity Central macular thickness (not extracted) *Length of follow-up:* 3-months

Participant characteristics, %

	Saffron, n=29	**Placebo, n=25**	**P value**
Age, years mean (SD)	70.04 (8.5)	68.9 (8.26)	0.66
Sex, % male	65.2	34.8	
BCVA logMAR	0.46 (0.41)	0.62 (0.55)	0.124 or 0.517
Results			
	Saffron, n=29	**Placebo, n=25**	**P Value**
Mean (SD) BCVA logMAR at 12 weeks	0.41 (0.41)	0.65 (0.54)	0.001
Comments			
Contrast sensitivity baseline at 12 weeks, mean (SD)	16.31 (3.63) 18.18 (3.40)	14.8 (4.91) 14.4 (4.53)	0.152 0.001
Comments			
QOL score, mean (SD) Baseline at 12 weeks	 33.82 (3.91) 34.06 (3.7)	 29.48 (5.97) 30.56 (5.61)	 0.002 0.008
Comments			
Adverse events	Not reported	Not reported	
Comments			
Subgroups			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Says randomly assigned but no details
Allocation concealment (selection bias)	Unclear	No details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Pharmacist distributing capsules which were labelled A and B had no further information. No further details
Blinding participants and personnel (performance bias), Subjective outcomes	Unclear	Pharmacist distributing capsules which were labelled A and B had no further information. No further details
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No details
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	No details
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Drop outs by study group not reported, reasons partially reported
Incomplete outcome data (attrition bias), Subjective outcomes	Unclear	Drop outs by study group not reported, reasons partially reported
Selective reporting (reporting bias)	Low	Appears to report stated outcomes
Other biases	Low	No other apparent biases

Falsini et al., 2010{#431}

Study details	**Participant details**
Falsini B, Piccardi M, Minnella A, Savastano C, Capoluongo E, Fadda A, et al. Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration. Investigative Ophthalmology & Visual Science 2010;51:6118-24.	*Number of Participants*: Total 25 1. Saffron then placebo, n=11 2. Placebo then saffron, 14 *Number of eyes* Total 25 *Sample attrition/dropout*: None.

Potential overlap with of participants with Piccardi 2012 cohort study *Country:* Italy *Design:* Randomised crossover trial (pilot) *Number of centres:* one *Funding:* States no sponsor but also states funded in part by non-commercial grants *Trial ID:* NCT00951288	*Sample crossovers:* None. *Inclusion criteria:* bilateral early AMD (when any of the following primary lesions in the macular area of one or both eyes was identified: soft distinct or indistinct drusen; areas of hyperpigmentation associated with drusen; or areas of hypopigmentation of the RPE associated with drusen, without any visibility of choroidal vessels); best corrected visual acuity of ≥0.3 in the study eye, central fixation, normal colour vision, no signs of other retinal or optic nerve disease and clear optical media. One eye, (typically with best visual acuity), was selected as the study eye. *Exclusion criteria:* no explicit criteria reported but confirmation of no geographic atrophy or RPE detachment was required

Intervention details	**Outcomes**
Intervention *1.* Saffron 20mg *2.* Placebo *Dose details:* saffron 20 mg, no further details *Dose modifications:* Not reported. *Concurrent treatment:* None was taking medications known to affect macular function or to interfere with carotenoid absorption. No other systemic pharmacologic treatments were given. *Duration of treatment:* 90 days of first randomised intervention (saffron or placebo), 15 days washout period, then 90 days of second intervention	*Outcomes (state if primary)* focal Electroretinogram (fERG) amplitude, phase, fERG function slope (primary outcomes) – not data extracted; visual acuity *Length of follow-up:* 90 days on each treatment

RPE: retinal pigment epithelium

Participant characteristics, %			
	All patients, n=25		
Age, years mean (SD)	65 (5)		
Sex, % male	48		
Classification, % *Intermediate AMD*	 100% of eyes		
visual acuity, Snellen, mean (SD)	0.7 (22)		
lesion size			
Mean number (range) drusen	9 (4-22)		
Focal RPE abnormalities extending for ≥10% of one of the middle subfield areas in the macular region, %	24		
Key comorbidities, % *Moderate systemic hypertension*	 20		
Family history			
Results			
	Saffron, n=25	**Placebo, n=25**	**P Value**
Mean Snellen visual acuity after 90 days (SD)	0.80 (SD 0.20)	0.72 (SD 0.24)	P<0.01
Visual acuity, % *increase by one line* *unchanged*	 80 20	 0 100	

Adverse events	0	0	
Compliance			
States 'compliance was judged to be satisfactory, since none of the treated subjects refrained, for any reason, from taking the daily dose of supplement or placebo during the treatment period'			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States random, no details
Allocation concealment (selection bias)	Unclear	States patients were assigned to the two treatment groups by two ophthalmologists (AM, CS) who did not participate in electrophysiological and clinical data collection. No further details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Described as double-blind but no further details
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Macular grading was undertaken by masked investigators, but not reported for visual acuity
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	Low	States none of the treated subjects refrained, for any reason, from taking the daily dose of supplement or placebo during the treatment period.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	Low	Outcomes reported as stated on clinical trial register
Other biases	Low	No other biases from cross-over design

Lashay et al

Study details	**Participant details**
Lashay A, Sadough G, Ashrafi E, Lashay M, Movassat M, Akhondzadeh S. Short-term Outcomes of Saffron Supplementation in Patients with Age-related Macular Degeneration: A Double-blind, Placebo-controlled, Randomized Trial. Med Hypothesis Discov Innov Ophthalmol 2016;5:32-8. *Country:* Iran *Design:* RCT *Number of centres:* one *Funding:* none (saffron donated by manufacturer) *Trial ID:* IRCT 201205219820N1	*Number of Participants*: total 30 with dry AMD; saffron 15; placebo 15 (30 with wet AMD also randomised, subgroup not extracted) *Number of eyes:* total 30; saffron 15; placebo 15 *Sample attrition/dropout*: lost to follow-up dry AMD saffron 3; placebo 8. *Sample crossovers:* none *Inclusion criteria:* age ≥ 65 years, physical status class of I-II based on the American Society of Anaesthesiologists classification system, a clinical diagnosis of dry (or wet) AMD confirmed by fluorescein angiography, BCVA 20/400-20/40 in the study eye, clear optical media. *Exclusion criteria:* cataracts, glaucoma, corneal opacities, any sign of retinal or optic nerve disease other than AMD, or systemic disease.
Intervention details	**Outcomes**

Intervention *1.* Saffron *2.* Placebo *Dose details:* 2 oral capsules, 15mg saffron extract. Placebo was shaped similarly with the same dose and duration. *Dose modifications:* Not reported *Concurrent treatment:* other nutrients or supplements not permitted. No other systemic pharmacological agents were administered. *Duration of treatment:* 6 months	*Outcomes (state if primary)* Macular thickness (primary outcome) ERG amplitude (primary outcome) *Length of follow-up:* 6 months

Participant characteristics, %			
	Saffron, dry AMD n=12	**Placebo, dry AMD n=7**	**P value**
Age, years mean (SD)	68.4 (4.7)	63.0 (6.8)	0.52
Comments 60% of the wet+dry AMD completers (n=40) were male, no significant difference between saffron and placebo groups, not reported for dry subgroup. 17.5% of the wet+dry AMD completers (n=40) were smokers, no significant difference between saffron and placebo groups, not reported for dry subgroup.			
Results			
	Saffron, dry AMD n=12	**Placebo, dry AMD n=7**	**P Value**
Macular thickness, micron *Baseline* *6 months*	 227.92 (31.5) 225.64 (30.3)	 239.87 (37.4) 238.54 (22.3)	 0.32 0.28
Comments			
ERG amplitude, Mvolt *Baseline* *6 months*	 100.68 (31.3) 102.9 (3.1)	 85.88 (35.4) 89.6 (3.5)	 0.20 0.12
Adverse events			
Comments: states no major side effects in either groups, no reports of severe complications eg bleeding.			
Subgroups			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Computer generated numbers
Allocation concealment (selection bias)	Unclear	Sealed envelopes but not clear if opaque or sequentially numbered.
Blinding participants and personnel (performance bias), Objective outcomes	Low	Patients and personnel blinded, placebo matched
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Low	States all individuals involved in the study were blind to assigned treatment group, assume this includes outcome assessors
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition	High	In the dry AMD subgroup differential drop-out

bias), Objective outcomes		rates between groups
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Unclear	Unable to locate trial record to check
Other biases	Low	No other apparent biases.

Piccardi et al

Study details	**Participant details**
Piccardi M, Marangoni D, Minnella AM, Savastano MC, Valentini P, Ambrosio L, et al. A longitudinal follow-up study of saffron supplementation in early age-related macular degeneration: sustained benefits to central retinal function. Evidence-Based Complementary & Alternative Medicine: eCAM 2012;2012:429124. *Country:* Italy *Design:* Before and after study (one group) *Number of centres:*1 *Funding:* Hortus Novus provided saffron pills and other support *Trial ID:* Not reported	*Number of Participants*: N=29 *Number of eyes:* N=29 (1 per participant, typically the eye with the best visual acuity) *Sample attrition/dropout*: Note reported *Sample crossovers:* Not applicable *Inclusion criteria:* bilateral early AMD, best-corrected visual acuity of 0.5 or better in the study eye, central fixation (assessed by direct ophthalmoscopy), normal colour vision with Farnsworth D-15 testing, no signs of other retinal or optic nerve disease and clear optical media. *Exclusion criteria:* Not reported

Intervention details	**Outcomes**
Intervention *1.* Saffron oral supplementation *2.* None *Dose details:* Saffron oral supplementation (20mg/day) *Dose modifications:* Not stated *Concurrent treatment:* None *Duration of treatment (mean):* 14 months (SD 2)	*Outcomes (state if primary)* Focal-electroretinograms (fERG) macular (18◦) flicker sensitivity, derived from the estimated response amplitude thresholds (reported at baseline, 3, 6, 9, 12, and 15 months) (primary outcome). fERG is presented as fERG amplitude and fERG function, threshold and slope (using log_{10} values). Secondary outcomes included visual acuity, compliance and adverse effects *Length of follow-up:*15 months

Participant characteristics, %			
	Saffron, n=29		
Age, years mean (SD)	69.3 (7)		
Sex, % male	55.2		
visual acuity	0.75		
Moderate systemic hypertension	8 (27.6%)		
Results			
	Saffron, n=29		
Focal Electroretinograms (fERG)	See comments		

Comments: After three months of supplementation, mean fERG threshold decreased and sensitivity improved by 0.3 log units compared to baseline values repeated measures ANOVA, $F = 4.6$; df : 6,168; $P < 0.01$). These changes remained stable over the follow-up period, since comparisons at various times of follow-up did not show any significant change. The mean fERG slopes did not change significantly throughout the follow-up.			
Compliance	100%		
Comments: compliance was judged to be satisfactory, since none of the treated subjects refrained, for any reason, from taking the daily dose of supplement during the treatment period.			
Visual Acuity, mean	0.9		
Comments: Mean visual acuity improved by two Snellen lines compared to baseline values (0.75 to 0.9, $P < 0.01$). These changes remained stable over the follow-up period.			
Adverse events			
Comments: No adverse systemic side effects were recorded			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	y		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	y		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?	y		
5. Was the sample size sufficiently large to provide confidence in the findings?	y		
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	y		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	y		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		n	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	y		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	y		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		n	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating:Good

*CD, cannot determine; NA, not applicable; NR, not reported

Marangoni et al

Study details	Participant details
Marangoni D, Falsini B, Piccardi M, Ambrosio L, Minnella AM, Savastano MC, et al. Functional effect of Saffron supplementation and risk genotypes in early age-related macular degeneration: a preliminary report. Journal of Translational Medicine 2013;11:228. It is likely that some of these participants are the	*Number of Participants*: Total 33 *Number of eyes* 33 *Sample attrition/dropout*: none *Sample crossovers:* not applicable

same as those reported in Piccardi 2012 (and potentially Falsini 2010) above *Country:* Italy *Design:* Prospective cohort study *Number of centres:* one *Funding:* Saffron tablets provided by manufacturer Hortus Novus; non-commercial grant also *Trial ID:* not reported	*Inclusion criteria:* bilateral early AMD (established when any of the following primary lesions in the macular area was identified: soft distinct or indistinct drusen; areas of hyperpigmentation associated with drusen; or areas of hypopigmentation of the retinal pigment epithelium associated with drusen, without any visibility of choroidal vessels); best corrected visual acuity of ≥0.5 in the study eye, central fixation, normal colour vision, no signs of other retinal or optic nerve disease and clear optical media. One eye, (typically with the best visual acuity), was selected as the study eye. *Exclusion criteria:* No additional criteria

Intervention details	**Outcomes**
Intervention *1.* Saffron *Dose details:* Saffron oral supplementation 20 mg/day *Dose modifications:* not reported *Concurrent treatment:* None was taking medications (e.g., chloroquine) that are known to affect macular function or to interfere with carotenoid absorption. No other systemic pharmacologic treatments *Duration of treatment:* average 11 months (range, 6–12)	*Outcomes (state if primary)* Focal electroretinogram (fERG) amplitude and macular sensitivity from estimated response amplitude thresholds (primary outcomes) Visual acuity (data not reported) Compliance Adverse events *Length of follow-up:* average 11 months (range, 6–12)

Participant characteristics, %			
	Saffron, n=33		**P value**
Age, years mean (range)	68.4 (15-85)		
Sex, % male	45.5		
Key comorbidities, % Moderate systemic hypertension Other systemic disease	 24 0		
Results			
	Saffron, n=33		**P Value**
fERG amplitude and fERG sensitivity			
After three months of supplementation, mean fERG amplitude and fERG sensitivity improved significantly when compared to baseline values ($p < 0.01$). These changes were stable throughout the follow-up period. Data presented in figures for subgroups, not extracted.			
Compliance			
States 'In all cases, compliance was judged to be satisfactory, since none of the treated subjects refrained, for any reason, from taking the daily dose of supplement during the treatment period'			
Adverse events	0		
Subgroups			
No significant differences in clinical and fERG improvements were observed across different CFH or ARMS2 genotypes. Data presented in figures for subgroups, not extracted.			

Cohort and Cross-Sectional Studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in	x		

the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			CD
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?			NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Fair/poor

*CD, cannot determine; NA, not applicable; NR, not reported